EPIDEMIOLOGY OF TYPE 1 DIABETES COMPLICATIONS IN AFRICAN-AMERICANS

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Unlike type 2 diabetes, where prevention is possible, type 1 diabetes is a lifelong incurable metabolic disorder. The annual incidence of type 1 diabetes continues to rise annually. Despite increased access to treatment and improved disease management, type 1 diabetes is associated with excess morbidity and early mortality. African-Americans with type 1 diabetes are at increased risk of premature mortality compared to Caucasians. This disparity is likely fueled by differences in the prevalence of complications; however, there is limited information available on the racial differences in type 1 diabetes complications in individuals of African descent (i.e. African-American, Afro-Caribbean). Using the data from the U.S. Virgin Islands Childhood Diabetes Registry, this dissertation provides contemporary insights on the incidence of childhood diabetes in African-American youth and for the first time evaluates type 1 diabetes mortality in African-Americans, in the U.S. Virgin Islands. In addition, this dissertation assesses racial differences in the prevalence of type 1 diabetes complications and risk factors using a national sample from the National Health and Nutrition Examination Survey.

The incidence of type 1 and type 2 diabetes in youth in the U.S. Virgin Islands is rapidly increasing. The well-established pubertal increase in type 1 diabetes incidence appears to be missing in African-American boys. Individuals diagnosed at later ages (>14), have significantly higher risk of mortality compared to those diagnosed at earlier ages. Despite advances in diabetes care, there were no temporal improvements observed in mortality in the U.S. Virgin

Islands. African-Americans in the U.S. Virgin Islands had a similar type 1 diabetes mortality experience as African-Americans in Allegheny County, PA. African-Americans in the national sample had significantly higher rates of nephropathy and retinopathy. Race was associated with both complications, even after adjusting for clinical and demographic factors.

The public health implications of this dissertation are considerable, as it provides insight on the burden of type 1 diabetes in the U.S. Virgin Islands and African-Americans in the U.S. These findings provide evidence to support additional services and potentially intensive diabetes management strategies for African-Americans with type 1 diabetes.

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PREFACE

I must express sincere appreciation to many people who have made this academic journey possible. First, I extend many thanks to Dr. Trevor Orchard for his mentorship over these past 3 years. Dr. Orchard has dedicated countless hours and energy to my academic development and I am forever grateful for his investment in my life. Secondly, I am indebted to Dr. Eugene Tull for his guidance and mentorship, and for providing the opportunity for me and other graduate students to gain valuable public health experience in the U.S. Virgin Islands. In addition, I am very appreciative to each of my other committee members, Dr. Ronald LaPorte and Dr. Vincent Arena, for their support, input, feedback, criticisms, and encouragement.

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Lastly, I wish to dedicate this dissertation to my late grandmothers, Doris Mildred Bloomfield and Maggie Leola Washington, both of which died of diabetes complications. Both of your love and support continues to be a guiding light for me in life. Thank you "Granny" for encouraging me to dream, and work until my dreams become reality. I would also like to thank my parents, Raymond F. Washington, Jr. and Arlene B. Garnett, for their love and support, and tireless effort to ensure that I was afforded every opportunity life offered. In addition, much appreciation goes to my brother, Raymond F. Washington, III, and the many family members and friends that have supported me during my academic journey. Finally, and most importantly I praise God for blessing me with this opportunity and His provision of the necessary tools and strength.

1.0 INTRODUCTION

Type 1 diabetes is associated with considerable excess morbidity and early mortality. Despite significant advances in disease management and care, African-American youth have been shown to have poorer management of T1D, often confounded by poor socioeconomic conditions, which likely increases risk for complications. Research has demonstrated that African-Americans are at nearly 3-fold increased risk of mortality associated with T1D, compared to Caucasians. This is likely fueled by disparities in the morbidity of complications, however this difference remains unclear. While epidemiologic investigations have extensively described the natural history of T1D and complications in various populations, there is limited information available on the prevalence of complications and risk factors specifically in African-Americans, in comparison to other racial groups, particularly Caucasians. Existing prospective cohort studies have insufficient ethnic diversity to allow for racial comparisons. There is currently no information on the prevalence of T1D complications and risk factors in the U.S. Virgin Islands, a culturally unique and predominantly African-American population where the incidence of T1D seems to be increasing.

As such, the objectives of this dissertation are to:

1. Estimate the annual incidence of childhood diabetes in the U.S. Virgin Islands in recent years, including an analysis of contemporary trends, demographics and risk profiles.

2. Estimate mortality in an African-American cohort in the U.S. Virgin Islands and compare to a predominantly Caucasian cohort, using similar data collection methods.

3. Compare the prevalence of T1D complications and risk factors in African-Americans and Caucasians in the U.S. using data reported in the National Health and Nutrition Examination Survey.

The outcomes of this dissertation will expand the current knowledge of diabetes complications in African-Americans and the U.S. Virgin Islands and create a foundation for understanding disparities in T1D-related health outcomes in the U.S.

2.0 BACKGROUND

2.1 DIABETES MELLITUS

Diabetes mellitus is a group of metabolic diseases marked by increased levels of blood glucose as a result of inadequate insulin production or defects in insulin activity and in many instances a combination of both. World Health Organization estimates that more than 220 million people worldwide have diabetes, with approximately 1.1 million diabetes-related deaths occurring annually.[1] Centers for Disease Control and Prevention estimates that approximately, 23.6 million (7.8%) U.S. adults and children have diabetes, with over 5 million undiagnosed cases, and estimated 54 million having pre-diabetes.[2] The prevalence of diabetes in the U.S. is expected to increase by nearly 42.4% by 2030.[3] Diabetes is the currently the 6th leading cause of death in the U. S. with most deaths occurring as result of an acute or chronic complication of diabetes.[4] African-Americans are disproportionately affected by diabetes, predominantly due to increased prevalence of T2D in African-American adults.[2, 5, 6, 7] Despite increased access to treatment and improved disease management, the major complications of diabetes persist as significant sources of morbidity and early mortality; thereby further fueling the increasing burden of the disease. The three major types of diabetes are Type 1(T1D), Type 2(T2D), and gestational.

Type 1 Diabetes

T1D (formally known as insulin-dependent diabetes mellitus (IDDM)) is characterized by deficiencies in pancreatic β cell insulin production. Insulin is a peptide hormone usually secreted by pancreatic β cells in response to food uptake. The digestive system is responsible for the conversion of food to glucose, which eventually diffuses into the bloodstream. Insulin allows cells to properly uptake glucose from the bloodstream to be metabolized for energy or stored. When insufficient amounts of insulin are available, cells do not receive the necessary fuel to perform functions and glucose builds up in the blood stream, leading to high blood glucose levels, also known as hyperglycemia. In some instances, there is too much insulin available, most often due to administering higher insulin doses than necessary, resulting in low blood glucose levels, or hypoglycemia. The exact etiology of T1D remains unclear, but it is believed to be caused by a combination of autoimmune, genetic, and environmental factors, resulting in the immune system attacking pancreatic β cells and diminishing insulin production over time.[8, 9, 10] Long-term pancreatic β cell destruction eventually results in total insulin deficiency, requiring lifelong exogenous insulin administration. In addition to hyperglycemia, individuals with T1D typically present at onset with increased symptoms, such as thirst and polyuria, resulting from the excess glucose levels being excreted in the urine, and increased appetite, caused by glucose-deprived cells sending signals to the brain to increase food intake.[8] T1D is most often diagnosed at young ages, but can be diagnosed at any age, and accounts for approximately 5-10% of diabetes in the U.S.[2]

Type 2 Diabetes

T2D (formally known as non-insulin dependent diabetes mellitus (NIDDM)), the predominant and preventable type, accounts for 90-95% of diabetes in the U.S and is traditionally associated

with obesity, older age, family history of diabetes, physical inactivity, and certain ethnicities, including African-Americans and Hispanics.[6, 7] With the growing obesity epidemic, prevalence of T2D continues to rise in all age groups and ethnicities, most notably children. T2D results from a combination of insulin deficiency, due to insufficient insulin production by pancreatic β cells, and insulin resistance, inadequate use of available insulin by cells.[2, 7] At onset of T2D, the pancreas usually produces sufficient amounts of insulin, but due to increased insulin resistance, the body's cells do not effectively use the available insulin, resulting in hyperglycemia. The pancreas produces more insulin to account for increased blood glucose and energy starved cells signal the process of hepatic glucose production further increasing blood glucose levels. The liver may also become insulin resistant, decreasing its uptake of blood glucose and sensitivity to restricting glucose production. Prolonged over working of pancreatic β cells leads to reduced function and insulin production, and may eventually lead to the need for insulin therapy.

Gestational Diabetes

Gestational diabetes accounts for <1% of cases in the U.S. and results from glucose intolerance during pregnancy, and often subdues during the post-partum period, often recurring later in life.[2]

2.2 EPIDEMIOLOGY OF TYPE 1 DIABETES

The global incidence of T1D continues to rise approximately 3% annually.[11, 12] The WHO DiaMond Study is an international study of childhood onset T1D.[11] This study fostered the development of a large number (approximately 150) of population-based T1D registries across the world. Compiled data from these registries indicates high variation in the incidence of T1D in the respective countries, ranging from <1 per 100,000 per year in populations from South

America and China to the highest of 40.9 per 100,000 per year in Finland. Other studies assessing the incidence of T1D in various countries world-wide have also shown similar variations in T1D incidence.[13, 14]

United States

The prevalence of T1D in the U.S. varies by race, ethnicity, age, and geographical location. The SEARCH for Diabetes in Youth Study, an ongoing effort to monitor the incidence of both T1D and T2D among U.S. youth, estimates the annual incidence of T1D to be 19.0 per 100,000.[15] The highest incidence of T1D occurs in non-Hispanic whites and those in the 10-14 age group. African-Americans maintained a lower incidence of T1D at 15.7 per 100,000 for all age groups, compared to 23.6 per 100,000 in Caucasians, for the 2001-2003 time period.[16] However, socio-demographic and clinical profiles for African-American youth were significantly worse than Caucasians, which may suggest an increased likelihood for poorer health outcomes. More than one-third of African-American youth with T1D had a household annual income less than $25,000, compared to less than 10% of Caucasians. Approximately 53.4 % of African-American youth lived in 1-parent households. More African-American youth (27.9%) seemed to present with diabetic ketoacidosis at onset, compared to Caucasians (21.8%). Consistent with previous studies of risk profiles in youth with diabetes, African-American youth with T1D had significantly worse glycemic control compared to Caucasians.(Table 1)[17] Glycemic control was associated with age in both races, with more older youth having poor glycemic control. In addition to poorer glycemic control African-American youth were more likely to be overweight, have increased LDL cholesterol, high blood pressure, high degree of depression-related symptoms, and meet fewer dietary recommendations, compared to Caucasians.

Table 1: SEARCH Study - Percent of Youth with T1D HbA1C ≥ 9.5% by Race and Age Group

	0-9 Years (%)	10-14 Years (%)	≥15 Years (%)
African-American	24.5	40.2	46.0
Non-Hispanic White	4.7	11.2	21.5

U.S. Virgin Islands

The U.S. Virgin Islands, a U.S. territory, consist of four inhabited islands (St. Croix, St. Thomas, St. John, and Water Island) with a total population of 108,612 individuals. Approximately 76.1% of the population are non-Hispanic blacks, and 13.1% are non-Hispanic whites, with the remaining being a combination of Hispanic and Asian ethnic groups.[18] Consistent with continental U.S., diabetes persists as a major source of morbidity and mortality for the U.S. Virgin Islands. Approximately 9.7% of the territories population has been diagnosed with diabetes.[19] Diabetes is the 5th leading cause of death in the territory.[20] A childhood diabetes registry was established in the U.S. Virgin Islands as a part of the WHO DiaMond Study to further evaluate the epidemiology of T1D in the territory. The registry is composed of cases from all hospitals and health clinics in the three main islands (St. Croix, St. Thomas, and St. John). Cases are defined as any individual diagnosed with T1D less than 19 years old living in the territory at the time of diagnosis.[21] Initial studies were conducted on individuals diagnosed between January 1979 and December 1988. This time period reflected an annual incidence of 7.5 per 100,000, with rates being significantly higher in non-Hispanic whites compared to non-Hispanic blacks and Hispanics.[22] The incidence of T1D in the U.S. Virgin Islands is higher than other Caribbean islands with similar ethnic compositions and distributions.[23] Recent data from the registry suggests an increasing incidence of T1D in the territory; however it has not been formally reported.

2.3 TYPE 1 DIABETES COMPLICATIONS

T1D is a lifelong metabolic disorder and chronic hypo- and hyperglycemia often experienced by patients can lead to many complications, including death. The major complications most frequently associated with T1D, and T2D, can be grouped as microvascular, including neuropathies, nephropathy, and retinopathy, or macrovascular, including atherosclerotic conditions such as coronary artery disease, peripheral vascular disease, and cerebrovascular disease. The presence or combination of these conditions often leads to the ultimate complication, premature death. Studies have shown clear racial differences in mortality associated with T1D; however, there are limited data comparing racial differences in the prevalence of T1D complications and risk factors.[24, 25, 26, 27, 28, 29]

Overview of Major Complications

T1D can cause various types of nerve damage leading to diabetic neuropathy. There are two major classifications of neuropathies: peripheral, resulting from nerve damage in the arms and legs, typically beginning in the hands and feet, and autonomic, resulting from damage to the nerves that regulate vital functions, including the smooth muscles of the heart and other vital organs.[30]

Distal Symmetric Polyneuropathy (DSP), a peripheral neuropathy occurring most often in the feet and legs, is the most common type found in patients with T1D.[31] The clinical symptoms of DSP typically begin with numbness, pain, and/or paresthesias in the feet and legs, which may eventually lead to ulcers and in severe cases, require limb amputation due to infection. DSP is usually diagnosed by signs of heightened sensory loss, motor loss, including weakness and atrophy, and depressed tendon reflexes.[30]

Cardiac Autonomic Neuropathy (CAN) is also common in patients with T1D. Previous studies have shown that CAN is significantly associated with increased risk of mortality in patients with T1D.[32, 33] CAN damages the autonomic nerve fibers innervating the heart and blood vessels. CAN causes abnormalities in heart rate control and hemodynamics, resulting in the inability of patients to regulate cardiac output or redirect blood flow. This inadequate regulation of cardiac output often leads to reduced heart rate variation, resting tachycardia, exercise intolerance, and orthostatic hypertension. [31] CAN is usually detected clinically by exercise stress test, blood pressure response to standing, and heart rate variability during deep breathing.[31]

The complete pathogenesis of diabetic neuropathy remains unclear, though chronic hyperglycemia is suspected to play a primary role in its development.[34] The Diabetes Control and Complications Trial (DCCT) provided further evidence for this causal relationship by demonstrating a significant decrease in the development and progression of neuropathy by improving glycemic control through intensive therapy.[35] This reduction of risk due to improved glycemic control was maintained in subsequent follow-up of the DCCT.[36] The complexity and varying methodologies of diagnosis has limited the inclusion of neuropathy in many early T1D complication studies and racial differences have not previously been investigated.[37, 38]

Diabetic retinopathy is the most common eye complication in diabetes and the leading cause of new cases of blindness among adults in the U.S.[39] Diabetic retinopathy is caused by damage to the blood vessels in the eye from chronic hyperglycemia. Diabetic retinopathy clinically presents in progressive stages. The first is commonly referred to as mild to severe non-proliferative diabetic retinopathy (NPDR). At the early stages of NPDR, microaneurysms, small areas of balloon-like swelling in the retina's small blood vessels, occur. As NPRD progresses, examination of the retina may also reveal small dot and blot hemorrhages and blockage of more

blood vessels in the retina. The more advanced form of diabetic retinopathy is referred to as proliferative diabetic retinopathy (PDR), which involves increased damage to circulation in the retina. In response, neovascularization occurs, resulting in the development of weak and fragile blood vessels in the retina and possibly the vitreous, the fluid space in the back of the eye. These fragile blood vessels tend to hemorrhage leading to leakage of blood in the eye causing clouded vision. Further progression of PDR can ultimately lead to blindness.[40]

Diabetic nephropathy is a progressive kidney disease caused by damage to the capillaries of the kidneys, likely due to chronic hyperglycemia and genetic susceptibility.[41, 42, 43] This process begins with thickening of the kidney glomerulus, the blood vessels in the kidney responsible for filtering blood and forming urine. Further thickening of the glomerulus results in increased amounts of serum protein (albumin) in urine, known as microalbuminuria. Microalbuminuria is the first stage of diabetic nephropathy and is detectable by urine analysis for an increased albumin excretion rate. Routine urine analysis is essential for patients with diabetes as microalbuminuria is typically asymptomatic and early detection is critical to delay and prevention of further progression. As kidney damage worsens, the concentration of protein in urine increases eventually progressing to overt nephropathy, clinically diagnosed by “dipstick” positive urinalysis, and eventually End Stage Renal Disease (ESRD).

Cardiovascular disease is a group of macrovascular complications caused predominantly by the development of atherosclerosis in blood vessels throughout the body. Atherosclerosis is a slow progressive process in which the artery walls thicken due to build-up of fatty materials leading to the formation of plaques. Plaques are formed in large part due to the accumulation of cholesterol resulting from the formation of foam cells, following low-density lipoproteins penetration into the arterial wall. Plaques can make the artery narrow and less flexible, restricting

blood flow, leading to angina and more significantly they may rupture, leading to the formation of a blood clot which completely blocks blood flow. Pieces of plaque can also break off and move through the affected artery to smaller blood vessels, blocking them and causing tissue damage or death. There are three major types of CVD most often associated with T1D: CAD, peripheral vascular disease (PVD), and cerebrovascular disease.

CAD is the development of atherosclerosis in the blood vessels supplying oxygenated blood to the heart. The most common symptom of early CAD is chest pain, referred to as angina pectoris. Cardiac ischemia, or reduction of blood flow to the heart muscle, may also be detected by electrocardiogram (ECG), either at rest or during exercise (a stress test); however, it can often be undetected. A major complication of CAD is the rupturing of a plaque, leading to myocardial infarction, which is commonly known as a heart attack, and is often fatal. Other coronary complications of atherosclerosis include arrhythmias, abnormal speed and rhythms of the heartbeat, ischemic cardiomyopathy, deterioration of heart muscle, or heart failure, caused by prolonged weakening of heart muscle from oxygen-deprivation. Confirmed myocardial infarction, angioplasty (surgical procedure to increase blood flow in obstructed blood vessels), and CAD death, are classified as “hard CAD”, while early stages of disease (i.e. angina and electrocardiogram (ECG) changes), which are more difficult to define, are considered “soft CAD”.

Peripheral vascular disease (PVD) is the presence of atherosclerosis in areas outside of the heart and brain. Lower-extremity arterial disease (LEAD) is a common manifestation of PVD in T1D. LEAD is obstruction of circulation in the blood vessels in the legs and feet. LEAD typically begins with symptoms of claudication during physical activity, including pain, weakness, fatigue and discomfort in the legs and feet; which subdue after rest. Overtime, these

symptoms will appear while at rest, indicating further progression of occlusion of blood flow in the lower extremities. LEAD can cause foot ulcers and in severe cases leads to gangrene and limb amputation.

Cerebrovascular disease is caused by atherosclerosis in the blood vessels in the brain. The major complication of cerebrovascular disease is stroke, damage to brain tissue resulting from occlusion of blood flow to the brain due to atherosclerosis (ischemic) or rupturing of weak blood vessels (hemorrhagic). Ischemic stroke may occur from a blood clot forming at the site of atherosclerosis in a blood vessel supplying blood to the brain, known as thrombotic stroke. Ischemic stroke may also be caused by a blood clot that formed some place other than in the brain, for example the heart, that traveled to the small blood vessels of the brain leading to an embolic stroke. Unlike ischemic stroke, hemorrhagic stroke results from a weak blood vessel bursting and leaking blood into the brain. Blood vessel weakening is typically caused by blood vessel malformations or brain aneurysms (ballooning of a blood vessel in the brain).

2.4 EPIDEMIOLOGY OF TYPE 1 DIABETES COMPLICATIONS

Several key studies have been integral in establishing current knowledge of the epidemiology of T1D complications in both Caucasian and African-American populations; these include: the Epidemiology of Diabetes Complications Study and the New Jersey 725 Study.

Epidemiology of Diabetes Complications Study

The Epidemiology of Diabetes Complications Study (EDC) was initiated in 1985 as a 10-year prospective follow-up of a cohort of patients with Type 1 Diabetes diagnosed in childhood.[44, 45]

After 23 years of follow-up the EDC Study continues to provide an array of data concerning the prevalence, incidence, and inter-relationships of T1D complications and risk factors. Participants for the EDC Study were originally recruited from Children's Hospital in Pittsburgh, PA. Eligible participants were diagnosed with T1D before age 17 years during 1950-1980. A total of 658 individuals met the established criteria and were examined at baseline between 1986- 1988 to assess complication and risk factor status, and another 130 completed only surveys.

