

MORTALITY TRENDS IN A POPULATION-BASED TYPE 1 DIABETES COHORT

by

Aaron M. Secrest

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M.P.H., University of Pittsburgh, 2008

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This dissertation was presented

by

Aaron M. Secrest

It was defended on

May 25, 2010

and approved by

Committee Members:

Dorothy J. Becker, M.B.B.Ch.
Professor, Department of Pediatrics
School of Medicine, University of Pittsburgh

Sheryl F. Kelsey, Ph.D.
Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Ronald E. LaPorte, Ph.D.
Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Dissertation Advisor:

Trevor J. Orchard, M.B.B.Ch., M.Med.Sci.
Professor & Interim Chair, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

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Individuals with type 1 diabetes (T1D) have significantly higher mortality rates than their peers in the general population. Major advances in the management of T1D occurred during the 1980s and 1990s, but recent data on their long-term effects on overall and cause-specific mortality are limited, especially in the United States. A phenomenon, known as *dead-in-bed* syndrome, is of particular concern as it occurs in young, healthy T1D individuals who are unexpectedly found dead in bed. Using follow-up data from a large population-based cohort, this dissertation provides contemporary mortality rates in persons with long-standing T1D. Cause-specific mortality is also explored, focusing on how mortality rates from major causes compare to the general population and on characterizing T1D deaths that meet the criteria for *dead-in-bed* syndrome.

Overall, the mortality of individuals with T1D is seven times higher than seen in the general population. T1D individuals diagnosed more recently have significantly lower mortality rates than those diagnosed earlier, even after controlling for age. The greatest improvements in mortality have occurred in deaths from diabetes-related causes (diabetic coma, renal disease, cardiovascular disease, or infection), suggesting long-term benefits to improved T1D care. In a pattern quite contrary to what is seen in the general population, females with T1D have a higher mortality than males with T1D, especially from diabetes-related causes. While African-

Americans with T1D have much higher mortality rates than T1D Caucasians in this cohort, this racial difference was similar to that seen in the general population. Finally, *dead-in-bed* syndrome in this population appears associated with male sex, low BMI, and disturbed metabolic control (high HbA_{1c}, high daily insulin dose, and a history of severe hypoglycemia).

The public health implications of this dissertation are considerable, as it provides insight into the causes of premature mortality in T1D, permitting the development of more effective and targeted preventative strategies. These findings also have the potential to change routine care practices to address disparities by race and sex in T1D mortality, and resolve disparities in health and life insurance provisions, since antiquated T1D mortality estimates are currently used, which do not account for recent advances in T1D treatments.

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PREFACE

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1.0 INTRODUCTION

Diabetes mellitus refers to a cluster of diseases where abnormal insulin production or action leads to high levels of blood glucose. Persistent elevations in blood glucose lead to a myriad of acute and chronic complications, and often, to premature death. Advances in the detection and treatment of diabetes and its complications have dramatically improved life expectancy in individuals with diabetes over the past century.

Diabetes mellitus can be broadly grouped into two main entities: type 1 (T1D) and type 2 (T2D). Although the etiology of and risk factors for T1D and T2D are quite different, both result in chronic hyperglycemia, which leads to similar renal, cardiovascular, neurologic, and ocular complications. T2D incidence is increasing, driving the current *diabetes epidemic*, and accounting for the vast majority (90-95%) of the estimated 23.6 million diabetic persons in the U.S.¹ Worldwide estimates project diabetes to affect 439 million individuals by 2030, up from an estimated 285 million at present.² Recent yearly estimates of diabetes-related deaths range from 1.1-4 million worldwide, including nearly 250,000 deaths in the U.S. alone each year.¹⁻³

This review focuses on T1D, which roughly accounts for the other 5-10% of people in the U.S. with diabetes.¹ The incidence of T1D is on the rise both in the U.S. and worldwide.^{1, 4-10} U.S. T1D incidence rates are currently 14.3, 22.1, 25.9, and 13.1 per 100,000 for youth aged 0-4, 5-9, 10-14, and 15-19, respectively; however, worldwide incidence rates vary dramatically.^{11, 12} Approximately one in 500 children/adolescents in the U.S. has T1D. As T1D is often diagnosed earlier in life than T2D, premature mortality disproportionately occurs in T1D.

2.0 BACKGROUND

2.1 PATHOPHYSIOLOGY OF TYPE 1 DIABETES MELLITUS

T1D is an autoimmune disease characterized by the destruction of insulin-producing beta cells in the pancreatic islets of Langerhans, through a cell-mediated immune response. The etiology of T1D (formerly termed insulin-dependent diabetes, juvenile diabetes, and early-onset diabetes) is currently unknown but thought to result from an environmental trigger in genetically susceptible individuals.^{7, 13-17} Genetic susceptibility plays a significant role in the development of T1D, in that the disease has up to 50% concordance in identical twins.¹⁴ The body produces autoantibodies against the environmental factor(s), and these antibodies inappropriately recognize beta cells as foreign leading to cell-mediated destruction of these cells, with a consequent decline in beta cell function. This autoimmune process develops over a period of months to years, gradually rendering the individual insulin-deficient.¹⁸

Insulin is a peptide hormone secreted from pancreatic beta cells in response to food intake to tightly regulate glucose metabolism in the body. Insulin binds to receptors in many cells (particularly adipocytes and myocytes) to enhance cellular uptake of glucose either to be metabolized for energy or stored for later use. Without insulin to help maintain glucose homeostasis, levels of glucose in the blood rise precipitously. The body attempts to filter and excrete the excess circulating glucose through the kidneys, but large amounts of water must also

be excreted with the excess glucose. Meanwhile, the muscle and liver cells cannot uptake glucose and signals are sent to the brain to increase caloric intake. This perpetuates the cycle and leads to persistent hyperglycemia. The combination of these processes produces a classic triad of symptoms – polyuria, polydipsia, and weight loss. These symptoms typically do not appear until at least 80% of the body’s beta cell mass has been destroyed and often emerge during an acute illness. Unless exogenous insulin is administered, the process leads to muscle wasting and eventually death.

2.2 NATURAL HISTORY OF TYPE 1 DIABETES MELLITUS

Sometimes, after the initial diagnosis of T1D, a “honeymoon” phase occurs wherein the body can achieve good glycemic control with smaller doses of insulin. The “honeymoon” phase lasts weeks to months and is thought to be due to partial recovery of beta cell function.

Diabetes is a progressive chronic disease with multiple complications, including premature death. These complications are the result of either vascular or nerve damage caused by chronic hyperglycemia. Nerve damage can be either autonomic or peripheral neuropathy. Autonomic neuropathy can lead to multiple complications, including cardiac arrhythmias or gastroparesis. Peripheral neuropathy (combined with lower extremity arterial disease) can lead to diabetic foot ulcers, gangrene, and amputations.