New Jersey 725 Study

The New Jersey 725 Study is the first large cohort study specifically investigating epidemiology of T1D complications in African-Americans. The study recruited 725 African-American participants from hospitals reporting to the New Jersey State Department of Health Diabetes Registry. The registry receives reports from 116 hospitals statewide, but IRB approval for medical chart review was only granted for 31 of the 116 hospitals. Eligible individuals were diagnosed with T1D before age of 30 between 1982 and 1996. The baseline examines were conducted between 1997 and 1999. The initial primary objective of the study was to assess the prevalence and risk factors for diabetic retinopathy in African-American patients with T1D, but subsequent follow-up included other major complications of T1D.[46]

Neuropathy

Diabetic neuropathy occurs in approximately 50% of patients with T1D by 20 years duration.[31] More than two-thirds of the EDC cohort had clinically detectable DSP by 30 years diabetes duration at baseline.[31] The cumulative incidence of confirmed DSP in the EDC Study cohort at 25 years diabetes duration was 20.8% in the 1970-74 diagnosis cohort compared to 33.6% 1965-69 diagnosis cohort, indicating a reduction of DSP morbidity in the later cohort.[47] Diabetes

duration, glycemic control, smoking, height and hypertension were significant risk factors for DSP.

The prevalence of symptomatic CAN in EDC study cohort was nearly 39% at 25-years duration.[32] Subsequent follow-up in the EDC study reported and incidence-density of 5.9 cases of CAN/100person-years. Age, glycemic control, and nephropathy were significant predictors of CAN.[34] The prevalence and risk factors for neuropathy have not been reported in the NJ 725 Cohort.

Retinopathy

In a national sample, diabetic retinopathy was more prevalent among men and non-Hispanic blacks. In addition, minorities appear to be more vulnerable to vision loss as a result of diabetic retinopathy.[39] The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) showed that patients diagnosed early with diabetes (before age 30, likely T1D) were at increased risk of developing diabetic retinopathy illustrated by a higher prevalence, 4-year incidence and proportion progressing to PDR, compared to patients diagnosed later in life (after age 30, likely T2D).[40]

In the EDC Study, at 20 years duration, nearly 100% of EDC study participants had developed diabetic retinopathy. PDR was prevalent in more than 67% of cases by 30 years duration at baseline.[45] The major risk factors for retinopathy were hypertension, glycemic control, and nephropathy.[48]

At baseline, approximately 63.9% of the participants in the NJ 725 had some degree of diabetic retinopathy, with an average duration of 12.2 years, diagnosed by stereo fundus photography. Nearly 100% and 59.7% of those age 40 years and older had any diabetic retinopathy and PDR, respectively. In addition to diabetes duration and glycemic control; age,

hypertension, and proteinuria were significant risk factors for any diabetic retinopathy.[46] At six years follow-up over 56% of the individuals at risk progressed to a more severe form of diabetic retinopathy. Consistent with previous findings poor glycemic control, diabetes duration, and hypertension were significant predictors of progression of diabetic retinopathy. Renal disease and age were explicitly predictive of progression to PDR.[48]

Arfken *et al* conducted a prospective cohort study evaluating the comparable risk of developing PDR specifically in patients with T1D. African-Americans (*n=97)* had a nearly 2-fold increased risk of developing PDR compared to Caucasians (*n=215).* At baseline, the African-Americans had poorer risk profiles than the Caucasians, including poorer glycemic control, higher systolic blood pressure and higher serum creatinine levels. The African-American subjects were older (mean age = 27 ± 15) compared to the Caucasian subjects (mean age = 19 ± 11). However, there was no significant difference in the mean duration for African Americans (9.2 ± 7.0) compared to Caucasians (8.0 ± 6.4). After controlling for these risk factors, race did not significantly predict development of PDR. Consistent with previous studies, other significant risk factors were age, diabetes duration, and glycemic control.[49] This is one of the few studies investigating racial differences in T1D complications exclusively in a cohort of T1D patients.

Nephropathy

Diabetic nephropathy is the leading cause of ESRD in the U.S., causing an estimated 28,000 new cases of ESRD per year. Despite the lower prevalence of T1D, nearly 50% of all diabetes-related ESRD occur in patients with T1D.[50] Approximately 29% of patients with T1D develop microalbuminuria within the first 20 years of having diabetes.[51] The prevalence of any proteinuria at 30-years duration in the EDC cohort was 84% in males and 59% in females at baseline, suggesting a significant gender difference in nephropathy. This difference was also

noted in the prevalence of overt nephropathy.[37] In comparison, microalbuminuria was prevalent in 77.5% of those with at least 25-years duration in the NJ 725 Study.[52] Consistent with findings in the EDC Study, at baseline, males were more than twice as likely to have microalbuminuria compared to females.[53] Several studies, including EDC Study and NJ 725 Study, have shown that the major predictors of nephropathy are diabetes duration, glycemic control and the presence of hypertension.[52, 53, 54]Abnormal lipid profiles were also significant risk factors in the EDC Study.[54] Subsequent follow-up in the NJ 725 Study also indicated depression as a risk factor for any diabetic nephropathy[52]; however, this association remains unclear and has not been duplicated.

African-Americans with T1D appear to be at increased risk for developing diabetic nephropathy, though this risk has not been clearly quantified. Few population-based studies have shown an increased risk of ESRD for African-Americans with diabetes, both T1 and T2, compared to Caucasians.[55, 56, 57] Cowie *et al* found a 2.6-fold higher incidence of ESRD in African-Americans compared to Caucasians after adjusting for the higher prevalence of diabetes among African-Americans. The study included patients with T1D and T2D; interestingly most African-Americans with ESRD had T2D, while most Caucasians with ESRD had T1D.[57]

Numerous studies have shown overt nephropathy to be a major risk factor for coronary artery disease (CAD) and mortality in patients with T1D.[58, 59] The precise mechanism mediating the association with CAD is not clear, but likely involves increased blood pressure, insulin resistance, and abnormal lipid profiles associated with diabetic nephropathy.

Coronary Artery Disease

CAD is the leading cause of death and diabetes-related deaths in the U.S. [4] Young adults with T1D have an estimated 10-fold increased risk of developing CAD compared to the general

population.[59] At 25-years duration, 8% of EDC Study participants developed CAD.[27, 60, 61] At 6-years follow-up, 15.9% of the NJ 725 study participants had some CAD, at 25-years duration.[62] Unlike the previously discussed microvascular complications, the role of hyperglycemia is not well defined in CAD. Lehto *et al* reported that poor glycemic control was a significant predictor of CAD in the late 1990's.[62] In contrast, larger studies have shown weak or no association between glycemic control and CAD.[60, 63, 64] The EDC and other cohorts suggest that renal disease has a major impact on CAD outcomes. Interestingly, though neither baseline nor cumulative glycemic control were predictors in EDC, a follow-up analysis showed that change in glycemic control over time was a powerful predictor of CAD.[61] The relationship between glycemia and CAD remains unclear, but it is possible that glycemic control may be a more significant predictor of CAD in the absence of renal disease, which would be consistent with Lehto *et al* and the DCCT, which showed that improved glycemic control for six years had a profound protection against 20 year CAD risk, as unlike the EDC Study, in DCCT/EDIC, renal disease was rare.

Peripheral Vascular Disease

LEAD is a major cause of disability and morbidity in patients with T1D. Hospital discharge data indicate that 45% of all amputations in the U.S. are performed on patients with diabetes, and patients with diabetes are 15 times higher risk of amputation than patients without diabetes.[65] This includes amputations due to peripheral vascular disease in the extremities and those resulting from inadequate care of foot wounds and ulcerations. In the general, population African-Americans are at increased risk of LEAD.[66] The WESDR and WHO DiaMond studies both reported increased mortality in T1D patients with amputations.[67, 68] Previous studies have shown African-Americans and people of African-descent to be at increased risk of diabetes-

related lower extremity amputation.[69, 70] These studies were conducted in general diabetic populations and T1D specific analysis was not performed.

At baseline in the EDC Study, 27% of those with greater than 25 years duration had PVD. Major predictors of LEAD were diabetes duration, low-density lipoprotein-cholesterol, heart rate, estimated glucose disposal rate, nephropathy, retinopathy, glycemic control, and low ankle brachial index (ABI).[71]

Approximately 19% of the patients seen at the six-year follow-up in the NJ 725 study developed LEAD at 22-years duration. The overall prevalence in the cohort was 10.7 per 10,000. Similar to the EDC, the major risk factors for LEAD in this cohort were diabetes duration, hypertension, retinopathy, and presence/history of foot ulcers.[72] In contrast to the EDC Study, however, males (16.7%) were at increased risk for developing LEAD, compared to females (10.2%) at 22-years duration, in the NJ 725 cohort. LEAD was defined as present if the patient had a limb amputation, angioplasty for poor circulation in the lower limbs, absence of one or more major arterial pulses in the lower limbs, or physician diagnosis, in the NJ 725 Study. In contrast, ABI, history of claudication as determined by the ROSE questionnaire and self-report of amputation or ischemia were used in the EDC Study.

Cerebrovascular Disease

Individuals with T1D have increased risk of stroke.[73] Due to sample size restrictions, few studies have evaluated the magnitude of this risk. A study in the U.K. Diabetes Cohort, a cohort of all T1D patients, revealed that men of all ages had 3-fold increased risk of death from stroke, and women of all ages over 4-fold increased risk of death from stroke, compared to the general population.[73] Other studies have reported up to a 6-fold increased risk of ischemic stroke in women with T1D.[74]

Over 18 years of follow-up, 4.4% of EDC Study participants had incident cerebrovascular events. In comparison, at six-year follow-up, 9.3% of the NJ 725 Study participants had incident cerebrovascular events. At 30-years duration, the cumulative incidence of stroke in the EDC cohort was 3.5%. At 23-years duration, the cumulative incidence of stroke in NJ 725 was 5.1%. Major predictors of stroke in the EDC were diabetes duration, non-HDLc, systolic blood pressure, and microalbuminuria. Roy *et al* did not report risk factors explicitly associated with stroke.[62]

Mortality

Premature death is the ultimate complication of T1D. Development of new and effective insulin therapies and management plans has greatly improved survival rates; however, patients with T1D are still at increased risk of death compared to the general population.[26, 27, 29] The Diabetes Epidemiology Research International (DERI) Study has pioneered investigating mortality associated with T1D in population-based cohorts worldwide. DERI Study began as an effort to establish T1D registries in select countries, eventually merging with the previously described WHO DiaMond Study. Recent follow-up studies in DERI have focused primarily on T1D mortality in Allegheny County, PA, Finland, Israel, and Japan.[75] These studies showed increased T1D mortality in the U.S. (represented by Allegheny County, PA cohort) compared to the other countries. A recent report from the Allegheny County, PA T1D Registry Cohort, initially affiliated with DERI, indicated that over 85% of deaths in the cohort were diabetes-related.[29] The study also reported cause-specific mortality trends which showed that with increased diabetes duration the major causes of death shift from predominantly acute complications with in the first 10 years of diabetes, to predominantly chronic complications in the later years (>20 years). Another major finding of this study was that African-Americans had nearly 3-fold increased risk

of death, compared to Caucasians. This disparity has been noted in previous studies in this cohort and others, as shown in Table 1.[29]

Table 2: Mortality Rates (per 100,000 person-years (95% C.I.)) in T1D Cohorts by Race

	Caucasians	**African-Americans**
Allegheny County Registry (1996)	380 (240 , 480)	910 (340, 1480)
Allegheny County Registry (2001)	571 (478, 672)	1,388 (895, 2012)
Allegheny County Registry (2005)	492.1 (412.1, 572.9)	1318.4 (1168, 1468.8)
New Jersey 725 Cohort (2006)	---	2725.6 (1987.1, 3464.1)
Chicago T1D Registry(2007)	48.2 (5.8, 174)	447.8 (283.9, 671.7)
Allegheny County Registry (2010)	742.2 (648.1, 836.3)	1851.3 (1277.6, 2425.1)

In 1996, Tull *et al* reported 2-fold excess mortality in African-Americans compared to Caucasians in the Allegheny County, PA Registry cohort, with females being at increased risk compared to males in African-Americans while no gender differences were present in Caucasians. This same study showed that African-American deaths were more likely (40%) due to acute complications compared to Caucasians (23%).[24] A later follow-up of the same cohort by Nishimura *et al* showed overall improvements in survival for the individuals with shorter duration of diabetes, but the racial disparity persisted with African-Americans having 3-fold increased risk of mortality compared to Caucasians. There were no significant gender differences reported in this follow-up.[26] A subsequent study in the Allegheny County, PA Registry cohort in combination with the Children's Hospital of Pittsburgh Registry cohort supported previous findings, showing that African-Americans were at nearly 3-fold increased risk of mortality. In addition, this study confirmed earlier findings that African-Americans were at increased risk of death from acute complications compared Caucasians (Hazard Ratio = 4.9 (95% C.I. 2.0, 11.6)).[27]

Studies evaluating racial differences in T1D mortality currently provide the strongest evidence of disproportionate T1D health outcomes in African-Americans. Other studies have shown similar results to those seen in the Allegheny County registries. Lipton *et al* reported that African-Americans were at nearly 9-fold increased risk for early mortality (<25 years of age) from acute complications in the Chicago T1D registry.[25] There were no significant racial differences shown in overall mortality in a later study, but the analysis was limited by a small sample of non-Hispanic whites.[28]

The 3-year crude mortality rate for the NJ 725 cohort was 8.6% [95%CI (6.6, 10.6)]. There were no significant gender differences in survival rates. Age, diabetes duration, nephropathy, presence of other major complications and heavy alcohol consumption were significant independent predictors of mortality in this cohort.[76] Results from the EDC also indicated age, diabetes duration, and presence of other major complications as independent risk factors for mortality, but not alcohol consumption.

In addition to premature death due to acute and chronic complications, a separate category of deaths exists in T1D, often referred to as "dead in bed syndrome". Dead in bed syndrome was first reported in 1991, occurring in 22 young, apparently healthy T1D patients who were found dead in their beds.[77] The typical characteristics of dead in bed syndrome are death during sleep, with no evidence of terminal struggle, sweating, or obvious cause of death.[77, 78, 79] Early researchers suggested that dead in bed syndrome was the result of nocturnal hypoglycemia, while contemporary hypotheses focus largely on some dysfunction in the autonomic system, specifically reduced parasympathetic activity; however the exact etiology remains unclear.[77, 80, 81] Some evidence suggested that use of human insulin may be associated with reduction of typical hypoglycemic symptoms (sweating, dizziness, tremors, extreme

hunger/thirst); which may play a role in dead in bed syndrome.[82] Recent studies reported that approximately 5-6% of all T1D deaths result from dead in bed syndrome.[83]

Table 3: Summary of Current T1D Complications Knowledge by Racial Group

COMPLICATION	AFRICAN-AMERICAN	CAUCASIAN
NEUROPATHY Distal Symmetric Polyneuropathy	▪ There is currently no data on the prevalence or risk factors of DSP in AAs with T1D	*EDC Study Cohort† (1990)* ▪ At baseline, more than two-thirds had clinically detectable DSP by 30 years duration.[45] ▪ Risk Factors for DSP: Diabetes duration, glycemic control, smoking, height and hypertension.[44]
Cardiac Autonomic Neuropathy	▪ There is currently no data on the prevalence or risk factors of CAN in AAs with T1D	*EDC Study Cohort† (1990)* ▪ The prevalence of symptomatic CAN was 39% at 25-years duration.[32] ▪ Risk Factors for CAN: Age, glycemic control, and nephropathy.[32]
RETINOPATHY	*Arfken et al (1998)* ▪ 17.5% of African-Americans progressed to proliferative retinopathy from baseline at 7 years follow-up.[49] *NJ 725 Study Cohort (2000)* ▪ At baseline, approximately 63.9% had some diabetic retinopathy and 18.9% had proliferative retinopathy; with a mean duration of 12.2 years (±9.4).[46] ▪ 93% of cohort >45 years old had some diabetic retinopathy.[46] ▪ At the 6-year exam, 72.3% of patients at risk, developed diabetic retinopathy.[48] ▪ Risk Factors for Any and Proliferative Diabetic Retinopathy: Diabetes duration, glycemic control, age, hypertension, and nephropathy.[46,48]	*EDC Study Cohort† (1990)* ▪ At 20 years duration, nearly 100% developed some diabetic retinopathy.[45] ▪ At 30 years duration, nearly 67% developed proliferative retinopathy.[45] ▪ Risk Factors for retinopathy: hypertension, glycemic control, and nephropathy.[44] *Arfken et al (1998)* ▪ 10.2% of Caucasians progressed to proliferative retinopathy from baseline at 7years follow-up.[49]
NEPHROPATHY	*Cowie et al (1989)* ▪ Incidence of diabetic end-stage renal disease was 2.6-fold higher among AAs compared to Caucasians.[55] *NJ 725 Study Cohort (2002)* ▪ At baseline, 84.6% of males and 45.5% of females had any proteinuria at **25** years duration.[46] ▪ Risk factors for any proteinuria: diabetes duration, glycemic control, hypertension, depression.[52]	*EDC Study Cohort† (1990)* ▪ At baseline, 84% of males and 59% of females had any proteinuria at **30** years duration.[45] ▪ Risk factors for any proteinuria: diabetes duration, glycemic control, hypertension, abnormal lipids[53]
CORONARY ARTERY DISEASE Any CAD	*NJ 725 Study Cohort (2007)* ▪ At 6-years follow-up, 15.9% had clinically detectable or diagnosed CAD at 25-years duration.[62]	*EDC Study Cohort† (1990)* ▪ At baseline, approximately 8.0% had clinically detectable or diagnosed CAD at 25-years duration.[45]

Table 3- Continued

	▪ Risk factors for CAD: age, BMI, hypertension, nephropathy, retinopathy, and depression.[62]	▪ Risk factors for CAD: age, diabetes duration, hypertension, BMI, total cholesterol.[44]
CEREBROVASCULAR DISEASE Stroke	*NJ 725 Study Cohort (2007)* ▪ At 6-years follow-up, 9.3% of the NJ 725 Study participants had incident cerebrovascular events. [62] ▪ Approximately 5.4% reported a stroke at 23-30 years duration.[62] ▪ Did not report significant risk factors for stroke in cohort.	*EDC Study Cohort[†] (1990)* ▪ At 18 years of follow-up, 4.4% of EDC Study participants had incident cerebrovascular events ▪ At 30-years duration, the cumulative incidence was 3.5% ▪ Risk Factors for Stroke: diabetes duration, non-HDLc, systolic blood pressure, and microalbuminuria
PERIPHERAL VASCULAR DISEASE Lower Extremity Arterial Disease	*NJ 725 Study Cohort (2008)* ▪ At 6-years follow-up, 18.7% of those with greater than 25-years duration developed LEAD.[72] ▪ Risk Factors for LEAD: diabetes duration, hypertension, retinopathy, and presence/history of foot ulcers, male gender.[72]	*EDC Study Cohort[†] (1990)* ▪ At baseline, 27% of those with greater than 25-years duration had LEAD.[45] ▪ Risk factors for LEAD: diabetes duration, LDL Cholesterol, heart rate, estimated glucose disposal rate, nephropathy, retinopathy, glycemic control, and ABI.[44]
MORTALITY	*Chicago T1D Registry (1999)[25]* ▪ Annual case-fatality rate was 451.3/100,000 for African-Americans. ▪ Most (91.4%) of the AA deaths resulted from diabetes-related causes. *Allegheny County Registry (2001)[26]* ▪ Crude Mortality rate was 1,388/100,000 person-years for African-Americans. ▪ Standardized Mortality Rate was 645/100,000 person-years for African-Americans. *Allegheny County Registry (2005)[27]* ▪ Crude Mortality rate was 593.2/100,000 person-years for African-Americans. ▪ Mortality rate due to chronic complications was 659.1/100,000 person-years for African-Americans. *NJ 725 Study Cohort (2006)[76]* ▪ The overall 3-year crude mortality rate for the whole cohort was 8.6% [95% confidence interval (CI) 6.6, 10.6], for men 10.6% (95% CI 7.1, 14.1) and for women 7.1% (95% CI 4.7, 9.5) ▪ Diabetes duration, BMI, glycemic control, exercise, and presence of other complications were all significant predictors/risk factors for mortality; Alcohol consumption	*Chicago T1D Registry (1999)[25]* ▪ Annual case-fatality rate was 48.7/100,000 for Caucasians *Allegheny County Registry (2001)[26]* ▪ Crude Mortality rate was 571/100,000person-years for Caucasians ▪ Standardized Mortality Rate was 530/100,000 person-years for Caucasians. *Allegheny County Registry (2005)[27]* ▪ Crude Mortality rate was 75.2/100,000 person-years for Caucasians ▪ Mortality rate due to chronic complications was 311.2/100,000 person-years for Caucasians *Allegheny County Registry (2010)[29]* ▪ Crude Mortality rate was 618.0/100,000 person-years for Caucasians

Table 3- Continued	was exclusively predictive of mortality in males. *Allegheny County Registry (2010)*[29] ▪ Crude Mortality rate was 1851.3/100,000 person-years for African-Americans.	
Note: EDC cohort is approximately 98% Caucasian		

Prevention of T1D Complications

The Diabetes Control and Complications Trial (DCCT) was a hallmark study elucidating the prevention of major complications of T1D through intensive diabetes management. Study participants were randomized to either conventional therapy (one or two daily insulin injections, daily monitoring of blood glucose, 3-month check-ups) or intensive therapy (three or more daily insulin injections or insulin pump, at least three blood glucose checks daily, monthly check-ups). The intensive intervention group maintained glucose levels close to normal values throughout the study. The intensive therapy successfully delayed onset and slowed progression of retinopathy, nephropathy, and neuropathy. At the conclusion of the trial, there were no significant differences in macrovascular complications, possibly resulting from the young age of the cohort, and scarcity of events. [84] As previously mentioned, a later report with over 11 years of post-trial follow-up reported a profound decrease in CAD risk in the former intensive treatment group (with improved glycemic control) compared to the conventional treatment group. In general, the results of this trial provide further evidence of the significant role hyperglycemia plays in development and progression of T1D complications, and the potential for prevention.