Vascular damage can be categorized as either microvascular or macrovascular. Microvascular damage leads to many various complications, such as retinopathy, nephropathy and neuropathy. Macrovascular complications consist of peripheral vascular disease (including

lower extremity arterial disease), coronary artery disease (CAD) and cerebrovascular disease. Most individuals with long-term T1D will develop one or more of these major complications, many of which cause or contribute to premature death.¹⁹ Renal disease and cardiovascular disease (CVD) often coexist, since kidneys help control blood pressure. The interplay between renal disease and CVD in T1D mortality, however, is poorly understood. Some individuals develop CVD without even subclinical evidence of renal disease (i.e., microalbuminuria). Therefore, insight into the true causes of death in T1D and the role diabetes plays in T1D mortality would prove beneficial.

2.3 MORTALITY IN TYPE 1 DIABETES

2.3.1 Pre-1980 Era

Prior to the discovery of insulin in 1921 and its availability in bovine form in 1922, dietary restrictions and supportive therapies could usually only delay mortality for 1-2 years after onset of T1D symptoms. Based on mortality data from the Joslin Clinic in Boston, MA, T1D patients dying within the first 10 years of life improved dramatically from 824.0/1000 in 1897-1914 to 386.1/1000 in 1914-1922 down to 61.4/1000 in 1922-1926, a six-fold reduction immediately after bovine insulin became available.²⁰ As the purity of bovine, and later porcine, insulin improved and more standardized treatment plans were developed, these mortality rates continued to decline to 1.0/1000 in 1950-1961 for T1D patients dying at age ≤ 10 years.²⁰

A number of other diabetes clinics also reported their T1D mortality experiences during the 1920s and 1930s. Mortality ranged from 30-50% for patients diagnosed with T1D in the 1920s and followed for at least 20 years, with little difference observed by sex.^{21,22} Looking at the causes of death at this time, acute diabetes complications like diabetic ketoacidosis or hypoglycemia were relatively common, ranging from 15-40% of all T1D deaths during the 1920s at various clinics.^{20,21,23,24} However, as insulin dosage improved, acute complications quickly became rare at these clinics, accounting for less than 5% of all T1D deaths by 1943.^{20,21,23} By the 1950s and 1960s, Joslin Clinic was reporting that diabetic comas accounted for 1% or less of all deaths in their patients.^{25,26}

Prior to the discovery of antibiotics in the 1940s, infections accounted for 10-20% of all deaths, but this figure dropped to 5-6% after antibiotic use became widespread.²⁰ In the 1950s, as studies now had follow-up data on T1D patients with 30+ years diabetes duration, the effects of long-term diabetes complications (i.e., renal disease, cardiovascular disease, hypertension, and neuropathy) became apparent in mortality studies.^{20,23,27} Although many T1D patients were now surviving to early adulthood with insulin therapy, their lifespan remained significantly shorter than the general population due to frequent T1D complications.²⁰ A Joslin Clinic study found that after 35 years of diabetes duration, cardiovascular disease was the most common cause of death.²⁸ Between 1956-1962, cardiovascular disease accounted for nearly 65% of all T1D deaths.²⁰ Another Joslin report showed that the proportion of deaths caused by combined cardiovascular and renal disease tripled by the 1960s compared to the pre-insulin era (76.6% vs. 24.6%).²⁹ Other researchers were also finding that both renal disease and cardiovascular disease were causing higher proportions of deaths in their T1D populations.^{30,31}

Interestingly, one of these studies (from Cincinnati, OH) was the first real attempt to standardize T1D cohorts and compare cumulative mortality at different clinics. This 1971 study reported that at 25 years T1D duration, cumulative mortality in Cincinnati was 20%, compared to 19% in Boston, and 22% in Stockholm, Sweden.³¹ In addition to this study, other studies reported that cumulative mortalities for long-term T1D were declining to less than 20% after 10 to 30 years T1D duration.³²⁻³⁴ This represents a notable decline from T1D patients diagnosed in the 1920s with cumulative mortalities between 30-50%.^{21, 22}

A few studies during this pre-1980 era used cohorts who purchased or applied for life insurance policies. A 1967 study did not differentiate T1D and T2D; however, looking only at those diagnosed by age 30 from 1935 to 1963, there was a six-fold greater mortality compared to that expected based on the non-diabetic population of policyholders, with excess mortality largely due to cardiovascular disease.³⁵ Using life insurance applicants between 1950 and 1971, those diagnosed with diabetes by 15 years of age had an 11.3-fold increase in mortality compared to that expected based on non-diabetic applicants. These data were used to calculate a life expectancy of 32 years for those with T1D.^{36, 37}

Through improved glycemic regulation with insulin, T1D patients avoided acute complications like diabetic ketoacidosis only to develop long-term complications, namely, diabetic nephropathy, retinopathy, neuropathy and cardiovascular disease.³⁸ Smaller studies provide insights into how T1D mortality varied by population and by country. One study examined only black T1D patients at two diabetes clinics in the U.S. The authors reported a two-fold excess in mortality compared to the general black population.³⁹ Another study from Denmark assessed mortality in an insulin-treated, population-based cohort after seven years of follow-up. Overall, the mortality in this population was four times the general population.^{40, 41}

The authors were the first to note a significant underreporting of diabetes on the death certificates of diabetic individuals.⁴¹ This topic will be addressed specifically later in this review.

Reports on T1D mortality from the Joslin Clinic in Boston and the Steno Clinic in Denmark are among the most reliable in terms of large, T1D clinic populations. However, these clinics were not representative. Diabetic patients were referred to these clinics from all over their respective countries, which explains why the Steno Clinic study included many patients whose first visit occurred at least 10 years after diabetes onset.³⁸ The Joslin Clinic studies limited inclusion to Massachusetts residents seen at the clinic within 1 year of diagnosis, decreasing the selection bias, but both of these clinics failed to address the representativeness of their cohorts to the T1D population in their respective countries.^{25, 42, 43} These reports estimated mortality rates 2-14 times higher than the general population with extremely high mortality rates occurring after age 35.^{20, 25, 38, 42-45} However, these studies might have overestimated mortality rates due to patient selection bias and failure to distinguish between T1D and T2D patients in the older age-groups.

The most reliable and accurate early T1D mortality data comes from work by Sultz and colleagues in Erie County (Buffalo), NY.⁴⁶ In a population-based analysis of all major childhood diseases, these researchers examined hospital, specialist, vital, and school records to ascertain childhood diseases (including T1D) in all persons < 16 years of age diagnosed between 1946 and 1961. They found 389 persons with T1D (13 were non-white) providing an annual incidence ranging between 5.8-12.6/100,000 children at risk. Only 7 deaths occurred during the study period, with higher case-fatality rates in females, low income, and non-white T1D persons. The overall mortality rate in this population was 4.1/1,000 patient-years.⁴⁶

In summary, the findings of these early studies showed dramatic improvements in overall mortality in T1D. Also, the mortality pattern in T1D patients shifted from mostly acute complications in the 1920s and 1930s to mostly chronic diabetes complications since the 1940s.

2.3.2 Post-1980 Era

During the 1980s, a major shift in T1D diabetes research occurred. Although the results from the large diabetes clinics greatly increased the body of knowledge about T1D, these clinics lacked the representativeness necessary to determine the actual burden of disease. A number of large, population-based T1D registries were developed to assess geographic variations in T1D incidence both within and across countries as part of two large international studies – EURODIAB and the World Health Organization’s DIAMOND Project. EURODIAB consisted of 13 T1D cohorts diagnosed since 1989 in 12 countries (total $n=28,887$).

Another goal of these registries was to determine the etiology of T1D. Though the etiology goal has not yet been realized, significant work has been done on the DIAMOND Project to show the wide variations in T1D incidence across populations.^{12, 47-50} In the seminal report on international variations of T1D incidence, incidences ranged from 0.1/100,000 in Venezuela and China up to 36.8/100,000 in Sardinia and 36.5/100,000 in Finland – a >300-fold difference.⁵⁰

2.3.2.1 Population-based Studies

Allegheny County Type 1 Diabetes Registry and Pittsburgh Epidemiology of Diabetes Complications (EDC) Study

An early attempt at obtaining a representative cohort came from a Children's Hospital-based T1D registry in Pittsburgh established in the 1980s.⁵¹ Researchers evaluated mortality in 1966 T1D individuals diagnosed between 1950 and 1981, which represented >60% of the T1D population in the county. The authors determined that demographic characteristics between the hospital-based registry and the population-based county registry were similar.^{52, 53} As seen in Figure 1, mortality among T1D patients in the hospital-based registry compared to that expected for the U.S. population of the same age ranged from 5.4 times higher for T1D males to 11.5 times higher for T1D females.⁵¹ Mortality rates were most dramatic in T1D persons over 25 years of age, where >2% died annually, which translated into mortality rate approximately 20 times higher than the general U.S. population.⁵⁴ The Pittsburgh EDC Study developed out of the Children's Hospital T1D registry in Pittsburgh.^{51, 54, 55}

A population-based county registry was also developed at this time – the Allegheny County Type 1 Diabetes Registry – which included all individuals diagnosed with T1D between 1965 and 1979 and treated with insulin in the county ($n=1,075$).^{52, 53} A detailed overview of this registry is presented in Section 3.1. Early Allegheny County T1D Registry findings showed that although Caucasian children had incidence rates 1.5 times higher than African-American children, African-Americans had 2.4 times the risk of early T1D mortality compared to Caucasians.⁵⁶ Recently, mortality in the Allegheny County T1D cohort was examined relative to a comparable T1D population in Cuba, where the incidence of T1D is much lower than in the

U.S. The study showed a two-fold excess in T1D mortality in Cuba, with nearly half of the Cuban deaths related to nephropathy (49% vs. 13% in Allegheny County).⁵⁷ Most interestingly, however, the proportion of T1D deaths due to acute complications was higher in Allegheny County than in Cuba. This finding paralleled previous results showing that the Allegheny County cohort had a higher proportion of T1D deaths due to acute complication than Finland (46% vs. 33%).^{58, 59} These findings suggest that cross-country differences exist in access to acute and chronic care in the two populations.

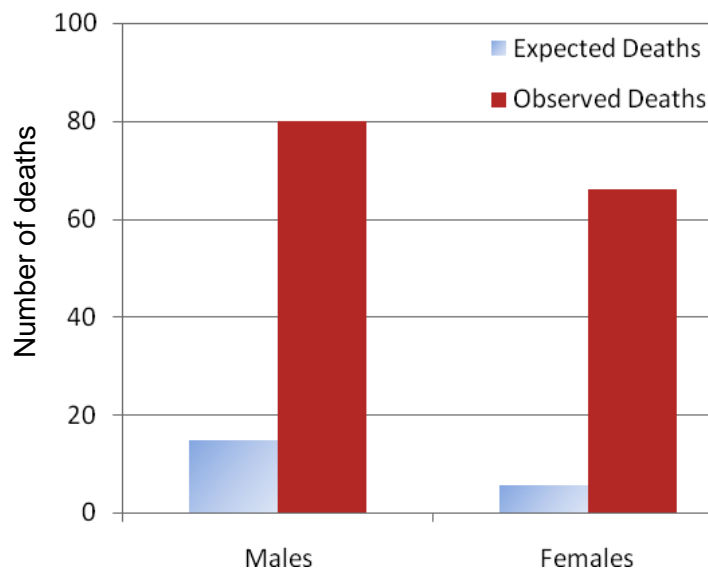


Figure 1: Number of deaths among T1D patients at Children’s Hospital of Pittsburgh compared to the U.S. population.⁵¹

Key Allegheny County/EDC Findings

Race/ethnicity

Two 1996 reports examining mortality in Allegheny County through 1990 stratified by T1D duration and found that African-American participants were 1.7-2.5 times more likely to die than Caucasians, confirming earlier speculation.^{56, 60-62} In fact, at the 1990 follow-up 14.9% of the African-Americans had died compared to only 6.6% of the Caucasian participants.⁶¹ As of

1999, the overall mortality rate in the Allegheny County T1D cohort was 627 per 100,000 person-years, with significantly higher mortality rates seen in African-Americans compared to Caucasians.⁶³ A more detailed analysis, combining data from both Allegheny County T1D Registry and Pittsburgh EDC studies, showed that African-Americans with T1D had nearly 5 times higher risk of death from acute complications compared to Caucasians, similar to findings in another recent study on T1D mortality in childhood.^{64, 65} Encouragingly, time trend analysis in this population showed decreasing trends in T1D mortality by diagnosis cohort.^{63, 64}

Risk factors for T1D mortality in EDC Study

1) Subclinical markers of atherosclerosis and renal disease

The Pittsburgh EDC Study examined predictors of mortality at 10 and 12 years follow-up. The authors found that an ischemic electrocardiogram (ECG) at baseline was an independent predictor of mortality, after adjusting for other known risk factors – T1D duration, prevalent coronary artery disease, overt nephropathy, non-HDL cholesterol, and smoking history.⁶⁶

Another study examined the predictive value of the metabolic syndrome as well as the individual components of the syndrome for mortality in T1D. Although many of the factors that define metabolic syndrome were predictive of mortality in T1D, the authors reported that microalbuminuria (MA) was the strongest predictor of diabetes-related mortality in the EDC population (HR = 9.2, 95% CI 3.2–26.1), similar to findings in other reports.⁶⁷⁻⁶⁹

2) Age at onset

A 1991 report using the Children's Hospital of Pittsburgh registry compared the age of T1D onset with the risk of mortality. Age at onset was converted to a dichotomous variable of

pubertal vs. pre-pubertal. Puberty was defined as ≥ 11 years in females and ≥ 12 years in males.