In addition to improving glycemic control, other risk factors are potential candidates for reducing morbidity of T1D complications. These risk factors often referred to as "modifiable risk factors" with glycemic control, include: hypertension, hypercholesterolemia, and smoking. These risk factors are modifiable with either clinical treatment or appropriate lifestyle modifications. Analysis from the EDC Study indicates that despite improved therapies and interventions to address these modifiable risk factors, more efforts are needed to control these factors in patients with T1D.[85] It is unclear what role, if any, these risk factors may play in the disparity seen between African-Americans and Caucasians in T1D health outcomes. In the SEARCH Study,

African-American youth diagnosed with T1D were significantly more likely to have higher HbA_{1c} levels compared to non-Hispanic white youth, 36% and 12% with poor glycemic control respectively.[16, 17]

2.5 CHALLENGES EVALUATING RACIAL DIFFERENCES IN TYPE 1 DIABETES COMPLICATIONS

As evident by the preceding discussion, there have been limited epidemiological studies investigating variations in the prevalence of major T1D complications among racial/ethnic groups, specifically African-Americans compared to Caucasians. Further research is needed to assess if racial differences seen in T1D mortality may possibly be attributable to disparities in prevalence of complications or risk factors. There are some notable challenges to exploring any potential racial differences in both frequency of major complications and risk factors.

Racial Distribution in Existing Long-term Prospective Cohorts

The incidence of T1D in African-Americans has historically been lower than Caucasians, and though the gap has been reduced, lower rates in African-Americans remains. As such, recruiting sample sizes of African-Americans in population based studies large enough to make racial comparisons has persisted as a major challenge. The EDC Study cohort has limited racial diversity, with only 2% being African-American.[31] This number of minority participants, though consistent with the demographic profile of the local population and incidence of T1D in African-Americans, is inadequate to permit any form of ethnic comparisons. The Allegheny County, PA Registry cohort has a higher percentage of African-Americans (7.3%), and as previously discussed reported significant racial differences in mortality.[29] However, the high mortality rate

in conjunction with the already low sample size, does not allow for racial comparisons in long-term complications. In addition, the NJ 725 Study was designed to specifically evaluate T1D complications in African-Americans, so all other racial ethnic groups were excluded. While this provides substantial information to understanding the morbidity of T1D complications in this population, it does not allow for racial comparisons.

Typology in National Samples/Datasets

Many national surveys currently collect relevant data from individuals diagnosed with diabetes on diabetes complications, other health conditions, health behaviors and risk factors. These include the National Health and Nutritional Examination and Survey (NHANES), National Health Interview Survey (NHIS), Behavior Risk Factor Surveillance System (BRFSS), and Medical Expenditure Panel Survey (MEPS). While these national datasets are very useful, they do not clearly distinguish between patients diagnosed with T1D and T2D. Given the differences in the pathophysiology of T1D and T2D, it is valuable to investigate differences in the natural history of both, including complications and risk factors.

3.0 PAPER 1: INCIDENCE OF TYPE 1 AND TYPE 2 DIABETES IN YOUTH IN THE U.S. VIRGIN ISLANDS, 2001-2010

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3.1 ABSTRACT

OBJECTIVE - To report the annual incidence of type 1 and type 2 diabetes among youth and to describe characteristics of youth diagnosed with diabetes in the United States Virgin Islands (USVI).

RESEARCH DESIGN AND METHODS – All residents ≤19 years of age diagnosed with diabetes between January 2001 and December 2010 were identified from review of medical records of all hospitals.

RESULTS – A total of 82 eligible patients were identified and the registry ascertainment was estimated to be 98.7% complete. The overall age-adjusted annual incidence rates (per 100,000) of type 1 and type 2 diabetes for the study period were 15.3 (95% CI 11.3, 20.1) and 9.6 (95% CI 6.8, 13.5), respectively. The incidence of type 1 diabetes increased significantly over the study period, with an epidemic-like 3-fold increase occurring from 2005 (8.7/100,000) to 2006 (26.4/100,000) (p=.05). The incidence of type 1 diabetes was highest in the 10-19 age group in girls (25.6/100,000), but no age difference was seen in boys, resulting from the lack of a pubertal peak in non-Hispanic black boys. The incidence of type 2 diabetes rose significantly between 2001 (5.3/100,000) and 2010 (12.5/100,000) (p=.03), with the highest incidence occurring in the 10-19 age group in both boys and girls.

CONCLUSIONS – The incidence of type 1 and type 2 diabetes in youth is increasing in the USVI, similar to global patterns. Further studies are needed to explore the missing pubertal rise in type 1 diabetes incidence in non-Hispanic black boys and factors associated with the epidemic-like increases observed over the decade.

3.2 INTRODUCTION

Over the past 20 years an increasing incidence of childhood-onset Type 1 and Type 2 diabetes has been reported worldwide.[11, 12, 86, 87] Standardized population-based registries are commonly used tools for monitoring incidence, and further investigation of etiology, risk factors, and complications.[88] In the late 1980s the U.S. Virgin Islands (USVI) Childhood Diabetes Registry was established, along with other registries in over 50 countries, as a part of the World Health Organization Multinational Project for Childhood Diabetes DIAMOND Study.[21, 89] The DIAMOND Study estimated that the worldwide incidence of type 1 diabetes is rising approximately 3% annually, with very high global variation. Annual incidence rates in the 1990s in youth less than 15 years old ranged from 40.9/100,000 in Finland to 0.1/100,000 in Venezuela.[11, 12]

Initial studies in the USVI were conducted in 1989. The estimated annual incidence of type 1 diabetes for 1979-1988 was 7.5/100,000 (95% CI 4.7,10.3) for persons less than 15 years old, with rates being significantly higher in non-Hispanic whites compared to non-Hispanic blacks and Hispanics and also higher than rates reported in other Caribbean islands.[22] The estimated annual incidence subsequently increased to 12.8/100,000 (95% CI 8.1, 18.8) for the period 1990-1996.[12] The SEARCH for Diabetes in Youth Study, an ongoing effort to monitor the incidence of both type 1 diabetes and type 2 diabetes among U.S. youth since 2000, has also shown a similar type 1 diabetes pattern, and a dramatic increase in type 2 diabetes. Consistent with earlier reports from the USVI, the highest incidence of type 1 diabetes in the SEARCH Study was in those in the 10-14 age group, particularly in girls.[15] To determine if the global increasing incidence of type 1 diabetes is affecting the USVI, we now report data for years 2001-

2010, including for the first time incidence of type 2 diabetes, along with further exploration of gender differences.

3.3 METHODS

3.3.1 Study Population

The U.S. Virgin Islands, a U.S. territory, consist of four inhabited islands (St. Croix, St. Thomas, St. John, and Water Island) with a total population of 108,612 individuals. Approximately 76.1% of the population are non-Hispanic blacks, and 13.1% are non-Hispanic whites, with the remaining being a combination of Hispanic and Asian ethnic groups. The 2000 Census reported 37,093 individuals less than 19 years old living in the territory.[18]

3.3.2 Data Collection

The detailed methods used to develop the registry have been described in previous reports.[21] Cases were defined as individuals diagnosed with diabetes, age $\leq$ 19 years, and living in the USVI at the time of diagnosis or onset of symptoms. Individuals that were pregnant (likely gestational) or on steroid therapy for an existing condition were excluded.

Primary cases were ascertained through retrospective medical record review at all medical centers in the USVI, including 2 hospitals and 3 community health clinics, as of December 31, 2010. All diabetes-related ICD-9 codes were queried for individuals less than 20 years old at the time of the encounter from January 2006 – December 2010. Data were collected

using the Childhood Diabetes Registry Data Collection Form, developed in initial registry studies and used in subsequent registry updates. Data on race, gender, health insurance, clinically-reported diabetes type (Type 1 or Type 2), height, weight, symptoms at diagnosis, blood glucose at diagnosis, $HbA1_C$ at diagnosis, cholesterol, triglycerides, family history of diabetes, and insulin dosage at discharge were collected. Data for some clinical characteristics were inconsistently available, however for all cases race, gender, health insurance, diabetes type, blood glucose at diagnosis, and insulin dosage at discharge were available. Race was obtained from medical records, based on patient self-report, and classified as Non-Hispanic Black, Non-Hispanic White, Hispanic, or Other. Health insurance was classified as public (i.e. Medicaid), private, or none.

Degree of case ascertainment was determined using the capture-recapture method, with secondary case ascertainment being completed through surveying local medical providers.[90] All physicians serving pediatric patients, including specialists, were identified through the USVI Department of Health Medical Licensing Office. Physicians were contacted via postal, telephone and fax with requests for reports of childhood diabetes cases and the associated reporting form. In addition, school nurses were all identified through the USVI Department of Education and contacted via postal, telephone, and fax with requests. Completed reports were received by the USVI Department of Health Bureau of Epidemiology and Surveillance. 94.1% of physicians and school nurses submitted completed reports.

3.3.3 Revalidation of Previous Years

The accuracy of hospital data for registry case ascertainment has been extensively discussed.[91] A large majority of population-based childhood diabetes registries rely primarily on hospital data

for primary case ascertainment.[11, 12] Cases for years 2001-2005 were first ascertained in January 2006 using the methods described above, but were not formally reported. We re-ascertained cases for years 2001-2005, using the same methods described above during this study to determine the completeness of the case ascertainment previously conducted.

3.3.4 Statistical Methods

Student's t-test and one-way ANOVA were used to compare continuous variables and the chi-squares and Fisher's exact tests were used to compare categorical variables between race groups by type of diabetes, with adjustment for multiple comparisons using the Bonferroni correction. Annual incidence rates were calculated for each calendar year. There are no intermediate Census projections for the USVI since the 2000 U.S. Census; however the Virgin Islands community survey reported the estimated population size for years 2001-2005. The Virgin Islands community survey is a population-based survey designed to estimate the annual population and housing units in the territory, conducted by the Eastern Caribbean Center at the University of the Virgin Islands. These reports indicated an average 1.5% decrease in population size in youth (ages 0-19) annually for years 2001-2005.[92] The community survey population estimates were used to estimate incidence for years 2001-2005 and the annual population size for years 2006-2010 was estimated assuming that the population decline remained consistent for subsequent years. Given the small change in population size annually, there is likely no quantitative bias in using this method. In addition, recent U.S. census estimates indicated that the overall USVI population declined by 2.0% from 2000 to 2010. 95% confidence intervals were calculated using the Poisson distribution of cases. Poisson regression analysis was used to test for differences in incidence between years and various sub-groups. Statistical significance was considered as a p-

value less than 0.05. For race, gender, and age group comparisons, multiple years were combined to make larger numbers available for numerators and denominators allowing greater stability of the rate estimates within subgroups. The denominator for multiple year incidence rate estimates was the sum of the total population for all respective years. For race comparisons, Non-Hispanic White, Hispanic, and Other races were collapsed to a single "Other" race category, due to extremely small sample sizes. Weighted moving averages (WMA) of the annual incidence rates were calculated using the annual incidence for the previous and following 3 years where values closer to the middle of the interval are more heavily weighted than values further in the past and future. Statistical analysis was performed using Statistical Analysis Software (SAS, Inc.).

3.4 RESULTS

A total of 91 newly diagnosed patients 19 years and younger were ascertained during 2001-2010, comprising of 57 with type 1 diabetes, 32 with type 2 diabetes, and 2 with gestational diabetes. 7 cases with type 1 diabetes were excluded because they were not residents of the USVI (typically visiting the territory for vacation) and cases with gestational diabetes were not included, resulting in 50 cases with type 1 diabetes and 32 cases with type 2 diabetes being included in the analysis. Completeness of the ascertainment using capture-recapture methodology and medical provider reports as the secondary source was estimated to be 98.7%.

3.4.1 Type 1 diabetes

The estimated annual incidence of type 1 diabetes for the entire study period is 15.3/100,000 (95% CI 11.6, 20.1). (Table 4) The annual incidence varied throughout the study period ranging from 2.8/100,000 (95% CI 0.4, 19.7) in 2003 to 26.8/100,000 (95% CI 14.0, 51.6) in 2007. The annual incidence rate of type 1 diabetes in 2010 was 18.7/100,000 (95% CI 8.4, 41.6). The WMA illustrates a steady increase in incidence from 2003-2007, which leveled off thereafter. (Figure 1A)

There was no difference in the overall annual incidence of type 1 diabetes between the 0-9 (11.2/100,000) and 10-19 (19.1/100,000) age groups (p=.19). The incidence was similar in both age groups in boys (p=.77), while there was a nearly 2.5-fold increase in the 10-19 age group compared to the 0-9 age group in girls, 25.6/100,000 compared to 10.1/100,000 (p=.05). (Table 4)

The annual incidence did not differ for other race groups (10.0/100,000) compared to non-Hispanic Blacks (7.4/100,000) in 2001-2005 (p=.65). There was a 3-fold increased incidence in non-Hispanic Blacks for the 2006-2010 period (21.4/100,000) (p=.04), compared to the 2001-2005 period (7.4/100,000) (p=.03)

Characteristics of youth diagnosed with type 1 diabetes are shown in Table 5. The largest proportion of cases was in the 10-14 age group at diagnosis, with a significantly higher proportion of other race youth being diagnosed in this age group compared to non-Hispanic black youth (p=.05). The mean $HbA1_C$ was significantly higher for non-Hispanic blacks (12.9%) compared to other race groups (10.1%) (p=.04), while a similar proportion had HbA1C values greater than 9.5% at diagnosis (p=.44). 100% of youth diagnosed with type 1 diabetes initiated insulin therapy at diagnosis.

3.4.2 Type 2 diabetes

The annual incidence of type 2 diabetes ranged from 2.8/100,000 (95% CI 0.4, 20.0) in 2003 to 18.2/100,000 (95% CI 8.2, 40.4) in 2008. The annual incidence increased sharply from 2003-2007, and leveled off thereafter, shown in Figure 1B. The incidence of type 2 diabetes was significantly lower in the 0-9 age group (2.5/100,000) compared to the 10-19 age group (16.1/100,000) (p=.01). (Table 4) The incidence increased nearly 2.5 times from 2001-2005 to 2006-2010 periods for non-Hispanic Black youth (p=.05). There were no cases of type 2 diabetes in other race groups during 2001-2005, yet the incidence increased to 23.7/100,000 in 2006-2010. The overall incidence of type 2 diabetes increased significantly from 2001-2005 to 2006-2010 (p=.03). (Figure 1B)

Non-Hispanic black youth had a significantly higher mean HbA1C (p=.05), compared to other race youth, while a similar proportion had HbA1C values greater than 9.5% at diagnosis (p=.69). Nearly two times more non-Hispanic black youth were uninsured compared to other race youth (p=.04). (Table 5)

The incidence of type 1 diabetes (11.19/100,000) is significantly higher than the incidence of type 2 diabetes (2.49/100,000) in the 0-9 age group (p=.02). (Table 4)

3.5 DISCUSSION

The incidence of childhood diabetes has increased significantly in the USVI over the past decade, compared to published rates from the 1980s and 1990s.[11, 22] This finding is consistent with general increases in childhood diabetes noted around the world.[11, 12, 86, 87] Despite some

variation, the rates of type 1 diabetes and type 2 diabetes have more than doubled in the territory. A rapid epidemic-like rise in incidence of type 1 diabetes and type 2 diabetes occurred around 2005, in which the incidence rates for the following years were nearly 2 times higher than the years prior. While the rapidly rising rate of childhood obesity is likely a major contributor to the increase in type 2 diabetes, the reason for the epidemic like increase in type 1 diabetes incidence is less clear; however a similar epidemic-like increase of type 1 diabetes was reported in the USVI in the 1980s.[22] Gender differences may play a role in this particular epidemic-like increase. The annual incidence for boys in the USVI was much lower in the earlier half of the decade prior to the epidemic-like increase, but a sharp increase in incidence in boys occurred between 2005 (11.6/100,000) and 2007 (35.96/100,000). Incidence rates in boys remained high in the latter half of the decade, and were no longer lower than rates in girls. Epidemic-like increases in incidence of type 1 diabetes have been reported in other studies in the US.[93, 94] While these epidemic-like increases remain largely unexplained, some attribute concomitant changes in incidence of viruses that have been associated with triggering the onset of type 1 diabetes.[95] Additional studies are needed to identify the factors that might be responsible for the epidemic-like increases in type 1 diabetes.

Historically, the issue of childhood obesity has not been associated with type 1 diabetes, as these youth were more commonly underweight and underdeveloped at diagnosis; however recent data suggest that the prevalence of obesity in youth with type 1 diabetes is increasing.[96, 97, 98] This may also be a contributor to the increasing incidence of type 1 diabetes in the USVI. Equal amounts of youth (20%) were classified as underweight and overweight at diagnosis in this study; though this observation is limited by the classification of weight being determined by

health professional report and not actual BMI measurement (due to large amount of missing height and weight data in medical records).

An increase in the incidence of non-Hispanic black cases of type 1 diabetes also appears to be a major contributor to the overall increase of type 1 diabetes in the USVI. In 1988, the incidence of type 1 diabetes in non-Hispanic Blacks was 5.8/100,000, compared to 21.4/100,000 in 2006-2010, a nearly 3.5-fold increase. Figure 2 illustrates the increasing incidence of type 1 diabetes in non-Hispanic Blacks in various population-based registries in the U.S. and Caribbean throughout the last three decades.[5,11, 12, 15, 22, 93, 94, 98, 99, 100, 101, 102] The incidence rate for the first half of the decade in the USVI (8.1/100,000) are lower than the incidence rates for the first half of the decade found in the SEARCH study (15.7/100,000); however, the rates for the latter half of the decade in the USVI are much higher (20.4/100,000). Recent data from SEARCH is not available so it is unclear if this increase occurred in the contiguous US as well. The incidence rate in other race groups has slightly decreased to 23.7/100,000 in 2006-2010, compared to 28.9/100,000 in 1988.[22] This decreasing incidence in other race groups in the USVI may be attributed to the low population of non-Hispanic white youth and adults of child-bearing age in the territory and the increasing population of Hispanics, who are included in the other race groups and commonly have lower rates of type 1 diabetes.

Consistent with previous studies, girls had higher overall rates of both type 1 diabetes and type 2 diabetes.[5,22, 94] In the SEARCH Study, non-Hispanic black girls had nearly 2-fold higher incidence compared to non-Hispanic Black boys.[5] In the present study, the highest incidence of type 1 diabetes in non-Hispanic black girls occurred in the 10-14 age group, consistent with the well-recognized pubertal/adolescent peak seen in many studies.[5, 22, 94, 100, 101] However, there was no such peak for non-Hispanic black boys with rates for 5-9, 10-14, and 15-19 age groups being

virtually identical. (Table 4) This male pattern is intriguingly inconsistent with the commonly reported significant pubertal rise in type 1 diabetes incidence. However, this finding is similar to those reported in SEARCH where the incidence of type 1 diabetes is significantly higher in non-Hispanic black girls in the 10-14 (pubertal) age group (26.1/100,000), compared to the 5-9 (pre-pubertal) age group (20.9/100,000); however in non-Hispanic black boys the respective rates are 17.8/100,000 and 16.7/100,000.[5] Further investigation is needed to explain why non-Hispanic Black boys seem to be protected from the traditional pubertal rise seen in type 1 diabetes.