The authors found that pubertal onset of T1D was an independent predictor of mortality (HR=2.30, 95% CI 1.44-3.69) by T1D duration.⁷⁰ Higher mortality in persons diagnosed with T1D in puberty has been confirmed in Japanese and Finnish population-based cohorts.^{71, 72}

3) Socioeconomic factors

Data presented at the 2006 Scientific Sessions of the American Diabetes Association showed that mortality rates in T1D varied significantly by income level and occupation level (professional vs. non-professional), but not by education level. The relationship between low income and mortality persisted after adjustment for sex, diabetes duration, education, and occupation (HR = 2.92, 95% CI 1.08–7.91).⁷³

Time trends in T1D mortality

When cause-specific T1D mortality was examined in the Pittsburgh EDC Study, large variations were seen by duration of T1D (Figure 2). Within 10 years of T1D diagnosis, most deaths were due to acute complications. However, between 10-20 years T1D duration, renal disease accounted for half of all T1D deaths. After 20 years duration, cardiovascular disease became the primary cause of death in those with T1D.^{51, 74}

Using the Pittsburgh EDC Study, Pambianco et al. reported a decreased trend in T1D mortality based on diagnosis cohorts. Specifically, at 25 years duration of T1D, cumulative mortality declined by 80% from 35% (1950-1959 diagnosis cohort) to 7% (1970-1974 diagnosis cohort).⁷⁵

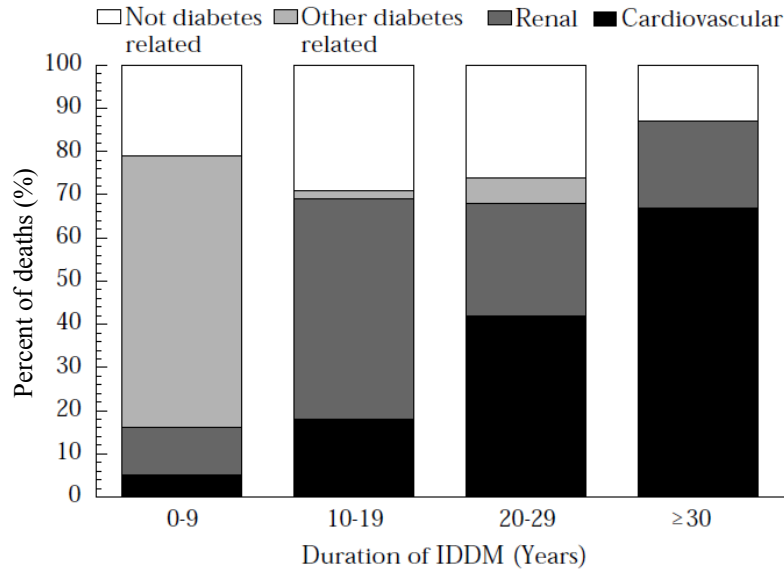


Figure 2. Causes of Death by T1D Duration in Pittsburgh EDC Study. Other diabetes-related causes were typically acute diabetic coma.^{51, 74}

Survival after renal replacement therapy in the Allegheny County T1D Registry cohort

Using survey data on diabetic complications, Nishimura et al. determined the incidence of end-stage renal disease (ESRD) in the Allegheny County T1D cohort, as well as survival from ESRD. At 25 years duration of T1D, the cumulative incidence of ESRD was 11.3%; however, when examining incidence by diagnosis cohort at 20 years T1D duration, the authors report a significant decline in ESRD in the later cohorts. Cumulative survival 10 years after starting renal replacement therapy was 51%, and survival was significantly better for those who received kidney transplants rather than remaining on renal replacement therapy.⁷⁶

Diabetes Epidemiology Research International (DERI)

Diabetes Epidemiology Research International (DERI) began as described above – it was originally a group of 10-15 T1D registries established in countries all over the world.^{12, 47, 77} The World Health Organization (WHO) saw the value of these incidence registries, and the DERI

registries became part of the WHO DIAMOND Project Group. By the end of the 1980s, DIAMOND had almost 70 T1D registries in over 40 countries worldwide.⁷⁸ The DIAMOND Group showed huge variations in childhood T1D incidence worldwide – varying from 0.6/100,000 in Korea and Mexico to 35.3/100,000 in Finland. Most recently, the DIAMOND Project Group reported childhood T1D incidence rates from over 100 populations in 57 countries. Analysis of trends in T1D incidence showed that incidences were increasing in the 1990s all over the world, except in Central America and the West Indies.⁷⁹

Since the early 1990s, DERI has come to be known as referring to a series of T1D mortality studies in four countries – Finland ($n=5146$), Japan ($n=1428$), the U.S. ($n=1075$) (represented by the Allegheny County, PA, cohort), and, initially, Israel ($n=681$). Participants were diagnosed with diabetes between 1965 and 1979 before their 18th birthday and treated with insulin.^{58, 80}

Researchers from each country developed a standardized protocol for determining causes of death using not only death certificates, but also any other available data – medical records, autopsy/coroner’s reports, and interviews with next-of-kin.⁵⁸ Early reports showed that Japan had a much higher mortality rate than the other countries, despite (or perhaps due to) having the lowest incidence of T1D. The excess in mortality was due to acute complications and renal disease.^{58, 80} Finland had an excess in number of violent deaths (often suicide) in young T1D males. None of the other countries’ sex-specific rates varied significantly by cause of death.⁸¹ Looking specifically at diabetes-related deaths, diabetes contributed to only 64% of deaths in Finland, compared to 96% in Japan, 83% in Israel, and 75% in the U.S.⁵⁸

Key DERI findings

Age-adjusted mortality rates

As indicated, DERI has provided T1D mortality information from comparable T1D populations in countries with large variations in T1D incidence. Japan's excess T1D mortality persisted in the second international comparison through January 1, 1990 (See Table 1). The authors estimated that if the U.S. had the same T1D mortality rates as Finland, more than half of the T1D deaths each year in the U.S. would not occur.⁸² In a two-country follow-up through 1994, the authors reported that Finland's overall mortality rates continued to rise, as would be expected with increasing age and T1D duration, whereas Japan's overall mortality rates were decreasing for T1D, indicating dramatic improvements in T1D care in Japan.⁷¹ This report also showed a temporal trend of lower absolute and relative mortality rates when comparing those diagnosed in the 1960s with those diagnosed in the 1970s. A larger study using multiple registries confirmed that Japan, along with Russia and Eastern Europe, had the highest T1D mortality rates, and that mortality rates varied 10-fold between countries in the WHO DIAMOND Project Group.⁸³

Table 1. Age-adjusted mortality rates (per 100,000 person-years) by country in DERI.^{58, 63, 71, 82}

Follow-up through:	Finland	Israel	Japan	U.S.*
1/1/1985	171	159	681	238
1/1/1990	250	158	760	408
12/31/1994	352	---	607	---
1/1/1999	---	---	---	627

*Allegheny County Type 1 Diabetes Registry cohort

Finally, the most recent mortality follow-up in the Allegheny County T1D cohort (through January 1, 1999) showed a dramatic increase in the overall mortality rate since the previous follow-up, as would be expected as the study population ages. The authors suggested

that the high costs of treating T1D, due to regular physician visits, expensive medications and equipment, combined with the higher mortality in the African-American segment of the cohort might explain why the overall T1D mortality rate has increased in this T1D cohort.⁶³ However, the most significant finding was that the 1975-1979 diagnosis cohort had a significantly lower risk of death compared to those diagnosed in 1965-1969 after adjusting for T1D duration (HR = 0.51, 95% CI 0.30–0.85).⁶³

Cause-specific variations in mortality

Results showed that a higher proportion of T1D deaths in Japan were due to renal disease, although this proportion has declined in recent years.^{84,85} A study comparing diabetic renal disease mortality in the Japanese and Allegheny County cohorts showed that Japan had incidence rates of dialysis twice as high as in Allegheny County. Not surprisingly, the renal failure-related mortality rates in Japan were also twice as high. The authors pointed to decreased accessibility to dialysis as the likely reason for the higher mortality, in that nearly one-third of the renal failure-related deaths in Japan had never been treated with dialysis, whereas all of the renal failure-related deaths in Allegheny County had received dialysis.⁸⁶

The Japanese DERI group recently examined whether diabetes education improved renal failure-related mortality in their cohort. They found that participants who had attended a large diabetes center in Tokyo were three times less likely to die and nearly five times less likely to develop ESRD compared to those who had not attended the center. They suggest that a multidisciplinary management system improves renal-related outcomes in T1D.⁸⁷ However, these findings are tempered by the fact that during that prior to 1975, Japanese T1D individuals could not inject themselves with insulin but had to go to a hospital for all insulin injections.⁸⁵

Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)

WESDR began in 1979 and consists of 996 T1D individuals (defined as age <30 years and on insulin therapy) in 11 counties in southern Wisconsin. Ascertainment of T1D participants in this region was 82.3%.⁸⁸ A 1991 WESDR report showed that T1D males had a 6.8-fold higher risk of mortality and T1D females had an 8.9-fold higher risk of mortality compared to the age-matched general population, with an even greater risk of cardiovascular-related death.⁸⁹ Diabetes was listed as the underlying cause of death on 44.1% of death certificates, with another 30.3% listing heart disease.⁸⁹

In a 20-year follow-up through 2002, Klein et al. reported 273 (27.4%) deaths in their study, 176 (64.4%) of which involved heart disease. They found that retinopathy and nephropathy status were significant predictors of cardiovascular mortality.⁹⁰ In a separate WESDR report, a significant association was found between mortality and hyperglycemia. Using baseline glycosylated hemoglobin (HbA1) levels, the authors examined mortality by quartile of HbA1. Compared to the lowest quartile ($\leq 9.4\%$), participants in the highest glycosylated hemoglobin quartile ($\geq 12.1\%$) had a higher risk of overall (RR=2.42, 95% CI 1.52–3.82) and cardiovascular (RR=3.28, 95% CI 1.77–6.08) mortality.⁹¹

Summary

Early data from these population-based studies strongly supported the concern that many T1D patients were avoiding early mortality with insulin therapy only to succumb to one of many long-term diabetes complications, of which cardiovascular disease and renal disease are most common. A string of new advances in T1D treatment occurred from the early 1980s to the early 1990s, namely, the widespread use of glycosylated hemoglobin (HbA_{1c}) testing,^{92, 93} blood

glucose self-monitoring kits,⁹⁴ angiotensin-converting enzyme inhibitors,⁹⁵⁻⁹⁷ and data that tight glycemic control delayed onset and progression of diabetes complications.⁹⁸⁻¹⁰⁰

2.3.2.2 Other Key Studies

Steno Diabetes Center

The Steno Diabetes Center in Copenhagen, Denmark, has treated and researched T1D patients since the pre-insulin era. Due to their status as a specialty center, they have treated T1D patients from all over Northern Europe. As such, they have excellent long-term follow-up data (> 40 years T1D duration). A series of reports in the 1980s examined T1D mortality over a 50 year time span, as well as mortality differences by duration of T1D.^{19, 40, 101-104} Using data on 1,001 patients with at least 30 years T1D duration, the authors found that relative mortality was dramatically higher in persons with persistent proteinuria (up to 50-fold).¹⁰² Two additional papers examined mortality in those with at least 40 years T1D duration relative to those dying within 35 years of T1D onset. The papers found that nearly 50% of those surviving to 40 years T1D duration had no major diabetes complications. Also, those who died within 35 years of onset tended to be male with poor glycemic control and infrequent clinic visits.

Other more recent reports have utilized the long-term follow-up (50+ years) data to show that relative mortality has been declining since the 1950s and 1960s in T1D, with a commensurate increase in median life expectancy in Denmark^{40, 103, 105}

Joslin Diabetes Center

The Joslin Diabetes Center in Boston, MA, is similar to the Steno Diabetes Center, in that it is a specialized diabetes care center with decades of experience. The Joslin Center has particularly focused on research in T1D, and much of the early T1D mortality data comes from data at Joslin Center.^{20, 25, 26, 28, 29}

In 2008, a study from Joslin described an association between mortality and self-reported insulin restriction in T1D women. Insulin restriction refers to patients taking less insulin than is prescribed and occurs for a variety of reasons. The authors showed a three-fold increase in mortality in T1D women reporting insulin restriction, after adjusting for age, BMI, and HbA_{1c} level. The authors found that insulin restriction in this population tended to be due to eating disorder problems, highlighting an understudied area of dramatically higher mortality in T1D women suffering from eating disorders.¹⁰⁶ Two reports in 2002 described tremendously higher risks of mortality (SMR \geq 14.5) for T1D women with concomitant anorexia nervosa after 10 years of follow-up.^{107, 108}