The overall incidence of type 1 diabetes in the USVI for the study period (2001-2010) is slightly lower (15.3/100,000) than recent results from the SEARCH study, which estimated the incidence for the U.S. to be 19.0/100,000 in 2002-2003.[5] This lower rate in the USVI is expected, given the historically lower rates of type 1 diabetes in non-Hispanic blacks in the Caribbean; however, you may predict a more drastic difference, as is the case with other black African-heritage populations in the Caribbean.[12, 23, 102] There are limited current population-based data on the incidence of childhood diabetes throughout the Caribbean, which makes comparison with other similar geographical and cultural populations difficult. However, earlier results from the DIAMOND Study and other Caribbean studies showed lower rates of type 1 diabetes throughout the Caribbean islands, compared to the USVI and US.[12, 102] (Figure 2)

The incidence rates of type 2 diabetes were not reported in early studies in the USVI as there were low to no cases occurring. The low incidence of type 2 diabetes found in earlier studies is unlikely due to diagnosis taking place in physician offices, as local physicians were also surveyed for validation. The incidence rate of type 2 diabetes (9.6/100,000) in the USVI is nearly two times higher than the estimated incidence in the US (SEARCH Study-5.8/100,000) and the Chicago Childhood Diabetes Registry (5.0/100,000).[5, 100] The increasing rates of type 2

diabetes may be partly attributed to the higher overall rates in girls, who are more likely to be overweight and obese, a primary risk factor for type 2 diabetes.[17, 103, 104] A higher proportion of youth with type 2 diabetes were overweight at diagnosis compared to youth with type 1 diabetes. However, similar to the SEARCH Study, more non-Hispanic black youth with type 1 diabetes were overweight at diagnosis compared other race groups.[17, 104] There are currently no data available on the long-term health outcomes of individuals diagnosed with type 1 diabetes in the USVI; however, results from U.S. studies have indicated that non-Hispanic blacks are at increased risk for premature mortality.[25, 27, 105] A recent study reported excess risk of cardiovascular risk factors for adolescents with type 1 diabetes who were also overweight.[106] The higher rates of obesity in non-Hispanic black youth with type 1 diabetes may possibly further increase the disparity seen in long-term health outcomes.

The USVI Childhood Diabetes Registry, a population-based registry, is the primary source of data on the rates and trends of childhood diabetes in the territory. Similar to other studies, we utilized data from medical records to update the registry.[5, 11, 12, 23, 93, 94, 99, 100, 101, 102] This presents several limitations for consideration. First, we relied on health care professional diagnosis to categorize the diabetic phenotype. The issue of typology remains a challenge for epidemiological studies. There are several factors contributing to this issue: (1) the mean age of diagnosis seems to be increasing thereby limiting the use of age as an indicator, (2) childhood obesity rates are increasing in all races and age groups, (3) lack of standardized diagnostic criteria, and (4) no definitive laboratory test to determine phenotype. The local health system of the USVI, addresses this dilemma in some ways. There are only 2 hospitals where individuals can seek medical care in the territory. The often acute onset of childhood diabetes leads for the need to seek emergency care and hospitalization. The small number of health care facilities and

medical professionals limits the variation in diagnostic methods, compared to similar studies involving larger number of centers and geographic locations. In the SEARCH Study, which also used physician diagnosis to classify diabetes type, the physician diagnosis abstracted from medical records corresponded well with autoantibody and c-peptide measures collected in the study follow-up.[17, 104]

The second issue that arises from use of medical record review is incomplete ascertainment. We used the capture-recapture method to estimate the completeness of ascertainment. Again, the limited number of health care professionals in the territory allows for maximal re-ascertainment of cases. There are two endocrinologists providing care to the majority of children with diabetes in the territory, which increases the likelihood of ascertaining all cases. However, there are an increasing number of pediatricians and family medicine physicians that are diagnosing and providing care for youth with type 2 diabetes. This is evident in the re-ascertainment of cases diagnosed in years 2001-2005. There was a significant increase in cases of type 2 diabetes and the majority of the cases not captured at the initial ascertainment, were individuals who were diagnosed by a local physician and only later seen in the hospital for diabetes complications. As such, we may be underestimating the actual incidence.

Finally, this analysis was limited by the small number of cases in various sub-groups, including age and race categories. For example, we were unable to create smaller age categories as are commonly reported (0-4, 5-9, 10-14, and 15-19), or analyze differences between non-Hispanic whites and Hispanics.

In conclusion, we report the annual incidence of childhood diabetes in the USVI for all age groups and races, which shows an increasing incidence of both type 1 diabetes and type 2 diabetes throughout the territory. In addition, these data also suggest non-Hispanic black boys do

not have a pubertal peak in type 1 diabetes incidence, a finding consistent with previous studies. As previously discussed, the local health care system has limited infrastructure to manage high volumes of youth with diabetes. With the majority of youth with diabetes being uninsured or having public health insurance, continued monitoring of the rates and trends, and further studies evaluating the overall burden of childhood diabetes in the USVI, including morbidity and mortality, are critical to improving the health outcomes and developing strategies for prevention.

3.6 TABLES

Table 4: Annual incidence (per 100,000) of type 1 and type 2 diabetes in the USVI by gender and age group (2001 – 2010)

	Boys		Girls		Total	
	n	Incidence (per 100,000) (95% CI)	*n*	Incidence (per 100,000) (95% CI)	*n*	Total (95% CI)
Type 1						
0-9 years	10	12.3 (6.6, 22.9)	8	10.1 (5.0, 20.1)	18	11.2 (7.1, 17.8)
10-19 years	11	12.6 (7.0, 22.7)	21	25.6† (16.9, 38.9)	32	19.0 (13.5, 26.8)
All (0 - 19 years)	21	12.4 (8.1, 19.1)	29	18.1 (12.7, 25.9)	50	15.3 (11.6 , 20.1)
Non-Hispanic Blacks						
0-4 years	3	8.4 (2.7, 26.1)	2	5.9 (1.5, 23.8)	5	7.2 (3.0, 17.4)
5-9 years	6	14.2 (6.3, 31.6)	5	12.0 (5.0, 28.8)	11	13.1 (7.3, 23.7)
10-14 years	5	12.7 (5.3, 30.6)	10	25.0 (13.4, 46.4)	15	18.9 (11.4, 31.4)
15-19 years	6	14.9 (6.9, 31.9)	5	13.7 (5.7, 32.9)	11	14.3 (8.5, 26.6)
Type 2						
0-9 years	2	2.5 (0.6, 9.8)	2	2.5 (0.6, 10.1)	4	2.5 (0.9, 6.6)
10-19 years	10	11.4† (6.1, 21.2)	18	21.0† (13.2, 33.3)	28	16.1† (11.1, 23.4)
All (0 – 19 years)	12	7.1 (4.0, 12.5)	20	12.1 (7.8, 18.7)	32	9.6 (6.8, 13.5)

† - p<0.05 (Based on Poisson regression analysis for comparison between 0-9 and 10-19 age groups within gender groups)

Table 5: Demographic and clinical characteristics at diagnosis of youth with type 1 and type 2 diabetes in USVI by race (2001-2010)

	Type 1 diabetes		Type 2 diabetes	
	Non-Hispanic Black	Other	Non-Hispanic Black	Other
n (%)	41 (82)	9 (18)	26 (81.2)	6 (18.8)
% Male	46.3	22.2 †	38.5	33.3
Age of diagnosis (years)	10.86 ± 4.8	11.93 ± 4.1	14.24 ± 3.61	13.49 ± 4.6
Age of diagnosis categories (%)				
0-4	12.2	11.1	3.8	---
5-9	29.3	---	3.8	33.3
10-14	31.7	66.7 †	46.2	33.3
15-19	26.8	22.2	46.2	33.3
Body Weight Phenotype (%)				
Underweight	17.1	22.2	---	---
Normal Weight	61.0	66.7	11.5	---
Overweight	22.0	11.1	88.5	100
Blood Glucose at diagnosis	504.2 ± 238.0	436.1 ± 149.8	386.9 ± 218.6	426.8 ± 165.5
Blood Glucose > 200 at diagnosis (%)	100	88.9	73.1	66.7
HbA1c (mean)	12.9 ± 1.7	10.1 ± 1.0 †	11.2 ± 1.0	9.25 ± .9†
$HbA1_C \geq 9.5$ at diagnosis (%)	46.7	44.4	61.5	66.7
Urine Ketones present at diagnosis (%)	34.1	33.3	34.6	33.3
Insulin at diagnosis (%)	100	100	46.2	50.0
Insurance (%)				
Private	26.8	33.3	42.3	50.0
Public	41.5	44.4	26.9	33.3
None (Self-Pay)	31.7	22.3	30.8	16.7†

† **- p<0.05** (Student t-test for continuous variables and χ^2 for categorical variables for comparison between race groups within diabetes type)

3.7 FIGURES

A B

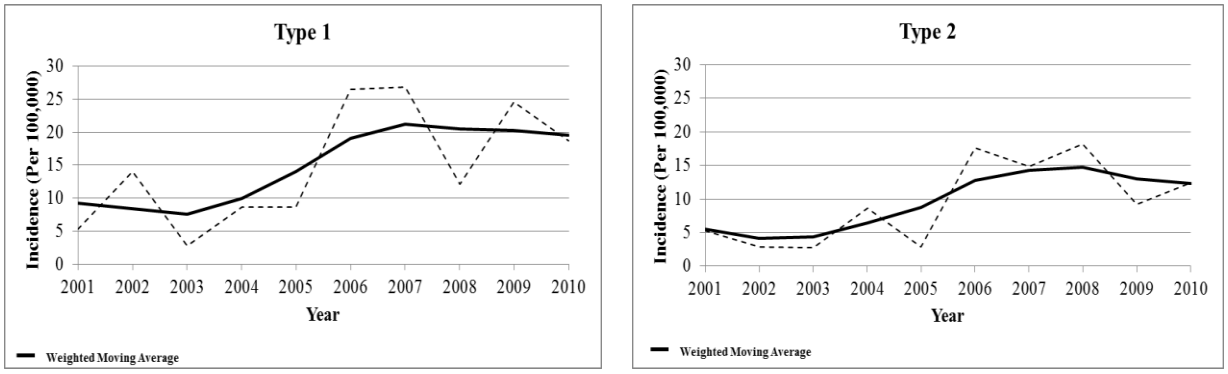

Figure 1: Annual incidence (per 100,000) of type 1 (A) and type 2 (B) diabetes in USVI by year (2001-2010)

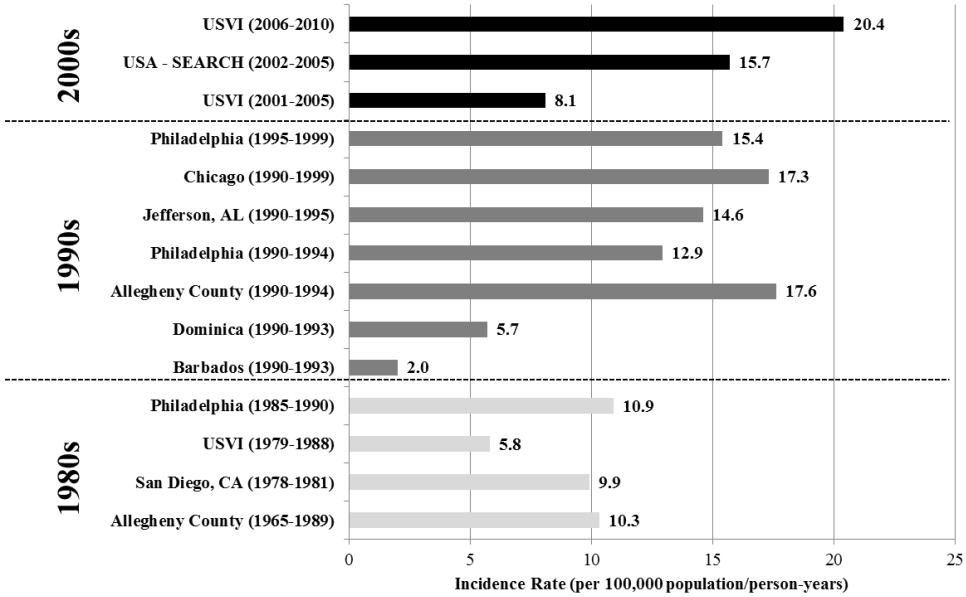

Figure 2: Annual incidence (per 100,000) of type 1 diabetes in non-Hispanic black youth <15 Years old in U.S. and Caribbean

4.0 PAPER 2: ALL-CAUSE MORTALITY IN A POPULATION-BASED TYPE 1 DIABETES COHORT IN THE U.S. VIRGIN ISLANDS

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4.1 ABSTRACT

OBJECTIVE: Type 1 diabetes remains a significant source of premature mortality; however, its burden has not been assessed in the U.S. Virgin Islands (USVI)

RESEARCH DESIGN AND METHODS: We report overall and 20-year mortality in the USVI Childhood (<19 years old) Diabetes Registry Cohort diagnosed 1979-2005. Recent data for non-Hispanic blacks from the Allegheny County population-based registry were used to compare mortality in the USVI to the contiguous US. USVI non-Hispanic black population mortality data were used to calculate standardized mortality ratios (SMRs) for non-Hispanic blacks.

RESULTS: As of December 31, 2010, the vital status of 94 of 103 total cases was confirmed (91.3%) with mean diabetes duration 16.8 ± 7.0 years. No deaths were observed in the 2000-2005 cohort. The overall mortality rates for those diagnosed 1979-1989 and 1990-1999 were 1852 and 782 per 100,000 person-years, respectively. Survival was worse for individuals diagnosed >14 years old (47%) compared to those diagnosed <10 years (95%, p=.03) and those 10-14 years old (80%, p=.09). The 20-year mortality and survival in non-Hispanic blacks did not differ between the USVI and Allegheny County cohorts. The overall SMR for non-Hispanic blacks in the USVI was 5.8 (95% CI 2.7-8.8), compared to 7.5 (95% CI 5.2-9.8) in Allegheny County.

CONCLUSIONS: This study, as the first type 1 diabetes mortality follow-up in the USVI, confirmed previous findings of poor disease outcomes in racial/ethnic minorities with type 1 diabetes. Continued follow-up and efforts to improve disease management and access to care in the USVI are critical.

4.2 INTRODUCTION

Unlike type 2 diabetes, where prevention is possible[107], type 1 diabetes (T1D) is currently a lifelong incurable metabolic disorder. Despite increased access to treatment, improved disease management, and successful reduction of complications through intensive therapy[108], the major complications of type 1 diabetes (retinopathy, nephropathy, neuropathy, and cardiovascular disease) persist as significant sources of morbidity and early mortality.[47] Prior mortality studies estimate T1D mortality in the U.S. to be 5-7 times higher than the general population[109]; higher than estimates in other developed nations.[26, 110] Recent reports from the Allegheny County population-based registry indicated that T1D mortality has improved in recent decades and the proportion of deaths due to often preventable acute complications has greatly decreased.[29, 105] Researchers also confirmed that African-Americans with T1D were at a nearly 2.5-fold increased risk of premature death compared to Caucasians, as shown in several earlier studies.[24, 25, 27, 28] Roy *et al* also reported long-term T1D mortality to be 6-12 times higher in an all-African-American cohort compared to the general population.[76] Thus, further assessment and understanding of the mortality associated with T1D in non-Hispanic blacks is critical. The United States Virgin Islands (USVI), a predominantly non-Hispanic black population, provides an ideal population. Diabetes has risen to the fourth leading cause of death in the USVI[111]; however, the mortality and survival associated specifically with T1D has yet to be evaluated and is of concern as the incidence of T1D in the USVI has risen over the past 30 years to levels higher than anticipated based on worldwide estimates.[11, 22]

We thus investigated mortality rates in a population-based childhood onset T1D cohort in the USVI with a mean follow-up of ≥15 years to assess trends in mortality by race, sex, age of

diagnosis, and year of T1D diagnosis and to compare rates to the non-Hispanic black cohort of the Allegheny County T1D Registry.

4.3 METHODS

4.3.1 Study Population

The USVI Childhood Diabetes Registry cohort includes any individual diagnosed with diabetes before age 19 and living in the territory at the time of diagnosis between January 1, 1979 and December 31, 2005.[21] Cases were ascertained through retrospective review of medical records at all hospitals and community health clinics. Individuals were excluded if pregnant (likely gestational diabetes) or not a USVI resident. Diabetes type was determined by health professional diagnosis. The registry cohort is composed of a total of 103 eligible T1D cases from all three islands (St. Croix, St. Thomas, and St. John).

4.3.2 Vital Status Ascertainment

Vital status was ascertained as of December 31, 2010, by first contacting all participants via postal mail and telephone to update registry contact information. When participants were not contactable via telephone or mail, attempts were made to contact family members listed in the registry via telephone. Finally, telephone books and internet search engines were used to identify updated contact information for participants.

The USVI Territorial Death Index, the U.S. Social Security Death Index (SSDI), and the National Death Index (NDI) were then searched to confirm possible deaths among non-contacted participants. Death certificates were obtained from the USVI Bureau of Vital Statistics for all deaths occurring within the territory. NDI data was ascertained for all deaths occurring outside of the territory, to determine cause of death.

4.3.3 Statistical Analysis

Student's t-test and one-way ANOVA were used to compare continuous variables across groups (sex, race, and diagnosis cohort), adjusting for multiple comparisons using the Bonferroni correction. The χ^2 (or Fisher's exact) test was used to compare categorical variables between groups. Diagnosis year was categorized into three groups, based on decade (1979–1989, 1990–1999, and 2000-2005) to assess temporal trends in overall mortality. Age at diagnosis was categorized as pre-pubertal (<10 yrs), peri-pubertal (10-14 yrs), and post-pubertal (>14 yrs). Race was categorized as non-Hispanic white (NHW), non-Hispanic black (NHB), and Hispanic (H), based on race abstracted from the USVI Childhood Diabetes Registry. Mortality rates were estimated using person-years method, and 95% CIs were determined using the Poisson distribution. Non-Hispanic whites were not included in the analysis, because no deaths have occurred to date. Each individual's person-years contribution was calculated from the date of diagnosis to the December 31, 2010, date of death, of the date of last follow-up. Life-table analyses by the Kaplan-Meier method were performed. Log-rank test was used to determine the statistical difference between survival curves by sex, race, diagnosis cohort, and age of diagnosis. Age- and sex-adjusted standardized mortality ratios (SMRs) were calculated as the observed divided by the expected number of deaths in each age, and sex category for non-

Hispanic Blacks. Expected mortality was calculated using population life tables for USVI, obtained from the USVI Department of Health Bureau of Vital Statistics.[112] Background mortality rates covering the same period were used. SMRs were not calculated for Hispanics due to the lack of population life tables for Hispanics in the USVI. 95% CIs were determined with the Poisson distribution. Mortality rates and SMRs were compared using rate ratio (RR) analyses and calculating 95% CIs.[113] Multivariate Cox proportional hazard models were used to assess the effects of sex, race, age at onset and year of diagnosis on mortality. Twenty (20)-year mortality rates in NHBs in the USVI cohort were compared to all-cause mortality rates in NHBs in the Allegheny County population-based T1D registry cohort, as a proxy for the contiguous US. Statistical significance was considered as a p-value less than 0.05. Analyses were completed using SPSS 18.0 (SPSS, Inc.) and SAS 9.2 (SAS, Inc.).

4.4 RESULTS

As of December 31, 2010, the vital status of 94 of the 103 total cases was confirmed (91.3%); though only 69 of 75 (92.0%) cases diagnosed 1979-1999 were confirmed and included in the analysis. There were no statistical differences in the proportion of males (46.9% male vs. 50.1% male) or mean age at onset (11.5 ± 4.4 vs. 11.0 ± 2.4) in the unverified sample, compared to the verified sample. Non-Hispanic blacks (94.7%) and Hispanics (90%) had similar proportions traced. However, individuals diagnosed 1979-1989 (80.6%) were less likely to be traced compared to the 1990-1999 (95.6%) and 2000-2005 (100.0%) cohorts (p=.04). Demographic characteristics and overall mortality rates of the USVI type 1 diabetes cohort are shown by sex, race, and year of diagnosis in Table 6.

The overall mortality rate was 1170 per 100,000 person-years (95% CI 727, 1883). There were no significant differences in overall mortality by sex, race, diagnosis cohort or age of onset in the USVI.

Results from Cox regression modeling showed that sex, race, and year of diagnosis were not significant and were not included in the final model. (Table 7) Age at onset, categorically and continuously, was the only significant predictor of mortality in the cohort. Individuals diagnosed after the age of 14 had a 9-fold increased risk of mortality compared to those diagnosed prior to age 10 (95% CI 2.0-42.3). The 10-14 age group had a nearly 4-fold increased risk, though not significant (95% CI 0.5-15.8). Each additional year in age at onset increased risk of mortality by 23% (hazard ratio – 1.2, 95% CI 1.1-1.4).

Survival curves up to 20 years duration by sex, race, diagnosis cohort, and age of diagnosis based on the Kaplan-Meier method are shown in Figure 3. Overall cumulative survival was 98% at 10 years, 91% at 15 years and 73% at 20 years. No difference was seen by sex, race, or diagnosis cohort. Individuals diagnosed age ≥14 had poorer survival compared to both the <10 and 10-14 age at onset groups (p=.03). Survival at 20 years for the <10, 10-14, and >14 age at onset groups was 95%, 80%, and 47%, respectively.

The 20-year mortality rates by sex, diagnosis year, and age of diagnosis for NHBs in the USVI and Allegheny County, PA are shown in Table 8.The 20-year mortality rate in NHBs did not differ between the USVI and Allegheny County, PA cohorts (p=.23). The overall SMRs for NHBs are also shown in Table 8. The overall SMR for non-Hispanic blacks in USVI was 5.8 (95% CI 2.7-8.8). There were no differences based on sex, diagnosis cohort, or age of diagnosis; however the SMR was highest for the 1979-1989 cohort (8.1, 95% CI 3.1-13.1) and for the >14 diagnosis age group (8.7, 95% CI 2.3-15.1). The SMR seemed to increase gradually by age of

diagnosis; however this pattern was not observed in Allegheny County, PA, with the highest SMR occurring in the <10 age group.

Survival curves up to 20 years duration comparing NHBs in the USVI to NHBs in Alleghany County are shown in Figure 4 There was no differences in cumulative survival between non-Hispanic blacks in the USVI and Allegheny County, PA cohort.

4.5 DISCUSSION

This study, for the first time, evaluated mortality in a population-based type 1 diabetes cohort in the USVI and compared the effects of race, sex, age of diagnosis, and calendar year period of diagnosis on survival. These data appear to reveal a major impact of age at onset on mortality, such that a post-pubertal onset increases mortality 9-fold; however, due to the small sample size, this was not statistically significant. Recent data from the Allegheny County, PA population-based registry cohort were also used to compare the mortality experience in the USVI to that of a county in the contiguous United States. Notably, there were no significant difference in 20-year mortality or survival for non-Hispanic blacks in the USVI cohort compared to non-Hispanic blacks in the Allegheny County, PA cohort, suggesting a similar mortality experience for non-Hispanic blacks across the different geographic locations. In accordance with reports from Allegheny County, PA cohort[26, 105] and other studies[76, 114] that have shown higher mortality in individuals with type 1 diabetes compared to the general population, mortality for non-Hispanic blacks with type 1 diabetes in the USVI was 5.8 (95% C.I. 2.7-8.8) times higher than the general USVI non-Hispanic black population. This SMR was similar to that of non-Hispanic blacks in the Allegheny County, PA cohort (SMR: 7.5 (95% C.I. 5.2-9.8)).

The paradox of comparable SMRs for non-Hispanic blacks and non-Hispanic whites, despite dramatically higher mortality rates in non-Hispanic blacks observed in Allegheny County, PA remains unclear. Unfortunately, too few non-Hispanic whites in the USVI precluded examination of this in the USVI. Nonetheless, the higher background mortality in Allegheny County, PA in non-Hispanic blacks compared to non-Hispanic whites in general was attributed to violent and accidental deaths in non-Hispanic blacks, and the absence of such deaths in the type 1 diabetes population.[105] This may also be a contributor in the USVI as well, as violent crimes (specifically assault/homicide) remain the third leading cause of death, accounting for approximately 7% of the deaths annually, but none of the deaths in the USVI cohort were due to violence; in fact, similar to Allegheny County, PA, all deaths in non-Hispanic blacks were due to diabetes-related acute and chronic complications.[111] Moreover, based on national estimates non-Hispanic blacks without type 1 diabetes are at greater risk compared to non-Hispanic whites for renal disease in the general population, also a major cause of death in the general population the USVI.[111, 112, 115, 116] As such, it is likely a combination of these factors contributing to the excess mortality in the general non-Hispanic black population, resulting in no observed disparity in the overall impact of type 1 diabetes between whites and blacks.

In addition, poorer outcomes in non-Hispanics blacks with type 1 diabetes may also be associated with poor socioeconomic status and other environment factors, including access to care. The SEARCH Study found that non-Hispanic black youth diagnosed with type 1 diabetes had poorer socioeconomic profiles, and were more likely to be uninsured or utilizing public insurance.[17] In concert, the USVI has high rates of poverty and uninsured, coupled with a significantly high cost of living, which results in poor overall socioeconomic conditions.[117] The poor socioeconomic conditions impact the entire population, with and without diabetes, but are

likely to still be associated with poor prognosis and increased mortality in type 1 diabetes[118], and would not be detected in the SMR.

Mortality between non-Hispanic blacks and Hispanics did not differ, but the sample size of the latter precludes further analysis. Regrettably, apart from this study, there is no long-term follow-up of mortality in Hispanics with type 1 diabetes in the literature.

No sex differences in mortality for men and women was observed in the USVI, consistent with several previous studies,[109, 76, 118] but not all[110, 119] In the New Jersey 725 Study there were no significant differences in mortality for men and women; however the SMR for women was significantly higher than for men (10.5 vs. 7.0).[76] This difference was not observed in the USVI, as SMRs for men and women were virtually identical (6.0 vs. 5.5); however, a difference was seen in the Allegheny County cohort, where females had a nearly 4-fold increased SMR compared to males (4.0 vs. 15.6). This may be attributed to the smaller sex gap in overall mortality seen in the general non-Hispanic black population in the USVI compared to Allegheny County and New Jersey.

In contrast to the overall Allegheny County, PA cohort and other studies abroad[110, 120] , no temporal improvement in mortality was observed in the USVI, as there were no significant differences in mortality based on diagnosis cohort. Importantly, follow-up was worse for the earlier diagnosis cohort (80.6% vs. 95.6%). As such, we evaluated the mortality and survival, applying the same mortality in the traced individuals to the untraced individuals, as well as estimated mortality assuming that all untraced individuals were deceased, and mortality (p-values: 0.27, 0.21) and survival (p-values: 0.62, 0.41) still did not significantly differ. Notably, in Allegheny County, PA, there was also no significant temporal improvement in mortality for non-Hispanic blacks, as survival did not differ across diagnosis year cohorts. Interestingly, while

overall mortality did not differ between diagnosis cohorts, survival, particularly at 10-15 years duration, seemed worse for the later diagnosis cohort (1990-1999, 90.0% at 15 years) compared to the earlier diagnosis cohort (1979-1989, 96.1% at 15 years) in the USVI, though this difference was not significant. While this may partly be an artifact of the small sample size, it is plausible that there has been no temporal improvement in mortality in the USVI. While disease recognition, care and treatment have improved, there are still major gaps in access to specialized diabetes care and treatment. There are few endocrinologists currently practicing in the territory, and none specializing in pediatrics.[121] There is also minimal access to diabetes educators to provide additional training to patients and families. As a result, families often seek care in neighboring territories or stateside; however, this is limited to those financially advantaged families, as this is often not covered by medical insurance providers and in cases where coverage is provided, travel expenses remain the burden of the individual family.

Age of diagnosis was the only significant predictor of mortality in the USVI, with a significantly better survival in those diagnosed before puberty (<10) compared to those diagnosed during the pubertal (10-14) (p=.09) and post-pubertal (>14) (p=.03) periods. This difference also seemed to occur specifically in non-Hispanic blacks, as 20-year mortality increased by 4.5-fold between the <10 age group and the >14 age group; this difference was significant. The overall SMRs also seemed to follow a similar pattern as the SMR in the <10 age group was 2.6, compared 8.7 in the >14 age group (not significant). This pattern was not observed in non-Hispanic blacks in Allegheny County, PA, where the SMRs did not differ dramatically across diagnosis age groups. Other studies have shown higher mortality rates in individuals diagnosed during and after puberty, compared to those diagnosed before puberty.[109, 110, 119, 122] While the factors associated with this increased risk remain unclear, and it is possible

that care-related factors play a role (e.g. resistance to self-management and compliance by maturing adolescents). In addition, there is some evidence that suggests that the earliest years of type 1 diabetes (pre-puberty) are largely free of complications, and as such, the pattern seen may be an effect of age, as opposed to a true difference in mortality.

The major limitation of this present study is the small sample size and as a result no confirmed deaths were seen in non-Hispanic whites. This prohibited racial comparisons between non-Hispanic whites and other race groups in the USVI. However, based on survival estimates for non-Hispanic whites in Allegheny County, PA, we would expect 92% survival at 24-years duration (mean duration of non-Hispanic whites in USVI), which equates to only .48 expected deaths. Another limitation of the study is that the living status of 8.7% of participants was not determined. Nonetheless, the likelihood of death in these individuals is low, as the USVI Territorial Death Index, Social Security Death Index, and National Death Index were all searched for these individuals. A final limitation for consideration is the impact of migration from the USVI to the contiguous US on the interpretation of these results specific to factors in the USVI. Approximately 35% of deaths occurred outside of the USVI; however, some of this is accounted for by individuals seeking ambulatory care stateside.

In conclusion, this is the first population-based type 1 diabetes mortality follow-up in the USVI and Caribbean region. This study confirms previous findings of poor disease outcomes in racial/ethnic minorities with type 1 diabetes, particularly if diagnosed after puberty. Mortality outcome seems however comparable to Allegheny County, PA non-Hispanic blacks. Continued follow-up and efforts to improve disease management and access to care in the USVI are critical.

4.6 TABLES

Table 6: Demographic Characteristics and Overall Mortality of USVI Type 1 Diabetes Registry Cohort (1979-2005) by Sex, Race, and Year of Diagnosis

	Sex		Race			Year of Diagnosis			Total
	Male*	Female	Non-Hispanic Black*	Non-Hispanic White	Hispanic	1979-1989*	1990-1999	2000-2005	
n	49	54	77	6	20	36	45	22	103
Follow-up	89.8 (44)	92.6 (50)	94.7 (72)	50 (3)	90 (18)	80.6 (29)	95.6 (43)	100.0 (22)†	91.3
Male	--	--	48.1 (37)	66.7 (4)	40.0 (8)	55.6 (20)	44.4 (20)	40.9 (9)	47.6 (49)
Age of diagnosis (years)	10.9 ± 4.7	11.7 ± 4.4	11.6 ± 4.7	8.8 ± 2.4	11.1 ± 4.5	10.9 ± 4.4	11.2 ± 5.2	12.4 ± 3.2	11.3 ± 4.5
Mean diabetes duration (years)	17.5 ± 7.2	16.1 ± 6.9	16.7 ± 7.0	23.8 ± 2.7	15.4 ± 7.0	24.3 ± 4.2	15.2 ± 3.0‡	7.5 ± 1.5‡	16.8 ± 7.0
Mean Age (years)	28.4 ± 7.3	27.8 ±7.8	28.3 ± 7.4	32.6 ± 4.5	26.5 ± 8.6	35.2 ±5.2	26.4 ± 5.3†	19.9 ±3.3‡	28.2 ± 7.5
Diagnosis Cohort									
1979-1989	40.8 (20)	29.6 (16)	31.2 (24)	83.3 (5) ‡	35.0 (7)†	--	--	--	35.0 (36)
1990-1999	40.8 (20)	46.3 (25)	48.1 (37)	16.7 (1) †	35.7 (7)	--	--	--	43.7 (45)
2000-2005	18.4 (9)	24.1 (13)	20.8 (16)	--	30.0 (6)	--	--	--	21.4 (22)
Race									
Non-Hispanic Black	8.2 (4)	3.7 (2)	--	--	--	66.7 (24)	80.0 (36)	72.7 (16)	5.8 (6)
Non-Hispanic White	75.5 (37)	74.1 (40)	--	--	--	13.9 (5)	2.2 (1)	--	74.8 (77)
Hispanic	16.3 (8)	22.2 (12)	--	--	--	19.4 (7)	15.6 (7)	27.3 (6)	19.4 (20)
Deaths	20.4 (10)	13.0 (7)	18.2 (14)	0 (0)	15.0 (3)	33.3 (12)	11.1 (5)	0 (0)	16.5 (17)
Person-years of follow-up§	693.9	758.6	1200.0	--	252.5	648.1	639.0	165.0	1452.5
Overall Mortality Rate (95% CI)	1441 (775, 2678)	922 (440, 1936)	1167 (691, 1970)	--	1188 (383, 3684)	1852 (976, 3026)	782 (326, 1879)	--	1170 (727, 1883)

Data are % (*n*) or means ± SD.
†p<0.05; ‡p<0.01
* - Denotes reference category
§ Excludes non-Hispanic whites

Table 7: Cox Proportional Hazard by Age at Onset

	Unadjusted Hazard Ratio 95% CI	**p-value**
Continuous		
Age at Onset	1.2 (1.1-1.4)	0.01
Categorical		
Age at Onset		0.01
<10 years*	1.00	--
10-14 years	2.9 (0.5-15.8)	0.22
>14 years	9.1 (2.0-42.3)	0.01

* - Denotes reference category; Variables made available for selection: sex (categorical), race (categorical), age at onset (categorical/continuous), and year of diagnosis (categorical/continuous).

Table 8: 20-year Mortality Rates (per 100,000 person-years) and Overall Standardized Mortality Ratios (SMRs) by Gender, Diagnosis Cohort, and Diagnosis Age in Non-Hispanic Blacks in the USVI and Allegheny County, PA (1965-1979)

	USVI (1979-2005) (N=73)				Allegheny County (1965-1979) (N=80)			
	Deaths % (n)	Follow-up time (person-years)	Mortality Rate (95% CI)	SMR (95% CI)	Deaths % (n)	Follow-up time (person-years)	Mortality Rate (95% CI)	SMR (95% CI)
Overall	12.3 (9)	1095.2	822 (428, 1579)	5.8 (2.7, 8.8)	10.3 (8)	1522.9	525 (263, 1050)	7.5 (5.2, 9.8)
Gender								
Male	11.8 (4)	524.9	762 (286, 2030)	6.0 (1.5, 10.4)	6.1 (2)	671.8	298 (74, 1190)	4.0 (2.0, 6.0)
Female	12.8 (5)	570.3	877 (365, 2106)	5.5 (1.4, 9.6)	13.3 (6)	851.1	705 (316, 1569)	15.6 (9.5, 21.7)
Diagnosis Year								
1965-1969					17.9 (5)	510.4	980 (408, 2354)	10.0 (5.5, 14.5)
1970-1974					4.0 (1)	498.8	201 (28, 1423)	7.1 (3.1, 11.2)
1975-1979					8.7 (2)	513.7	389 (97, 1557)	5.1 (1.8, 8.4)
1979-1989	22.7 (5)	426.8	1171 (487, 2815)	8.1 (3.1, 13.1)				
1990-1999	11.8 (4)	548.1	729 (274, 1944)	3.2 (1.0, 6.3)				
Age at Onset								
<10 years	4.8 (1)	354.5	282 (40, 2003)	2.6 (0, 5.6)	13.0 (3)	427.0	703 (227, 2178)	6.0 (1.8, 10.1)
10-14 years	6.9 (2)	404.9	494 (124, 1975)	5.5 (1.1, 10.9)	6.9 (2)	629.2	318 (79, 1271)	9.1 (4.9, 13.4)
>14 years	26.0 (6)	335.8	1787 (803, 3977)	8.7 (2.3, 15.1)	12.5 (3)	466.7	643 (207, 1993)	6.9 (3.3, 10.5)

4.7 FIGURES

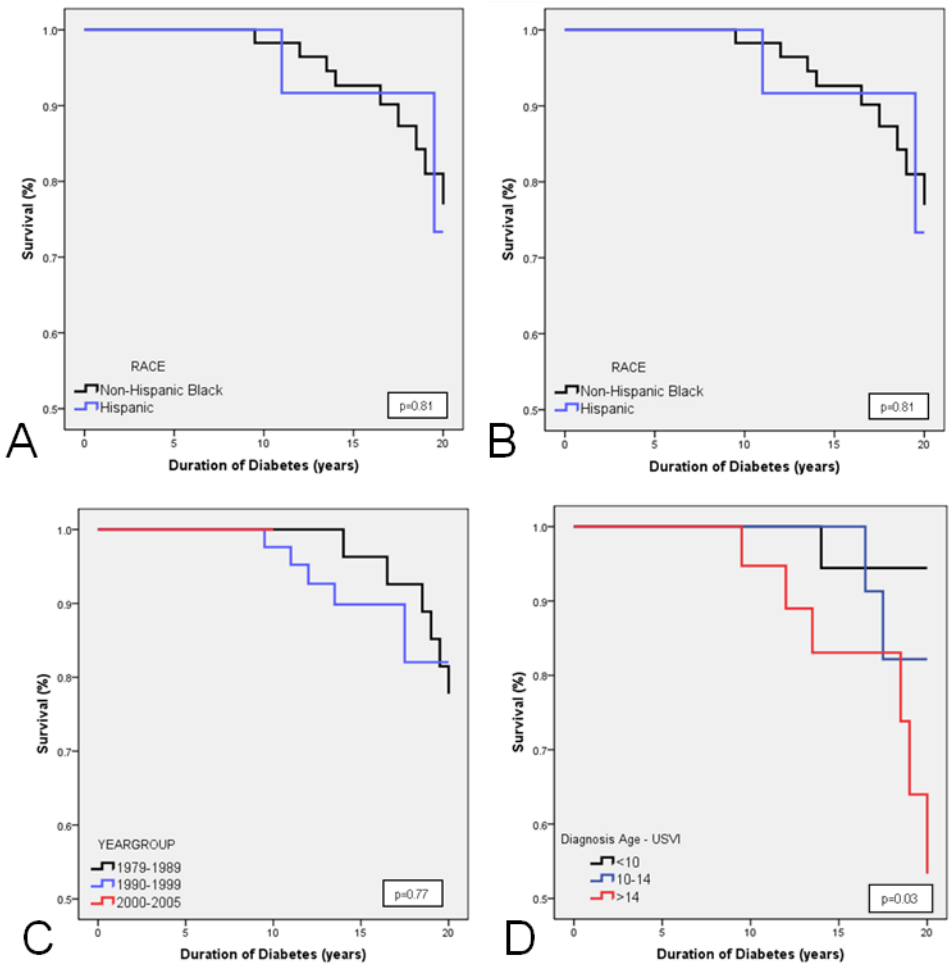

Figure 3: Life-Table Analysis by Sex (A), Race (B), Diagnosis Cohort (C), and Diagnosis Age(D) in the USVI

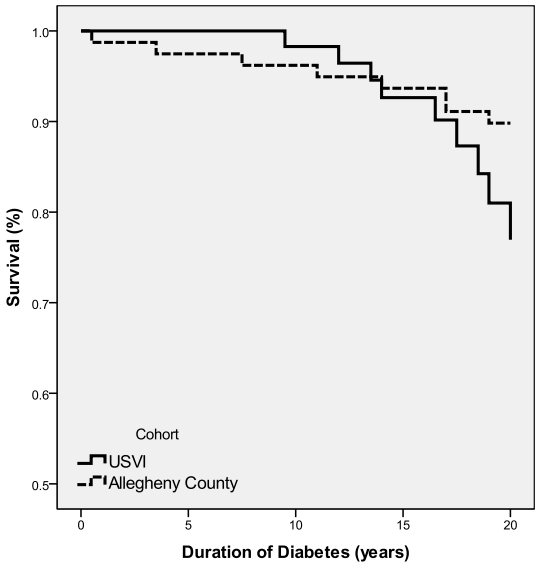

Figure 4: Life-Table Analysis Overall in Non-Hispanic Blacks in USVI (1979-2005) vs. Allegheny County, PA (1965-1979)

5.0 PREVALENCE OF MAJOR TYPE 1 DIABETES COMPLICATIONS AND RISK FACTORS IN WHITES AND BLACKS IN THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY, (1999-2008)

To be submitted for publication

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5.1 ABSTRACT

OBJECTIVE: The aims of this study were to compare the prevalence of type 1 diabetes complications (cardiovascular disease, nephropathy, and retinopathy) between non-Hispanic whites (NHW) and blacks (NHB) in a national sample and to evaluate the impact of modifiable risk factors and race on these outcomes.

METHODS: Eighty individuals (60% NHW, 40% NHB) with type 1 diabetes were identified in the National Health and Nutrition Examination Survey (1999-2008) (determined as individuals diagnosed with diabetes less than age 30 and on continuous insulin therapy). Complication and risk factor status were determined based on self-reported responses on the questionnaire and relevant laboratory components.

RESULTS: The prevalence of CVD did not differ by race group, and race was not associated with CVD after adjusting for risk factors. Univariately, the prevalence at > 20 years duration of both nephropathy and any retinopathy were significantly higher in NHBs (nephropathy: 48.6% vs. 18.4%, p=.01; retinopathy: 83.1% vs. 43.4%, p<.01). Furthermore, race was significantly associated with nephropathy [OR (95%CI): 1.18 (1.06, 1.30)] and retinopathy [OR (95%CI): 1.20 (1.04, 1.36)] after adjusting for other risk factors(age, sex, diabetes duration, hypertension, hypercholesterolemia, glycemic control, and smoking).

CONCLUSIONS: These data suggest that NHBs with type 1 diabetes are at increased risk of developing nephropathy and retinopathy, independent of well-established risk factors for these complications. The reasons for this disparity merit further investigation.