European Studies

EURODIAB, Diabetes UK Cohort, and various other diabetes studies and registries across Europe have added significantly to the literature on T1D mortality. Using data from the EURODIAB Prospective Complications Study ($n = 2,787$ T1D participants), researchers have reported a number of risk factors for mortality in T1D. Although macroalbuminuria, retinopathy and neuropathy (all HR $>$ 2.0) were the strongest predictors of mortality, other risk factors included older age, longer T1D duration, and higher non-HDL cholesterol levels.^{109, 110}

The Diabetes UK Cohort is the largest cohort to date ($n=23,751$) used to examine T1D mortality. Reports using this large cohort have shown important findings in both overall and cause-specific T1D mortality.¹¹¹⁻¹¹⁶ One paper examined cause-specific mortality in T1D and reported that acute complications accounted for 37% and 49% of all male and female T1D deaths with < 20 years T1D duration, respectively.¹¹² A follow-up nested case-control study showed that psychosocial and socioeconomic factors (e.g., living alone, previous drug abuse, previous psychiatric care) greatly increased the risk of mortality from acute complications.¹¹¹ Researchers looked specifically at deaths from cerebrovascular disease in T1D, an understudied area of T1D mortality research, due to its relatively rare occurrence in relation to other T1D complications. The authors found greater rates of mortality from cerebrovascular disease in T1D, three-fold (SMR = 3.2, 95% CI 2.2–4.3) for T1D males and four-fold (SMR = 4.4, 95% CI 3.1–6.0) for T1D females.¹¹⁶ Although the Diabetes UK study was an enormous representative sample of the T1D population, mortality data was extracted solely from death certificates, where diabetes is notoriously under-reported. Another report showed that T1D patients in the UK have a substantially greater risk of death compared to the general population (SMR = 2.7-5.7), with the relative risk of death higher for T1D females than T1D males at all ages.¹¹³ No sex differences were seen in mortality risk from cardiovascular disease in T1D, but younger T1D females (age 30-39) showed a 45-fold higher risk of CVD mortality compared to the general population, which in part explains the higher overall mortality risks in T1D females.¹¹⁴ Research from both the UK General Practice Research Database and the London Cohort of the WHO Multinational Study of Vascular Disease in Diabetes showed very similar results for overall and cardiovascular-related mortality in T1D, both noting the higher risk of mortality in T1D females.¹¹⁷⁻¹²⁰

Race/ethnicity

Recent studies highlight evidence for racial disparities in T1D mortality.^{65, 75, 121, 122} An analysis of national mortality data showed that in T1D persons aged 1-19 years, the annual average diabetes death rate per 1 million youths was 2.46 for African-Americans and 0.91 for Caucasians.⁶⁵ Similarly, in 2004, age-adjusted diabetes death rates for African-Americans in the U.S. were approximately twice those for Caucasians.¹²¹ The New Jersey 725 Study examined mortality rates in 725 African-Americans with a mean T1D duration of 8 years. These participants were randomly selected from a population of hospitalized African-Americans with a discharge diagnosis of diabetes mellitus, who were diagnosed prior to age 30 and treated with insulin. The authors found that the three-year mortality rates were 7.1% for women and 10.6% for men. Relative to the general New Jersey African-American population, standardized mortality ratios (SMR) of African-Americans with T1D were 12 and 6 times greater for women and men, respectively.¹²²

Contemporary mortality rates in younger T1D persons

A number of smaller studies throughout the world have been published reporting local figures for T1D mortality in younger T1D populations (diagnosed in between 1970 and 1999). Using data collected between 4 and 20 years of follow-up, the most recent mortality rates (MR, per 100,000 person-years) and standardized mortality ratios (SMR) for T1D for the following countries have been reported: Norway (MR = 220, SMR = 4.0), Sweden (MR = 268, SMR = 2.3), Finland (MR = 346, SMR = 3.9), United Kingdom (MR = 298, SMR = 6.4), Italy (MR not reported, SMR = 2.7), Japan (MR = 611, SMR = 12.1), and New Zealand (MR not reported SMR = 3.0).^{10, 123-133}

Although population-based data has not been available to report standardized mortality ratios for T1D in Africa, many researchers have noted mortality to be extremely high, 50% or more in some sub-Saharan countries, often due to acute complications or infections. Causes for these high mortality rates tend to be poor health care infrastructure, lack of insulin availability, and poor diabetes education.^{9, 134-138}

2.3.3 Sudden Death in Type 1 Diabetes

In 1991, Tattersall and Gill published a report on 22 young (12-43 years old), apparently healthy T1D persons who had been found dead in their beds.¹³⁹ The authors reported that 20 of the 22 persons were found in an undisturbed bed, which suggested no terminal struggle, without evidence of sweating or a clear cause of death found on autopsy. These characteristic features were later coined “*dead in bed syndrome*”. All 22 individuals were taking human insulin at the time of death. The authors postulated that, due to their timing, the deaths were in some way associated with nocturnal hypoglycemia.¹³⁹

This report was published after a 1987 paper described 3 case studies of T1D individuals who lost their normal warning symptoms of hypoglycemia (tremors, sweating, extreme hunger) after switching to human insulin from animal insulin.¹⁴⁰ The authors then interviewed 176 T1D patients who had switched to human insulin and found that 36% had lost some or all of their sympatho-adrenal symptoms (a phenomenon known as hypoglycemia unawareness) after switching to human insulin. A 1991 study (from the Pittsburgh EDC Study) examined hypoglycemic events in 628 T1D participants based on the type of insulin used. Although human insulin did not increase the risk of hypoglycemia, the authors found an association

between human insulin and a reduced awareness of hypoglycemia in those with poor blood glucose control.¹⁴¹ Although controversy still exists about the role of human insulin in reduced hypoglycemia awareness, renewed efforts have been made to determine the etiology of *dead in bed syndrome*.^{142, 143}

Since the 1991 report by Tattersall and Gill, more than 100 unexplained sudden deaths that meet the *dead in bed syndrome* criteria have been reported in Sweden, Denmark, Norway, and Australia.^{124, 143-147} Some of these individuals were found to be taking multiple daily doses of insulin and having frequent episodes of hypoglycemia prior to death.¹⁴⁶ Two studies have found that sudden deaths occur in >20% of all young T1D deaths (age < 50), compared to 1-5% of similar general populations.^{144, 147} A 1996 report examined sudden death in 35 to 44 year old white males in Allegheny County, PA, and showed that although diabetes prevalence is less than 1% in this population, >20% of all sudden deaths in this population were in individuals with T1D.¹⁴⁸

A 2008 report estimated that 5-6% of all T1D deaths fit the criteria of *dead in bed syndrome*.¹⁴⁹ A plausible theory has been postulated and developed over the last decade to try to explain the etiology of *dead in bed syndrome*.¹⁵⁰⁻¹⁵⁷ Nocturnal hypoglycemia rarely results in sudden death.¹⁵¹ In otherwise healthy, young T1D patients, those at risk of *dead in bed syndrome* likely have reduced parasympathetic activity and a relative sympathetic predominance, due to long-standing T1D and early stages of cardiac autonomic neuropathy.^{150, 156} This alone has been shown to lead to ventricular arrhythmias.