5.2 INTRODUCTION

A decreasing incidence of type 1 diabetes complications, particularly nephropathy, retinopathy, and neuropathy, has been reported in the U.S. and globally over the past 30 years.[47, 123, 124, 125] Studies have also indicated that type 1 diabetes mortality rates are declining in the U.S.[26, 105] Increased access to treatment and improved disease management are likely major contributors to this decline in type 1 diabetes morbidity and mortality.[108] However, mortality for African-Americans with type 1 diabetes remains nearly 2.5 times higher than Caucasians.[24, 25, 27, 28, 29] The factors contributing to this disparity are unclear. There have been limited epidemiological studies investigating variations in the prevalence of major T1D complications among racial/ethnic groups, specifically African-Americans compared to Caucasians. A single report from the Allegheny County, PA population-based type 1 diabetes cohort showed that African-Americans with type 1 diabetes were at significantly increased risk of developing end-stage renal disease (ESRD) at 20 years duration compared to Caucasians (21.9% vs. 5.2%).[126] Existing type 1 diabetes complications prospective cohort studies in the U.S. have very limited racial diversity, prohibiting any direct racial comparisons in the incidence of major complications and risk factors.[44, 46] The National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey which assesses the prevalence of a variety of health conditions, health behaviors and risk factors in adults and children in the U.S.[127] Prevalence of diabetes complications has been previously reported in NHANES for individuals with type 2 diabetes and all diabetes (type 1 and type 2 combined); however, there has been no analysis exclusively in the type 1 diabetes population.[39, 55, 128] While diagnosis of type 1 diabetes is not definitively collected as a diagnosed condition, other relevant factors (age of diagnosis and initiation/time of insulin therapy) are available to distinguish between type of diabetes; and has been used in previous

studies.[129, 130, 131] NHANES is also racially diverse allowing for analysis stratified by race. We therefore investigated the prevalence of major type 1 diabetes complications (coronary artery disease, renal disease, and retinopathy) and risk factors (hypertension, hypercholesterolemia, and smoking) for NHWs compared to NHBs using data collected from NHANES for 1999-2008. Specifically, the objectives of this analysis were to: (1) assess racial differences in the prevalence of diabetes complications, (2) determine if racial differences exist in factors associated with development of diabetes complications, and (3) assess the impact of race, as a risk factor itself, on the development of diabetes complications.

5.3 METHODS

5.3.1 Study Population

The National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention, became a continuous survey in 1999, and data are released in 2-year increments. Datasets for 1999-2000, 2001-2002, 2003-2004, 2005-2006, and 2007-2008 were combined. The NHANES 1999–2008 comprised a nationally representative sample of the non-institutionalized civilian US adults and children. Each NHANES oversamples NHBs, Hispanics, or both. Health examinations including physical measurements and blood and urine collections are conducted in a mobile examination center. Survey instruments and physical and laboratory measurements have been described previously.[132] The current study includes participants in NHANES 1999-2008, who underwent a health examination in the NHANES mobile examination center, and had available data for

diabetes diagnosis, age of diabetes diagnosis, insulin usage, and date of initiation of insulin usage.

All NHANES protocols were approved by the NCHS Research ethics review board (previously known as the NHANES institutional review board); all participants provided written informed consent.

5.3.2 Variable definitions

Demographics

Age, gender, race, and household income were all assessed by questionnaire. Race was self-classified as NHW and NHB; other and mixed racial groups were excluded for this study. Household income was categorized into $10,000 groupings up to $80,000 (i.e. $0-10,000, $10,001-20,000,…>$80,000).

Diabetes Definition

Type 1 diabetes for these analyses was defined as individuals diagnosed with diabetes less than age 30 and continuously on insulin therapy (initiation of insulin therapy within a year of diagnosis and current insulin use).

Cardiovascular Disease (CVD) Definition

CVD was defined as self-reported diagnosis of congestive heart failure (CHF), myocardial infarction (heart attack), coronary artery disease and/or angina. These CVD questions are only proctored to adults aged 20 and older. As such, for participants less than age 20, it was assumed that no clinical CVD was present.

Nephropathy Definition

Nephropathy was defined as self-reported diagnosis of weak/failing kidneys (excluding kidney stones, bladder infections, or incontinence) or self-reported of receiving dialysis within the last 12 months.

Retinopathy Definition

Retinopathy was defined as self-reported diagnosis of diabetes affecting the eyes or retinopathy.

Glycemic Control Definition

Glycemic control was assessed using HbA1C measures for each participant. The HbA1C measurements were taken using different laboratory methodologies over the study period. As such, the recommended correction equations were applied to the respective values. Poor glycemic control was defined as an HbA1C value less than 9.0%. This categorical term was used in logistic regression to further reduce any bias associated with the change in laboratory methodologies.

Hypertension Definition

Hypertension was defined as a mean resting blood pressure > 140/90 (either systolic >140, diastolic >90, or both), self-reported diagnosis of hypertension or use of hypertensive medication. Blood pressure was measured during the NHANES clinical examination. Three or more consecutive blood pressure measurements were taken (separated by 30 second breaks) after an initial 5 minutes of rest. The mean value was used in the analysis.

Hypercholesterolemia Definition

Hypercholesterolemia was defined as total cholesterol > 200 mg/dL, self-reported diagnosis of hypercholesterolemia or use of high cholesterol medication. Blood samples were collected during the clinical examination and later analyzed. Over the course of time, there were changes

in the instrumentation used to measure total cholesterol. Prior to 2006, total cholesterol was measured enzymatically in serum using the Roche Hitachi 717. In 2006, total cholesterol was measured enzymatically in serum using the Roche Hitachi 717 and 912. In 2007, total cholesterol was measured in serum using Roche Modular P chemistry analyzer. No adjustment of values was necessary to account for the change in instrumentation for total cholesterol between 2005-2006 and 2007-2008.[132]

Smoking Definition

Smoking was defined as self-reported smoking > 100 cigarettes in lifetime.

5.3.3 Statistical Analysis

All statistical analysis incorporated recommended NHANES weights to account for non-response bias and sampling methods. Student's t-test and one-way ANOVA were used to compare continuous variables between NHWs and NHBs. The $\chi 2$ (or Fisher's exact) test was used to compare categorical variables between groups NHWs and NHBs. Prevalence of complications and risk factors were calculated in 10-year duration groups (1-10, 11-20, and > 20), stratified by race groups. Multivariate logistic regression was used to assess the impact of modifiable risk factors in NHWs and NHBs separately, adjusting for gender, age, and age of diabetes diagnosis. Univariate and multivariate logistic regression models were used to assess the impact of race on development of complications, adjusting for clinical (duration, and modifiable risk factors) and demographic (age at exam, gender, and household income) characteristics. Nephropathy was also included in the models as an independent variable when assessing CVD and retinopathy, because of its established association with both. Statistical significance was

considered as a p-value less than 0.05. Statistical analysis was performed using Statistical Analysis Software (SAS, Inc.).

5.4 RESULTS

There were 80 participants (48 NHW and 32 NHB) that met the previously described type 1 diabetes definition in the 1999-2008 NHANES. Demographic and clinical characteristics of participants are shown by race in Table 9. NHBs were older with a mean age of diagnosis (18.9 ± 1.7) compared to NHWs (15.1 ± 1.3) (p=.08) and a lower mean duration of diabetes (14.7 ± 2.3 vs. 20.9 ± 2.7) (p=.08). NHBs had a higher mean body mass index and waist circumference (31.8 ± 2.1 kg/m2, 103.7 ± 4.9 cm) (p<.01). NHBs had a lower mean HDL, which trended towards significance (p=.07). Finally, NHBs had a significantly higher A/C ratio compared to NHWs (p=.02).

Prevalence of major complications and risk factors by duration groups are shown in Figure 5. There were no prevalent cases of CVD in NHW or NHB with less than 20 years duration; however, at >20 years duration NHWs had marginally higher rates (17.4% vs. 11.9%) (p=.08). NHBs with >10 years duration had significantly higher rates of nephropathy compared to NHWs (11-20 years duration: 55.1% vs. 1.3% (p<.01), 21+ years duration: 48.6% vs. 18.4% (p<.01)). NHBs had higher rates of retinopathy at all durations compared to NHWs, with rates being nearly 2-fold higher at greater than 20 years duration (83.1% vs. 43.4%) (p=<.01). NHBs with less than 20 years duration had significantly higher rates of hypertension compared to NHWs (p<.01), with rates been virtually identical at >20 years duration (67.4% vs. 67.0%). Interestingly, 100% of NHBs with 11-20 years duration had hypertension. NHBs also had higher

rates of hypercholesterolemia at <20 years duration groups compared to NHWs (p<.01). Rates of ever smokers was highest in the >20 year duration group, with rates being significantly higher in NHWs compared to NHBs (70.5% vs. 37%) (p<.01).

As shown in Table 10, NHWs with hypertension had 17% increased risk of CVD and 34% increased risk of nephropathy; while NHBs with hypertension had 20% increased risk of CVD and 14% increased risk of nephropathy. Hypertension was not associated with retinopathy in either race group. Hypercholesterolemia was associated with 15% and 20% increased risk of CVD in NHWs and NHBs, respectively. NHBs with hypercholesterolemia had 15% increased risk of nephropathy and 30% increased risk of retinopathy; however, hypercholesterolemia was not associated with either complication in NHWs. Glycemic control was not associated with CVD in NHWs or NHBs. However, glycemic control was associated with 30% and 40% increased risk of nephropathy in NHWs and NHBs, respectively. Glycemic control was associated with 17% increased risk of retinopathy in NHBs, no association was found in NHWs. Smoking was not associated with increased risk of CVD in either race group. Smoking was associated with a 8% increased risk of nephropathy in NHWs. Household income was significantly associated with CVD and retinopathy in NHBs, with 3% increase for every $10,000 decrease in household income; however, this association was not seen in NHWs. NHWs with nephropathy had 96% increased risk of CVD, while NHBs with nephropathy had 28% increased risk of CVD and 20% increased risk of retinopathy.

Race was univariately associated with CVD, nephropathy and retinopathy. (Table 11) NHBs were at decreased risk of CVD compared to NHWs (OR: .96 (.92, .99), p=.05); however, after adjusting for clinical characteristics and SES, there were no significant difference (OR: .92

(.81, 1.05)). NHBs had 18% increased risk of nephropathy and 20% increased risk of retinopathy compared to NHWs, even after adjusting for clinical characteristics and SES.

5.5 DISCUSSION

This study evaluated racial differences in the prevalence of CVD, nephropathy, and retinopathy and factors associated with the development of each in a national sample with type 1 diabetes. The results of this analysis indicated that NHBs with type 1 diabetes have higher rates of nephropathy and retinopathy, even after adjusting for a variety of demographic and clinical characteristics. In contrast, univariately NHBs were at lower risk of CVD, which became non-significant after adjusting for clinical characteristics, including diabetes duration, hypertension, hypercholesterolemia, and nephropathy, all of which were significant predictors of CVD. Similar risk factor associations with CVD were found in the Epidemiology of Diabetes Complications Study, a prospective cohort study of mostly NHWs, and the New Jersey 725 Study, a prospective cohort study of all NHBs.[60, 62] Household income was associated with CVD in NHBs, but not NHWs. No measure of socioeconomic status (i.e. education level, household income, etc.) was included in the NJ725 study; however, a recent report from the EDC Study showed that SES was associated with incident CVD in type 1 diabetes.[134] In addition, one might have predicted a higher prevalence of CVD in the NHBs because of the higher mean waist circumference and BMI and poorer lipid profile, but this was not the case. Of note, NHBs in this study had a lower mean HDLc, which trended toward significance (p=.07). Commonly, NHBs maintain higher rates of HDLc compared to NHWs, despite poorer cardiovascular risk profiles. No significant differences in HDLc were noted by sex; however, NHB women had a higher mean BMI and

waist circumference compared to NHB men. The lower HDLc in NHBs may result from a large proportion of NHB women with poorer lipid profiles due to multiple risk factors (i.e. high BMI/waist circumference, diabetes, hypertension, etc.).

NHBs in this study had significantly higher rates of nephropathy. Similarly, a report from the Allegheny County, PA Registry Cohort showed that at 20-years duration NHBs had a nearly 6-fold increased incidence of end-stage renal disease (ESRD) compared to NHWs.[126] The researchers did not assess factors associated with the disparity in incidence, but other reports have shown that NHBs in the general population with and without diabetes have higher rates of both chronic kidney disease and ESRD.[135, 136] Conversely, NHBs have been shown to have a 45% lower case fatality (given chronic kidney disease) compared to NHWs, in the general population.[137] It is possible the survival advantage of NHBs is contributing to the racial difference seen in this cross-sectional analysis.

Similar to the NJ 725 study, glycemic control, hypertension and hypercholesterolemia were all significant predictors of nephropathy in NHBs, who had higher rates of hypertension and hypercholesterolemia at <20 years duration in this study.[52] Yet, even after adjusting for these and other risk factors, NHBs remained at increased risk for nephropathy. Glycemic control has been previously shown to be a predictor of nephropathy.[138, 139] The EDC Study indicated that individuals in lower SES groups have poorer glycemic control.[135] While household income did not predict nephropathy in NHBs, the NHBs in this study had a higher proportion of individuals in the lowest SES category. This was the case in the SEARCH Study, where NHB youth had lower SES and poorer glycemic control, compared to NHW youth.[17] Finally, there is some evidence which suggests that NHBs are genetically more susceptible to chronic kidney disease compared to other race groups.[140]

NHBs also had higher rates of retinopathy across all duration groups, compared to NHWs. Notably, the prevalence of retinopathy in NHWs in this study seems lower than what has been reported in other studies, particularly in the 11-20 year duration group.[47, 141] The EDC Study estimated that nearly 25-39% of individuals with type 1 diabetes develop retinopathy by 20 years duration, compared to 10% in this study.[47] The Wisconsin Epidemiologic Study of Diabetic Retinopathy, a long-term prospective study, found similarly high rates of diabetic retinopathy at 20 years duration (~47.5%) to the EDC Study.[141] Both of these studies measured diabetic retinopathy in participants, compared to the self-reported data used in this analysis; this likely accounts for the lower rates found in this analysis.

Another study using the NHANES, also showed that NHBs with and without diabetes have significantly higher rates of retinopathy compared to NHWs (Diabetes: 38.8% vs. 26.4%; US Population: 9.6% vs. 2.9%).[39] Moreover, our findings are supported by a recent report from the SEARCH Study, indicating that minority youth with diabetes (including NHBs) are at increased risk of developing retinopathy, even after adjusting for diabetes duration and glycemic control.[142] It is possible that retinopathy outcomes are improving in NHWs, but the drastically higher rates in NHBs warrant further exploration.

In the NJ 725 Study of African-Americans with type 1 diabetes, diabetes duration, glycemic control, hypertension, and nephropathy were associated with the development and progression of retinopathy at baseline.[48] Subsequent follow-up in the NJ 725, also found socioeconomic status, in addition to depression to be associated with retinopathy in NHBs.[143] Depression was not included in our analysis, but glycemic control and socioeconomic status were associated with risk of retinopathy in NHBs. It is possible that depression is contributing to the increased risk of retinopathy observed in NHBs.

The interpretations of the results of this study are subject to several important limitations. The criterion used to identify NHANES participants with type 1 diabetes, while it is the best method available, does not guarantee accurate distinction of diabetes type. While this method has been used in previous studies and is clinically relevant, it has not been formally validated and some subjects included in this analysis may not have type 1 diabetes. Yet, any bias resulting from diabetes misclassification is likely consistent across race groups. This is a cross-sectional study of data collected over a 10-year period, thus interpretation of prevalence rates and causal associations must be made with caution. While, NHANES encourages combining multiple years of data to increase power, it is possible that the prevalence of complications and risk factors is changing. Future studies should explore the racial differences, particularly in nephropathy and retinopathy, in a prospective study design to further understand the impact of race on type 1 diabetes complication. Also, the complication status of individuals was largely based on self-reported variables. Finally, even with use of a national sample, there is a small absolute sample size. This limitation is partly accounted for with the weighting methods used to adjust for the NHANES sampling design.

In conclusion, this study indicated that despite improvements in diabetes management and care, NHBs have increased risk for complications, particularly nephropathy and retinopathy, compared to NHWs. Further research is needed to understand specific factors, both environmentally and genetically, associated with this increased risk. In addition, it appears that NHBs with type 1 diabetes may not maintain higher rates of HDLc, as has been commonly associated with NHBs. Finally, national surveys should consider revising existing protocols to more accurately identify patients with type 1 diabetes to expand research efforts in the prevalence of the disease and its complications.

5.6 TABLES

Table 9: Demographic and Clinical Characteristics of NHANES Cohort with Type 1 Diabetes (1999-2008)

	Non-Hispanic White NHANES 1999-2008 (n=48)	Non-Hispanic Black NHANES 1999-2008 (n=32)	p-value
Demographics			
Age, weighted mean (SD)	36.0 ± 2.4	33.6 ± 2.4	.50
Female sex, % (SE)	43.5 (9.7)	63.7 (8.5)	.14
Health insurance coverage, % (SE)	84.4 (5.9)	95.8 (4.1)	.59
Diabetes history, weighted mean (SD)			
Age of diagnosis	15.1 ± 1.3	18.9 ± 1.7	.08
Duration	20.9 ± 2.7	14.7 ± 2.3	.08
Physical measurements, weighted mean (SD)			
Body mass index, kg/m^2	24.2 ± 0.6	31.8 ± 2.1	<.01
Waist circumference, cm	85.4 ± 1.5	103.7 ± 4.9	<.01
Systolic blood Pressure , mmHg	114.7 ± 2.2	120.4 ± 2.7	.08
Diastolic blood Pressure, mmHg	65.6 ± 1.8	63.8 ± 2.8	.56
Laboratory measurements, weighted mean (SD)			
Non-fasting plasma glucose, mg/dL	248.5 ± 26.1	202.6 ± 45.0	.40
Hemoglobin A1C, %	8.6 ± 0.3	8.6 ± 0.5	.96
C-peptide, nmol/L	0.11 ± 0.04	0.17 ± 0.12	.80
Total cholesterol, mg/dL	184.8 ± 6.5	184.4 ± 7.8	.98
HDL cholesterol, mg/dL	61.0 ± 2.9	54.3 ± 2.2	.07
A/C Ratio, mg/mmol	23.8 ± 6.8	126.7 ± 43.3	.02

Table 10: Association between clinical and demographic variables and cardiovascular disease

	Cardiovascular Disease	
	NHW (R^2=.760) Odds Ratio (95% CI)	NHB (R^2=.481) Odds Ratio (95% CI)
Age at Exam (per year)	1.00 (.99-1.01)	1.02 (1.00-1.04) †
Gender		
Male	1.00 (ref)	1.00 (ref)
Female	.97 (.87-1.07)	1.01 (.90-1.13)
Diabetes Duration (per year)	1.00(.99-1.01)	1.01 (1.00-1.03) †
Glycemic Control	1.15 (.95-1.35)	1.13 (.97-1.29)
Hypertension	1.17 (1.01-1.33) †	1.40 (.85-1.98)
High Cholesterol	1.15 (1.05-1.36) †	1.20 (1.05-1.36) †
Smoking	1.12 (.97-1.30)	.99 (.93-1.04)
Nephropathy	1.96 (1.40-2.75) †	1.28 (1.13-1.44) †
Household Income	.99 (.97-1.02)	.97 (.95-.99) †

†- p<.05

Table 11: Association between clinical and demographic variables and nephropathy

	Nephropathy	
	NHW(R^2=.412) Odds Ratio (95% CI)	NHB (R^2=.423) Odds Ratio (95% CI)
Age at Exam (per year)	1.00 (.99-1.01)	1.02 (1.00-1.04) †
Gender		
Male	1.00 (ref)	1.00 (ref)
Female	.97 (.86-1.07)	1.16 (.82-1.61)
Diabetes Duration (per year)	1.00 (.98-1.02)	1.00 (.98-1.02)
Glycemic Control	1.30 (1.15-1.45) †	1.41 (1.23-1.59) †
Hypertension	1.34 (1.12-1.66) †	1.14 (1.07-1.30) †
High Cholesterol	.86 (.67-1.07)	1.25 (1.04-1.46) †
Smoking	1.08 (1.00-1.16) †	.81 (.59-1.11)
Household Income	.98 (.96-1.01)	1.00 (.95-1.04)

†- p<.05

Table 12: Association between clinical and demographic variables and retinopathy

	Retinopathy	
	NHW (R^2=.293) Odds Ratio (95% CI)	NHB (R^2=.493) Odds Ratio (95% CI)
Age at Exam (per year)	.98 (.96-1.00)	1.00 (.98-1.03)
Gender		
Male	1.00 (ref)	1.00 (ref)
Female	1.27 (1.10-1.43) †	1.12 (.83-1.52)
Diabetes Duration (per year)	1.03 (1.02-1.04) †	1.01 (.98-1.05)
Glycemic Control	1.10 (.99-1.21)	1.13 (1.03-1.23) †
Hypertension	.74 (.47-1.15)	.83 (.53-1.31)
High Cholesterol	.94 (.80-1.10)	1.03 (.94-1.12)
Smoking	1.07 (.88-1.26)	1.17 (.76-1.47)
Nephropathy	1.12 (.71-1.77)	1.30 (1.05-1.62) †
Household Income	.99 (.96-1.02)	1.03 (1.02-1.04) †

†- p<.05

Table 13: Association between race and cardiovascular disease, nephropathy, and retinopathy

	Model 1: Race (R^2=.550)	Model 2: Race +Clinical Variables[1] (R^2=.512)	Model 3: Race + Clinical Variables + SES[2] (R^2=.523)
CVD			
NHW	1.00	1.00	1.00
NHB	.96 (.92-.99) †	.93 (.90-1.33)	.92 (.81, 1.05)
Nephropathy			
NHW	1.00	1.00	1.00
NHB	1.22 (1.11-1.36) †	1.20 (1.08-1.32) †	1.18 (1.06, 1.30) †
Retinopathy			
NHW	1.00	1.00	1.00
NHB	1.42 (1.26-1.61) †	1.26 (1.09-1.44) †	1.20 (1.04, 1.36) †

†- p<.05

Model 1= Race

Model 2= Race + Age + Gender + Duration + Hypertension + High Cholesterol + Glycemic Control + Smoking Status + Nephropathy

Model 3= Race + Age + Gender + Duration + Hypertension + High Cholesterol + Glycemic Control + Smoking Status + Nephropathy + Household Income

5.7 FIGURES

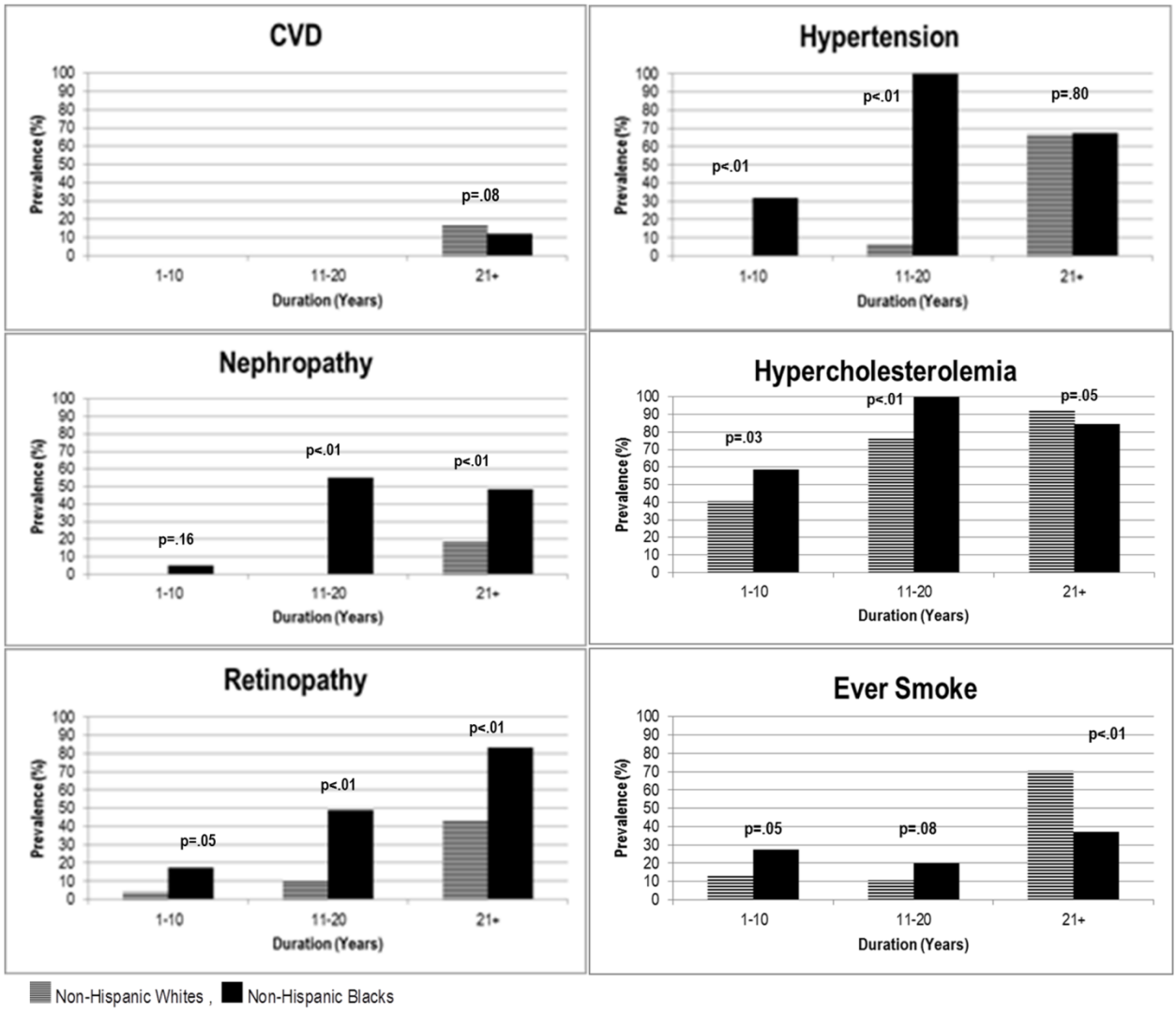

Figure 5: Cross-Sectional Prevalence of Complications and Risk Factors by Race and Duration

6.0 DISCUSSION

6.1 SUMMARY OF FINDINGS

The objective of this study was to evaluate the impact (incidence, morbidity and mortality) of type 1 diabetes on African-Americans (including, those of Caribbean-descent), largely focused on the U.S. Virgin Islands, a majority non-Hispanic black population. While the USVI differs geographically and culturally from the contiguous U.S., these results indicate that the impact of type 1 diabetes on African-Americans is comparable to the general U.S. population. The incidence of type 1 diabetes is steadily increasing in African-Americans in the USVI, with unexplained epidemic-like increases occurring throughout the past 30 years. African-American boys seem to lack the well-established pubertal rise in incidence, which is seen in African-American girls and other race youth. This study, for the first time, reported all-cause mortality in T1D in the USVI. African-Americans in the USVI have high type 1 diabetes mortality rates as seen in African-Americans in Allegheny County, PA, and other US-based studies. [24, 26, 28, 105] This study indicated that individuals diagnosed with type 1 diabetes after puberty were at nearly 9 times greater risk of death compared to individuals diagnosed before puberty (Cox Proportional Hazard: 9.1 (95% CI 2.0, 42.3). In addition, African-Americans in the USVI with type 1 diabetes die at a rate nearly 6 times higher than the general population (SMR: 5.8 (95% CI 2.7, 8.8).

This study also investigated racial differences in the prevalence of type 1 diabetes complications in a national sample, to further explore the etiology of the disparity observed in overall mortality. The results showed that AAs with T1D had significantly higher rates of nephropathy and retinopathy, but borderline lower rates of CVD, compared to Caucasians. AAs with T1D also had higher rates of hypertension and hypercholesterolemia, both known risk factors for type 1 diabetes complications. After adjusting for demographic and clinical characteristics and risk factors, AAs remained at increased risk of having nephropathy and retinopathy. These data suggest that factors, either environmental or genetic, other than the traditional risk factors for complications, may play a critical role in the development of complications in AAs. Further research efforts are needed to identify these factors.

6.2 INCIDENCE OF DIABETES IN AFRICAN-AMERICAN YOUTH

This study assessed modern trends in incidence of diabetes, both type 1 and type 2, among youth in the USVI. While the sample size was small, some very important epidemiologic outcomes were observed and must be considered. The first is the unexplained increasing incidence of type 1 diabetes in African-American youth. Historically, African-American youth have maintained significantly lower rates of type 1 diabetes.[99] Early reports in the USVI indicated that Caucasians (28.9/100,000) had nearly 5-times increased risk compared to African-Americans (5.9/100,000). Based on this present analysis, this racial divide has virtually disappeared, with overall incidence rates in African-Americans (21.4/100,000) being comparable to Caucasians (24.7/100,000) in years 2006-2010. A similar story has been shown across other studies in the U.S.[94] In the 1980s, an early report from Southern California indicated that Caucasians (28.6/100,000) had a 2.9 –

fold increased risk of developing type 1 diabetes compared to African-Americans (9.9/100,000) in the same community. A subsequent report from Allegheny County, PA showed a reduced racial disparity, with Caucasians being at 1.5-times greater risk of having type 1 diabetes compared to African-Americans.[144] Furthermore, contemporary studies have found little to no racial disparity. The SEARCH for Diabetes in Youth Study, found a small racial gap in incidence for Caucasians (47.5/ 100,000) and African-Americans (28.3/100,000), with only a 0.6-fold difference. The increasing incidence of type 1 diabetes in African-Americans may be explained by a combination of genetic and environmental factors, but little effort has been made to specifically elucidate causes in African-Americans. This is largely because the overall etiology of type 1 diabetes remains unclear. It is difficult to investigate changes in subgroups, when research has not clearly identified overall causes. However, greater increases in ethnic minority groups, are likely major contributors to the persistent increase in worldwide incidence. There are a variety of suspected environmental and genetic causes involved in the etiology of type 1 diabetes, many of which are currently being investigated, including, viral infections, dietary exposures, maternal risk factors, and immunizations.[144, 145] Multiple genes have been shown to play some role in the development of type 1 diabetes, but genetic epidemiology studies have not focused on racial differences in these studies.[147] Yet, if there is some genetic difference by race, it is possible that the increase of racial admixture is in part contributing to the rise in incidence. Future studies may consider evaluating the incidence of type 1 diabetes in various subgroups of African-Americans (i.e. based on percentage of racial admixture).

A recent study also indicated that an increased humoral autoimmune response (antibody response produced by B cells) to islet antigens may be contributing to the increasing incidence.[148] While additional efforts are needed to understand the environmental and/or lifestyle

factors that result in the intensified autoimmune response, there may be some link with the commonly discussed association of type 1 diabetes and concomitant infections. In an effort to explain the epidemic like –increases in incidence that have been observed in various populations[149], researchers have focused some attention on the co-occurrence of "outbreaks" of viral infections, such as varicella and Dengue fever, suggesting that the immune system response initiated by these conditions is associated the onset of type 1 diabetes in youth. There were no data collected on viral infections in this study, but future registry follow-up may consider adding recent infections to the data collection form.

In addition, obesity has been suspected as a contributor to type 1 diabetes in youth.[150] This study indicated that the proportion of youth with type 1 diabetes that are overweight at diagnosis has increased. In earlier studies in the USVI, the majority of youth diagnosed with type 1 diabetes were underweight. A U.K.-based study also found that a higher BMI in childhood was an independent risk factor for type 1 diabetes.[145] However, consistent with findings from the SEARCH Study[15], another study in the U.K. found no association between BMI and type 1 diabetes.[151] In contrast, obesity was associated with type 2 diabetes in both studies and is clearly contributing to the rapidly increasing incidence of type 2 diabetes observed in the USVI and worldwide. Efforts to combat obesity and delay the progression of type 2 diabetes in youth must remain a primary public health objective.

A final consideration for the increasing incidence of type 1 diabetes is the impact of socioeconomic status. In our study, limited information was available on socioeconomic status, aside from insurance coverage. African-Americans had a significantly higher proportion of youth uninsured and publicly insured compared to other races, indicative of lower socioeconomic status. Interestingly, the relationship of type 1 diabetes and socioeconomic status does not seem

to be disadvantageous to those at lower socioeconomic conditions. The SEARCH Study showed that youth with type 1 diabetes were more likely to live in more affluent communities, with higher occupation and education levels.[152] The opposite relationship has been associated with type 2 diabetes in youth.[151] As such, socioeconomic status may certainly be contributing to the increase in type 2 diabetes observed in the USVI, but it is less likely to be a factor contributing to the increase in type 1 diabetes incidence.

The other major finding of this study relevant to type 1 diabetes incidence was the missing pubertal rise in incidence in African-American boys. As previously discussed, this finding was shown, but not highlighted, in previous assessments in the USVI and other population-based studies in the US, including the SEARCH Study (Figure 6).[5] There were no apparent differences in characteristics between African-American boys and girls in this study or the SEARCH Study.[17] In the SEARCH Study, a greater proportion of African-American boys were underweight at diagnosis compared to girls; however, this difference occurred across all age groups, suggesting that obesity is likely not a factor in the missing pubertal rise in boys. After a thorough review of literature, no major hormonal differences in African-Americans boys compared to boys of other races were identified. However, African-Americans boys were found to have secondary sexual characteristics (i.e. pubic hair) at higher frequencies at earlier ages, compared to Caucasian boys.[153] While this may be indicative of an earlier initiation of pubertal processes in African-American boys, it would not negate the traditional pubertal age ranges. One may even argue that this early puberty would then likely increase rates in pre-pubertal African-American boys, which is not the case. However, if obesity, which is more prevalent in girls than boys, is contributing to the increased incidence of type 1 diabetes, this would result in lower overall rates in boys. The combined effect of the two causative associations may contribute to the

"missing" pubertal rise in incidence. Nonetheless, this phenomenon in African-American boys merits further exploration. Research efforts to determine the etiology of type 1 diabetes should include specific analysis in pubertal African-American boys.

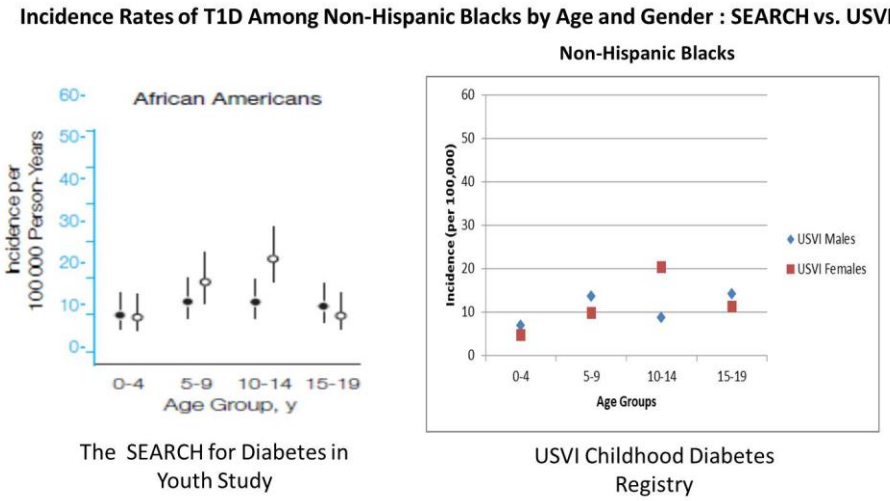

Figure 6: Incidence Rates of Type 1 Diabetes among Non-Hispanic Blacks by Age and Sex in the SEARCH and USVI Cohorts

6.3 TYPE 1 DIABETES MORTALITY IN AFRICAN-AMERICANS

This study also investigated type 1 diabetes mortality in African-Americans in the USVI using individuals registered in the Childhood Diabetes Registry during 1979-2005. While the study included all races, reflective of the general population, there were few cases of Caucasians (n=6) and Hispanics (n=20) in the cohort, and no deaths in Caucasians. This is the first ever mortality follow-up of type 1 diabetes in Hispanics. The overall mortality in Hispanics [1188 per 100,000 person years (95%CI 383, 3684)] was similar to African-Americas [1167 per 100,00 person years (95% CI 691, 1970)] in the USVI. Of greatest interest was mortality in African-Americans. There were no significant differences by race (African-Americans vs. Hispanics), sex, or

diagnosis year groups; however, there was a significant difference by age at onset groups. Individuals diagnosed post-puberty (>14) had significantly poorer survival than those diagnosed pre-puberty (<10) and during puberty (10-14). This finding was also observed in the Allegheny County, PA Registry cohort mortality follow-up, but not so dramatically. It has be postulated that the early years (pre-puberty) of type 1 diabetes are associated with minimal damage aside from acute complications and have a small impact on long term outcomes. In addition, it is possible that youth diagnosed later in adolescence are less likely to be compliant with recommended diabetes management and the lack of self-management during adolescent years may cause lasting damage and impact long term disease management. In the USVI, this phenomenon is likely further complicated by the limited health services available to youth with type 1 diabetes. As is likely the case in the contiguous U.S., education systems are not tailored to the specific needs of youth with chronic illnesses, particularly those that require daily management. In the USVI, many secondary schools have only one (or even no) school nurse, who is tasked with managing a large number of students. Thus, the youth are often on their own with maintaining their daily regimens, which often include at least three daily visits to the nurses' office to check blood glucose and/or administer insulin. This process is not only disruptive to the education process, but it can also be socially isolating for adolescents, which may encourage rebellion.

Many studies have reported worse type 1 diabetes mortality for African-Americans, compared to Caucasians.[24, 25, 26, 28, 105] As mentioned, there were no deaths in Caucasians in the USVI so a direct comparison could not be made; however, African-Americans in the USVI had significantly higher mortality compared to Caucasians in the Allegheny County, PA Registry cohort. Consequently, there were no significant differences in mortality or survival between African-Americans in the two cohorts. There has been a limited investigation into the exact

causes of the higher mortality seen in African-Americans. One possible mechanism is increased chronic complications. Though not a central focus of this study, all deaths (n=14), except one, in African Americans were due to chronic complications; the other death was due to acute complications. A similar pattern was observed in Allegheny County, PA. In contrast, in Caucasians in Allegheny County, PA, 16.7% of deaths were due to non-diabetes related causes, including accidents and cancer. Further understanding of type 1 diabetes complications in African-Americans may explain this disparity.

Also of interest, African-Americans in the USVI (SMR: 5.8 (95% CI 2.7, 8.8)) have comparable SMRs to African-Americans in Allegheny County, PA (SMR: 7.5 (95%CI 5.2, 9.8)) . Consequently, African-Americans in Allegheny County, PA also have similar SMRs compared to Caucasians in Allegheny County, PA (SMR: 7.5 (95% CI 6.3, 8.5)) . This paradox, of drastically higher mortality rates and comparable SMRs, remains unexplained. It is possible that similar factors contributing to increased background mortality are also contributing to the increased type 1 diabetes mortality in African-Americans; for example, increased risk of hypertension, chronic kidney disease, and coronary heart disease. Of note, there were no deaths due to accidents/violent crimes in either African-American cohort. The long term lifestyle modifications of patients with type 1 diabetes may impact their socialization and in fact protect them from risky behaviors that would lead to vulnerability to violent acts. In addition to further exploration of type 1 diabetes complications and risk factors in African-Americans, analysis of lifestyle factors may provide additional insight on the increased rates of type 1 diabetes mortality.

6.4 TYPE 1 DIABETES COMPLICATIONS IN AFRICAN-AMERICANS

Apart from mortality data, there are few data available exploring racial differences in type 1 diabetes complications. This type of analysis is critical, particularly in understanding the results of mortality studies and developing targeted approaches for reducing the morbidity of type 1 diabetes in African-Americans. The major finding of this study is that race appears to be associated with development of diabetic nephropathy and retinopathy, but not CVD. Glycemic control has been independently associated with nephropathy and retinopathy in both Caucasians and African-Americans with type 1 diabetes in the EDC Study and the NJ 725 Study.[52, 48, 138] Notably, significant racial differences have been observed in glycemic control. In the SEARCH Study, African-American youth had significantly higher HbA1C values at diagnosis, compared to Caucasian youth. A study, using NHANES data, demonstrated that African-Americans adults (36.9%) with diabetes were less likely to achieve optimal glycemic control compared to Caucasians (48.6%).[154]

A recent study using NHANES data indicated that nationwide rates of diabetic nephropathy are increasing.[130] It is not surprising that race significantly predicted nephropathy as African-Americans without diabetes are at increased risk for developing chronic kidney disease compared to Caucasians.[116] However, no direct comparison was made with the general population without diabetes. Future analysis may consider evaluating if the impact of race on nephropathy is greater in the type 1 diabetes population compared to the general population. In a multi-center study in the U.S. African-Americans with diabetes had 2.6-fold greater risk of microalbuminuria, compared to Caucasians.[136] Understanding the risk factors for developing nephropathy in African-Americans is critical. Researchers have postulated that African-Americans are genetically more susceptible to chronic kidney disease, through various genetic

pathways.[140] One report hypothesized that the over-expression or activation of a transform growth factor-beta (TGF-beta) signaling pathways may be contributing to the higher risk for various health conditions, including hypertension and ESRD, in African-Americans. Genetic studies have shown that African-Americans have a higher frequency of a specific mutation that may predispose them to TGF-beta over-expression and thereby increased disease risk.[155] The disparity seen in nephropathy may also be partially accounted for by African-Americans' increased risk for hypertension.