In addition, autonomic neuropathy is also associated with abnormal cardiac repolarization, as evidenced by prolonged corrected QT (QTc) intervals.^{155, 158} Prolonged QTc intervals have been shown to independently predict overall and cardiovascular-related mortality

in T1D.¹⁵⁹ In addition, data exists that hypoglycemia, especially severe episodes of hypoglycemia, also prolongs the QTc interval. Nocturnal hypoglycemia has a higher propensity to persist for hours at night due to the long standing T1D causing hypoglycemia associated autonomic failure (HAAF), where the body produces an inadequate response of glucagon and adrenaline when it senses hypoglycemia. HAAF has been shown to be reversible if T1D individuals carefully guard against all instances of iatrogenic hypoglycemia, keeping the body “primed” to respond to physiologic hypoglycemia.¹⁵²

Also, genetic predisposition to long QTc intervals exists in the population, as seen with familial long QT syndrome or Brugada syndrome.¹⁵¹ It is unclear how significant a role this might have in increasing the risk of a prolonged QTc interval in T1D. Regardless, the combination of early autonomic neuropathy, nocturnal hypoglycemia, and HAAF (from long-standing T1D), all predispose an individual to have prolonged QTc intervals at night, which could cause fatal ventricular arrhythmias.^{151, 152}

In addition to *dead in bed syndrome*, reports often describe other T1D deaths where the individual is found dead, but the cause of death is not determinable and the death does not fit the criteria for *dead in bed syndrome* (e.g., the person is > 50 years old or they are found dead in their car).^{139, 143, 147} It is possible that some of these unexplained deaths are the result of a self-administered insulin over-dose (suicide); however, without clear evidence of a suicide (previous suicide attempts, suicidal ideation, or a suicide note), these deaths tend not to be classified as suicide. More research is necessary to identify causes of and risk factors for all sudden unexplained deaths in T1D persons.

2.4 DEATH CERTIFICATE MISCLASSIFICATIONS

Epidemiological and clinical studies have long relied on death certificates to obtain mortality data, specifically data relating to the cause(s) of death. Studies in the 1970s attempted to validate the cause(s) of death on death certificates using registry data, medical records, and autopsy/coroner's reports. One key Swedish study in 1976 used data from the Swedish Twin Registry to validate the cause of death listed on 1,156 death certificates.¹⁶⁰ The authors found that the death certificates were quite valid for most forms of cancer, cerebrovascular disease, and most respiratory diseases, but *not* for diabetes mellitus. The authors concluded that “in selected clinical-epidemiological studies it is often necessary to collect all available documents prior to judging the cause of death.”¹⁶⁰

A more recent study in the U.S. “tested” physicians, residents, and senior medical students on their abilities to accurately complete the cause-of-death section of death certificates using six cases and comparing their results to the correct cause determined by a nosologist. The authors reported that each group correctly identified the cause of death about 56% of the time and concluded that misclassification, as well as substantial underreporting of mortality from diabetes, is widespread.¹⁶¹ Other studies have shown varying levels of accuracy on death certificates worldwide – with major errors (i.e., wrong cause or manner of death) occurring on 30-50% of death certificates surveyed.¹⁶²⁻¹⁶⁵ Additional errors commonly occur; for example, one report showed that county-of-residence was completed incorrectly on 14% of a sample of death certificates between two counties in Texas, causing mortality statistics in the two counties to vary dramatically.¹⁶⁶ Another study in rural Greece noted that the most frequent error (on 34% of the death certificates) was reporting the mechanism rather than the cause of death.¹⁶⁵

2.4.1 Under-reporting of Diabetes

Multiple studies have examined the extent to which diabetes is under-reported on death certificates worldwide.¹⁶⁷⁻¹⁷⁹ A 2006 study by Lu et al. compared death certificate errors in Sweden, Taiwan, and the U.S, when diabetes was listed anywhere on the death certificate. Looking for two specific errors, the authors found that U.S. physicians (19%) were less likely to report two or more diagnoses per line than physicians in Sweden (46%) and Taiwan (56%). However, Swedish physicians (5%) were less likely to list incorrect causal sequences than physicians in Taiwan (21%) and U.S. (28%). Based on these differences, the authors concluded that comparing mortality statistics based on death certificate data across countries might not be appropriate.¹⁷⁹ Lu and colleagues performed a similar analysis using death certificate data from Sweden, Taiwan, and Australia, and compared how often and where diabetes was mentioned on the death certificate. They found that some of the cross-country differences in diabetes mortality could be due to differences in reporting diabetes on the death certificates.¹⁷⁸

Two EURODIAB Subarea C Study Group papers showed large differences in listing diabetes as the underlying cause of death. Comparing death certificates to a central classification center's findings, the authors showed large discrepancies in national coding and central coding particularly when classifying deaths involving diabetes and cardiovascular-related diseases. They found discrepancies in the underlying cause of death in 26-44% of the death certificates.¹⁶⁷ As a follow-up to the first study, the authors sent six case histories to a representative sample of coding physicians in each of the nine European countries, all of which described the deaths of diabetic patients. They received results from about 220 physicians/country and comparing them to central coding results. They found under-coding of diabetes by 25-40% in three countries and

over-coding of diabetes by 60-80% in two countries (The Netherlands and Ireland). The authors conclusively report that “with such differences in the coding of diabetes, the currently published mortality rates for diabetes are not directly comparable between European countries.”¹⁷¹

Some studies looked for causes of why diabetes was underreported on death certificates, and they consistently reported that individuals treated with insulin (i.e., T1D persons) were significantly more likely to have diabetes listed on the death certificate.^{168, 170, 172, 173}

Often, however, deaths occurring in diabetic persons are unrelated to their diabetes (e.g., cancer, homicide, passenger in fatal motor vehicle crash), so diabetes justifiably should not be reported on all death certificates in diabetic persons. In many cases, an examination of medical records, autopsy/coroner’s reports, and interviews with next-of-kin is essential to accurately determine the role of diabetes in each death. Data presented at the 2007 Scientific Sessions of the American Diabetes Association showed that diabetes contributed to only 86% of all T1D deaths in three large T1D cohorts in Japan, Finland, and the U.S. The mortality rates for the remaining 14%, where diabetes did not contribute to the death, were not significantly different from those expected based on age-specific mortality rates for the general population of each country.¹⁸⁰ A recent report from the UK Prospective Diabetes Study looked specifically at cardiovascular-related death certificates in their cohort. They found that diabetes was only reported on 46% of death certificates where cardiovascular disease was listed as the underlying cause.¹⁷⁶ The authors concluded that there might be a lack of awareness of diabetes’ importance as a cardiovascular risk factor.