In previous studies, African-Americans have been shown to have higher rates of retinopathy compared to Caucasians, in cohorts with both type 1 and type 2 diabetes[156, 157, 158] and type 1 diabetes alone[49, 159], including a recent follow-up report from the SEARCH Study.[142] The NJ 725 Study, which was designed specifically to assess risk factors for retinopathy has reported that diabetes duration, glycemic control, age, and hypertension are associated with retinopathy in African-Americans, similar to the findings in this study.[48] As with nephropathy there is also some evidence that supports that genetics may play a role in development of diabetic retinopathy.[159]

Moreover, the results of this analysis indicate that factors other than the traditional risk factors are contributing to development of complications in African-Americans. One such risk factor is depression. The NJ 725 study demonstrated that depression was a risk factor for poor glycemic control, retinopathy, and nephropathy in African-Americans.[143] Individuals with depressive symptoms were nearly 2.5-times more like to develop retinopathy and 3.0-times more likely to develop nephropathy.[48, 143] The SEARCH Study found that African-American youth with diabetes were significantly more likely to have depressive symptoms compared to Caucasian youth.[160] Also, associated with depression and possibly with the increased risk of

complications in African-Americans is socioeconomic status. While household income was included in this analysis, future analysis may consider including a more comprehensive definition of socioeconomic status that accounts for geographic location, education level, and employment status. The EDC Study clearly demonstrated that lower socioeconomic status was associated with poorer glycemic control, which may the pathway to developing complications.

Of note, HbA1C was the primary indicator of glycemic control and individual diabetes management. While this is a relevant variable, it does not completely account for an individuals' diabetes management, particularly over a long period of time. Glycemic control combined with other variables, such as health care utilization and number of hospitalizations, would likely provide a more accurate account of individual diabetes management. These variables may possibly account for some of the racial differences in complications observed in this study.

A final consideration of these results is the poorer lipid profile observed in NHBs compared to NHWs. Despite similar mean total cholesterol, the mean HDL was lower for NHBs compared to NHWs. When stratified by sex, there were no differences between NHB males and females, as shown in Table 14 (below). When compared to the mean HDL of comparable age groups from the Lipids Research Clinics Program Prevalence Study[161] and the Bogalosa Heart Study[162], NHW males and females appear to have a higher mean HDL and NHB males and females have a comparable mean HDL. (Table 14) This suggests that NHWs with type 1 diabetes may have improved lipid profiles, compared to the general population; however, this advantage is not seen in NHBs. This difference may be associated with access and utilization of care. Patients with type 1 diabetes, likely have more contact with health care professionals for routine care. This may increase their likelihood of screening for co-morbid conditions as well as preventive care, such as statin therapy to reduce cholesterol. Though there were no race

differences observed in the overall use of such anti-cholesterol medications, there may be a difference in the time at which these therapies were initiated (prevention vs. treatment). This would support the hypothesis that NHBs have lower access to and utilization of the necessary health services, as a contributing factor to higher rates of complications.

Table 14: Mean HDL and Total Cholesterol for by race and sex in the NHANES T1D Sample, EDC Study (at baseline), LRC Prevalence Study, and Bogalusa Heart Study

	HDL Cholesterol (mg/dL)	Total Cholesterol (mg/dL)		HDL Cholesterol (mg/dL)	Total Cholesterol (mg/dL)
NHW Males			NHB Males		
NHANES Mean Age: 35.6± 2.1	58.8 ± 1.3	179.3 ± 1.9	NHANES Mean Age: 34.2±2.8	53.5 ± 3.0	182.5 ± 9.6
LRC Prevalence Study Age Group: 35-39	43.4 ± 0.6	201.3 ± 0.8	The Bogalusa Heart Study Age Group: 30-35	55 ± 2.6	191.6 ± 2.8
NHW Females			NHB Females		
NHANES Mean Age: 36.8±1.9	63.7 ± 2.5	191.4 ± 9.5	NHANES Mean Age: 33.0±1.6	54.6 ± 0.8	185.4 ± 2.6
LRC Prevalence Study Age Group: 35-39	55.0 ± 0.8	186.4 ± 0.7	The Bogalusa Heart Study Age Group: 30-35	56 ± 2.0	185.0 ± 1.8

Data are mean ± S.E.

In summary, the results of this study show racial differences in risk for nephropathy and retinopathy in type 1 diabetes. This increased risk is likely explained by a combination of increased genetic susceptibility, resulting in increased metabolic risk, and contributions of environmental factors, including socioeconomic status. While retinopathy is less commonly

associated with mortality, the increased risk of nephropathy in African-Americans with type 1 diabetes is likely a contributor to the consistently reported increased mortality.

There are some common implications of these studies. First, collectively these analyses, despite small sample sizes, suggest that African-Americans have increased morbidity and mortality due to type 1 diabetes compared to Caucasians. The increased risk of complications, as indicated by the NHANES analysis, is likely contributing to the increased risk of premature mortality, shown in this and previous mortality studies including African-Americans. In the mortality follow-up, 70.6% of deaths involved end-stage renal disease as a primary, contributing, or underlying cause of death. This is consistent with the increased risk of nephropathy in African-Americans found in the NHANES study. The increased morbidity and mortality coupled with the rising incidence of type 1 diabetes shown in the registry follow-up, depicts a progressing health disparity for African-Americans. Secondly, the similarities noted across these studies suggest that African-Americans experience similar disparate burden of type 1 diabetes across different geographic locations. This implication is supported by the similar incidence rates for non-Hispanic blacks in the USVI and other cohorts in the US, the comparable mortality experience in the USVI and Allegheny County, PA cohorts, and the confirmed rates of complications in the NHANES study compared to other cohort studies. This consideration is important for interpreting future epidemiologic investigations exploring racial differences in the burden of type 1 diabetes.

In addition, these studies strongly suggest that conventional knowledge of the natural history of type 1 diabetes may not fully account for the burden of the disease in African-Americans, including incidence patterns and risk factors for complications. Furthermore, these analyses confirmed findings related to the natural history of type 1 diabetes from previous U.S-

based studies.. This implication is particularly important in generalizing results from existing prospective cohort studies, both the EDC Study and the New Jersey 725 Study, which only reflect small geographic areas.

Finally, the individual analyses are handicapped by small sample sizes. In public health research, large samples are not always available and commonly not available for rare conditions or diseases. The results abstracted from these analyses provide an example of the significance of studying small populations, despite difficulties in detecting small differences, and the types of implications that can be made for larger populations and developing future research priorities. Various statistical methods to account for small sample sizes were used in each of these analyses, namely Fischer's exact test for categorical comparisons and the Poisson distribution for hypothesis testing.

6.5 STRENGTHS AND WEAKNESSES

This study has several strengths that should be noted. The study provides contemporary insights on the burden of type 1 diabetes in the USVI. The registry update had 96.7% case ascertainment, estimated using the well-established capture-recapture method. The mortality follow-up, which confirmed vital status of 91% of cases in population-based registry, is the first in this minority population and in the entire Caribbean region. This study serves as a foundation for investigating temporal trends in mortality in the territory. In addition, data from a nationally representative survey, with standardized methods, was used to investigate the impact of race on type 1 diabetes complications.

The primary weakness of this study is the small sample sizes in each of the individual analyses. The general population in the USVI is small and not ideal for epidemiological investigations of rare conditions; however, this does not negate the public health significance of understanding these conditions in this and other small populations. As indicated by this study, these studies can provide insight relevant to larger populations. In addition, the absolute number (n=80) of cases in the NHANES analysis was small; our power to detect differences was strengthened by the weighted adjustments for the sampling methods. In addition, as previously discussed, the NHANES analysis was limited by the exclusion of glycemic control as a risk factor for complications.

6.6 FUTURE RESEARCH

While this study has addressed the outlined objectives, there are several research questions that remain unanswered. First, additional research is needed to understand the environmental factors that contribute to the epidemic-like increases in type 1 diabetes incidence. To further explore the concomitant disease hypothesis, researchers may combine data from this study with incident data of varicella (Chicken Pox) and Dengue Fever in youth. Also, information about exposure to these conditions may be added to data collection for future registry updates. Secondly, the missing pubertal rise in African-American boys should be investigated further. The SEARCH Study may be an ideal place to expand this investigation as they have collected extensive demographic and clinical data on study participants.

The impact of race on type 1 diabetes complications also remains unclear. While there are obvious differences in mortality and prevalence of complications, the factors associated with

these differences need further epidemiologic investigation. A longitudinal prospective cohort study with a sufficient sample of African-Americans is of course the ideal method. However, combining individual level data from the Epidemiology of Diabetes Complications Study and the New Jersey 725 Study is a logical next step to establish clear research questions and hypotheses for a large cohort study. Finally, national surveys, including NHANES, National Health Interview Survey, and the Behavioral Risk Factor Surveillance System, should modify current questionnaires to clearly distinguish between types of diabetes. This will allow further exploration of frequency, distribution and determinants of type 1 diabetes and its complications in the nation. This would also allow continuous monitoring for temporal improvements.

6.7 PUBLIC HEALTH IMPLICATIONS

Despite significant advances in diabetes care, management, and outcomes in recent decades, African-Americans remain at increased risk of mortality and based on the results of this study, complications. The current study adds significantly to the knowledge of contemporary trends of type 1 diabetes incidence in ethnic/minorities. Ongoing efforts to monitor the increasing incidence must continue in the USVI and the contiguous US. The study, for the first time, assessed the morbidity of type 1 diabetes in the USVI. Historically, rates of type 1 diabetes in the territory have remained lower than the contiguous US, but this study has shown a dramatic increase over the past decade. This increase is of great public health significance, as the current health care infrastructure in the USVI is not designed to manage a large population of youth with diabetes. The results of this study should be used to support efforts to increase access to medical specialty and diabetes supportive services for youth in the territory; particularly, with the

apparent disproportionate impact of type 1 diabetes on African-Americans. Additional efforts to provide intensive care to high-risk African-American youth may be a possible approach to reducing the gap in complications and mortality. There are few studies evaluating racial differences in type 1 diabetes complications, but this study emphasizes the necessity for additional research to understand the factors contributing to poorer outcomes in African-Americans. Most studies have focused on racial differences in diabetes complications in cohorts with type 2 diabetes, but the etiological differences and management of type 1 and type 2 warrant separate analysis.

APPENDIX

Repeatability and Validity of a Self-Reported Survey of Complications in Type 1 Diabetes

Abstract submitted and accepted for publication by the *American Diabetes Association Scientific Sessions 2011*

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Abstract

Self-reported data on the epidemiology of T1D complications has not been extensively validated. The repeatability and validity of a 5-page survey, developed to collect self-reported data on physician-diagnosed diabetes complications, treatment, health-care utilization and demographic factors for randomly selected participants in the Allegheny County, PA T1D Registry were therefore evaluated. The characteristics of those discordant on the basis of agreement of repeated surveys (n=30) approximately 1 year apart for participants or for validity, the survey responses of 30 participants who were examined 2-3 years earlier. Kappa statistics (k) were calculated to determine agreement between repeated surveys and between the survey and clinical exam. High reliability agreement (k>.60) was observed for all complications and risk factors, except stroke (k=.03) and peripheral vascular disease (k=.46), both of which had a low overall prevalence, in the repeated surveys. A high level of agreement was also observed in the validation with clinical exam data, with lesser agreement (.40<k<.60) being shown for overt nephropathy (k=.46) and high triglycerides (k=.52). In the repeatability sample, individuals discordant for at least one complication appeared less likely to check blood glucose regularly (p=.160). In the validity sample, discordant cases were significantly less likely to have seen a physician in the last year for routine care of diabetes (p=.02) and, though statistically non-significant, were twice as likely to be male (p=.12) and less likely to check their blood glucose 3+ times daily (p=.10). There were no differences by concordance for mean age, diabetes duration, or HbA1c. Though the results of this analysis show high repeatability and validity and little bias of self-reporting of complications and risk factors among patients with T1D, less frequent physician follow up was associated with invalid survey responses.

Introduction

Patients with Type 1 diabetes often experience microvascular and macrovascular complications throughout their lives. Researchers investigating the epidemiology of these complications and risk factors often rely on self-reported data to ascertain incidence and prevalence.[44, 163] Validation studies in other populations have shown self-reported data to be an accurate tool for assessing prevalence of disease, but results are inconsistent for assessing incidence of disease.[164, 165, 166, 167, 168] In addition, previous studies evaluating the reliability and validity of self-reported data have demonstrated variability in the accuracy of patient reporting, based on the disease or condition.[169, 170, 171, 172, 173]

The Diabetes Epidemiology Research International Study, is a multi-centered population-based study of the incidence of Type 1 diabetes in 50 countries. The Allegheny County, PA center recently reported 30-year all-cause mortality.[29] As a part of this follow-up, researchers developed a brief questionnaire to assess the prevalence of complications in the population. The reliability and validity of this questionnaire is uncertain. The objective of this study was to evaluate the reliability and validity of this self-administered questionnaire through agreement of repeated surveys and clinical exams.

Methods

Survey development

A 5-page survey was developed to collect self-report data on physician-diagnosed diabetes complications, common diabetes treatments, health-care utilization, and demographic and socioeconomic factors for participants in the Allegheny County, PA Type 1 Diabetes

Registry. This survey was created based on surveys developed and validated for the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. [44]

Study population

The Allegheny County, PA Type 1 Diabetes Registry cohort (*n*=1,075) comprised all individuals diagnosed in Allegheny County, PA with childhood-onset (age<18 years) type 1 diabetes between 1 January 1965 and 31 December 1979, and placed on insulin at diagnosis. Ascertainment levels exceeded 95%.[29] Individuals with diabetes from a secondary cause (i.e., cystic fibrosis, Down's syndrome, or steroid-induced diabetes) were excluded.

To determine vital status as of 1 January 2008, all participants were mailed an Allegheny County, PA Type 1 Diabetes Registry survey and consent form. Individuals who failed to respond to mailings were contacted by telephone. The study protocol was approved by the University of Pittsburgh Institutional Review Board.

Data collection

To assess the reproducibility of the survey, we randomly selected 30 respondents, and mailed the same survey approximately one year after their initial response. We compared the responses between the two surveys.

To validate the self-report data in this study, we selected 30 Allegheny County, PA Type 1 Diabetes Registry participants who were also participants in the Pittsburgh EDC Study. Based on the18-year follow-up EDC examination data, an Allegheny County, PA Type 1 Diabetes Registry survey was completed.[75] This was then compared to the self-reported survey responses to determine the proportion of concordance. Incident cases of complications/risk factors were removed from all analyses for each complication/risk factor independently.

Statistical Analysis

Kappa statistics and their 95% confidence intervals were calculated to determine agreement between repeated surveys and the initial survey and the survey produced from exam results. Scores of 0.0-0.4 correspond to a low agreement; 0.4-0.6 , intermediate agreement; 0.6-0.8, high agreement; and 0.8-1.0, very high agreement. All statistical analysis was conducted using SPSS statistical software.

Results

The results of the repeatability analysis are shown in Table 1. Very high agreement was observed for coronary heart disease (k=.82), retinopathy (k=.80), neuropathy (k=.91), nephropathy (k=.87), hypertension (k=.93), high cholesterol (k=.80), high triglycerides (k=.84), current and ever smoking (k=1.00), and cataract (k=.86). High agreement was observed for glaucoma (k=.78). Low agreement was observed for both stroke (k=.03) and peripheral vascular disease (k=.46), both of which had very low prevalence in the sample.

The results of the validity analysis are shown in Table 2. Similar to the repeatability results, very high agreement was observed for proliferative retinopathy (k=.92) and hypertension (k=.91). High agreement was observed for neuropathy (k=.67), any proteinuria (k=.62), and high cholesterol (k=.73) and intermediate agreement was observed for overt nephropathy (k=.46) and high triglycerides (k=.53). Again, where very low prevalence of the health condition occurred, poor agreement was observed, as shown with peripheral vascular disease.

Characteristics of participants by reporting behavior and complication/risk factor status for the repeatability and validity samples are shown in Tables 3 and 4. There were no significant differences in characteristics between individuals with consistent reporting compared to those that reported discordantly in the repeatability sample. However, in the validity sample, concordant cases were more likely to have seen a physician with the past year for routine care of

diabetes (100%) compared to discordant cases (71.4%) (p=.02). Also, discordant cases were more likely to be uninsured (7.1%) compared to concordant cases with complications (0%) (p=.03).

Discussion

This analysis demonstrated the repeatability and validity of self-reported data collected via a self-administered questionnaire to patients with type 1 diabetes. Overall, repeatability was high for all complications and risk factors, except stroke and peripheral vascular disease. Of note, both of these conditions had a low overall prevalence in the sample population. This finding may be less associated with specific conditions, and more broadly suggests that self-reported data of low occurring conditions is less reliable. Similarly, the validity of the complications and risk factors was high for all conditions except overt nephropathy, which had a low overall prevalence. As overt nephropathy may or may not be symptomatic, it is possible that the case that was not confirmed had not been formally diagnosed; however, all study patients (and respective physicians) are notified of study results. Furthermore, these results also indicated that individuals who self-reported invalidated responses were more likely to not have seen a physician for routine care within the last year. Consequently, a higher percentage of individuals who self-reported invalidated responses were more likely to be uninsured, which is likely a factor in the decreased proportion receiving routing diabetes care. The primary limitation of this study is the small sample size. In addition, the validity analysis is limited in that the examinations occurred prior to the self-administered questionnaire, and there may be some impact of time, though conditions developed during the lapsed time were not included. In conclusion, these results provide useful insights into the reliability of self-reported responses in long-term follow-up studies of

individuals with type 1 diabetes and provide some significant implications for other studies utilizing self-reported data collected via self-administered questionnaire.

Table 15: Repeatability Analysis for Complications and Risk Factors – DERI Repeated Surveys Sample

Complication/Risk Factor	# Cases	# Confirmed Cases from Repeated Survey	# New Cases in Repeated Survey	Kappa Statistic	P-value
Coronary Heart Disease	8	6	0	.82	<.01
Stroke	1	0	1	.03	.85
Peripheral Vascular Disease	2	1	1	.46	.01
Retinopathy	15	13	1	.80	<.01
Neuropathy	11	11	1	.91	<.01
Nephropathy	14	12	0	.87	<.01
Hypertension	10	10	1	.93	<.01
High Cholesterol	17	16	2	.80	<.01
High Triglycerides	3	3	0	.84	<.01
Current Smoke	3	3	0	1.00	<.01
Ever Smoke	8	8	0	1.00	<.01
Cataract	10	10	2	.86	<.01
Glaucoma	2	2	1	.78	<.01

Table 16: Validity Analysis for Complications and Risk Factors – DERI and EDC C10 Medical Examination

Complication/Risk Factor	# Cases (Exam)	# Cases Confirmed by DERI	# Unconfirmed Cases by DERI	Kappa Statistic	P-value
Peripheral Vascular Disease	1	0	1	---	---
Proliferative Retinopathy	10	9	1	.92	<.01
Neuropathy	10	6	4	.67	<.01
Any Proteinuria	7	5	2	.62	.01
Overt Nephropathy	2	1	1	.46	.01
Hypertension	6	5	0	.91	<.01
High Cholesterol	15	11	4	.73	<.01
High Triglycerides	5	2	3	.53	.01

Table 17: Characteristics of Participants by Reporting Behavior and Complications/Risk Factor Status – DERI Repeated Survey Sample

	Concordant Cases		Discordant Cases (*n*=15)	p-value†	p-value‡
	No Complications/ Risk Factors (*n*=4)	Complications/ Risk Factors (*n*=11)			
Age (years)	36.0	45.9	47.3	.58	.20
% Female	75.0	40	45.5	.23	.70
% Disabled (*n*)	0	26.7	0	.11	.10
% Employed	75.0	80.0	81.8	.45	.40
% Check Glucose <3 times/day	25.0	20.0	45.5	.17	.16
% Not seen physician in last year for routine care of diabetes	0	6.7	18.2	.36	.26
Average # of Routine Care Visits	2.0	3.4	2.9	.10	.18
% Consulted with Diabetes Educator in Past Year	25	20	27.3	.68	.85
% Uninsured	0	0	0	--	--

†Student T-test of Independent Samples | Pearson χ^2 for Concordant Cases w/ Complications/Risk Factors vs. Discordant Cases

‡ Student T-test of Independent Samples | Pearson χ^2 for All Concordant Cases vs. Discordant Cases

Table 18: Characteristics of Participants by Reporting Behavior and Complications/Risk Factor Status – EDC/DERI Validity Sample

	Concordant Cases		Discordant Cases (*n*=14)	p-value†	p-value‡
	No Complications/ Risk Factors (*n*=7)	Complications/ Risk Factors (*n*=9)			
Age (years)	41.6	42.6	41.5	.85	.96
Diabetes Duration (years)	31.9	32.5	32.2	.62	.78
$HbA1_C$	7.4	7.1	7.1	.93	.81
% Female	71.4	44.4	28.6	.43	.13
% Disabled	14.3	22.2	7.1	.44	.38
% Employed	77.8	71.4	71.4	.99	.88
% Check Glucose <3 times/day	0	11.1	28.6	.22	.10
% Not seen physician in last year for routine care of diabetes	100	100	71.4	.07	.02
% Consulted with Diabetes Educator in Past Year	28.6	11.1	14.3	.87	.67
% Uninsured	0	0	7.1	.41	.03

†Student T-test of Independent Samples | Pearson χ^2 for Concordant Cases w/ Complications/Risk Factors vs. Discordant Cases
‡ Student T-test of Independent Samples | Pearson χ^2 for All Concordant Cases vs. Discordant Cases

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