2.4.2 Under-reporting of Type 1 Diabetes

Only one study to date has specifically examined the reliability of the cause of death on death certificates in individuals with T1D.¹⁸¹ Using a cohort of 3,674 T1D persons who attended a 5-day training program for intensive insulin therapy at one of ten German hospitals, the authors performed a mortality follow-up 10 years later. They compared the findings of their mortality review committee with the death certificates and the ICD-codes. They only found agreement between all three only when the cause of death was neoplasm. The committee agreed with death certificates when the cause of death was myocardial infarction, stroke, or accident. The committee found that only one of four hypoglycemic deaths was listed as such on the death certificate, and similarly, only four of seven deaths from diabetic ketoacidosis (DKA) listed DKA on the death certificate.¹⁸¹

In summary, the authors of the German study concluded that death certificates alone are not reliable when determining the true clinical outcome of deceased T1D patients.¹⁸¹

2.5 SUMMARY AND SIGNIFICANCE

Although many advances and improvements have greatly lowered overall mortality, T1D persons remain at a markedly higher risk of death. Estimates of early mortality (<20 years T1D duration) have improved in the United States and Western Europe from at least 7 times higher than comparably aged individuals in the general population in the 1980s to 2-4 times the general population presently.^{51, 63, 118, 123, 125, 182}

Few studies exist that have accurately quantified mortality risk and long-term complication status in large, representative samples of T1D patients. As mentioned above, these studies have either used small physician-based or hospital-based cohorts in homogeneous T1D populations or large population-based cohorts and basing their mortality rates and complication status estimates using only death certificate data. The proposed research aims to provide accurate mortality and morbidity rates in persons with T1D of 25-40 years duration using a large, population-based cohort.

These data will serve many purposes. Presently, life insurance coverage for T1D persons are based on antiquated mortality estimates, greatly inflating policy premiums. These estimates do not account for recent advances in T1D treatments and improved life expectancies.¹⁰⁵ Moreover, these data will provide insight into premature mortality and morbidity, and thus enable more effective preventative strategies to be developed, especially strategies to decrease the number of T1D persons who die suddenly of an unexplained death. The study also has the potential to change routine care practices to address racial disparities in T1D morbidity and mortality and changes in common causes of mortality at different durations of T1D. Finally, early Allegheny County T1D Registry results have recently been included in a summary report submitted to Congress to show evidence of improvements of T1D care.¹⁸³ This current study will help in determining the appropriate allocation of future T1D research funding.

3.0 SPECIFIC AIMS

Diabetes Epidemiology Research International (DERI) began in the 1980s as an effort to standardize the causes of death in the type 1 diabetic population across countries and compare mortality rates and causes across countries.⁸² The U.S. DERI cohort was taken from the Allegheny County Type 1 Diabetes Registry, which consisted of 1,075 persons diagnosed between 1965 and 1979 with T1D before 18 years of age in Allegheny County, Pennsylvania. For this study, we surveyed this cohort to determine: 1) time trends by diagnosis cohort (1965-69, 1970-74, and 1975-79), by race, and by sex in overall population-based mortality rates for long-term T1D (25-40 year duration) and factors associated with higher mortality; 2) time trends in cause-specific mortality by diagnosis cohort, by race, and by sex; and 3) the characteristics of sudden unexplained deaths, and specifically deaths that meet criteria for *dead-in-bed syndrome*.

Specific Aim 1: *To determine time-trends by diagnosis cohort (1965-69, 1970-74, and 1975-79), by race, and by sex, in overall population-based mortality rates for long-term T1D (25-40 year duration) and factors associated with higher mortality.* Vital status was last ascertained in the Allegheny County T1D Registry as of 1 January 1999, wherein 170 deaths were observed in 1,075 participants.⁶³ We re-contacted participants to ascertain vital status as of 1 January 2008. Our group has also been following a similar, hospital-based T1D population in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. Based on mortality figures in the comparable EDC population (T1D diagnosis between 1965 and 1979), 55% of

those deceased as of 2008 died since January 1999. Since the study populations are quite similar, we thus anticipated that a significant proportion of the Allegheny County population would have died since 1999, yielding as estimated 90-120 new fatalities. To assess trends in mortality over time, we divided the Allegheny County T1D population into three cohorts by year of diagnosis, to look at overall, sex-, and race-specific mortality by duration of T1D to explore whether rates have continued to decline by diagnosis cohort between 2000 and 2008, as we previously reported up to 1999.⁶³ We also obtained overall, sex-, and race-specific mortality rates and Kaplan-Meier survival curves to examine risk differences by race and sex, and to obtain cumulative survival rates up to 40 years duration of diabetes. Finally, we calculated standardized mortality ratios based on mortality statistics for the age-, race-, and sex-matched general population.

Specific Aim 2: *To examine time trends of cause-specific mortality by diagnosis cohort, by race, and by sex.* As mentioned above, the Allegheny County T1D population was divided into three cohorts based on year of diagnosis (1965-1969, 1970-1974, and 1975-1979) and was approximately evenly distributed across these three cohorts ($n = 354, 391, \text{ and } 330$, respectively). We also assessed variations in cause-specific time trends by race and sex. Cause(s) of death were determined based on all available information (at minimum, death certificate or National Death Index data). For example, we wanted to examine whether mortality patterns are changing over time (e.g. the proportion of fatal cardiovascular disease cases that are preceded by renal disease).

Specific Aim 3: *To determine the characteristics of sudden unexplained deaths, and specifically deaths that meet criteria for dead-in-bed syndrome, in T1D.* Finally, as an extension of the cause-specific analysis, we identified the proportion of deaths that are found dead without

a known cause of death. We combined current Allegheny County T1D Registry data with data from the comparable population in the Pittsburgh EDC Study (diagnosis between 1965 and 1979), based on vital status as of January 1, 2008. By using two populations, power was increased, thus allowing a better determination of the characteristics of individuals who are found dead of an unknown cause, a relatively rare but disturbing finding in T1D research.

3.1 OVERVIEW OF THE ALLEGHENY COUNTY TYPE 1 DIABETES REGISTRY METHODOLOGY

The Allegheny County Type 1 Diabetes Registry, originally developed in the 1970s, consists of persons diagnosed with T1D in Allegheny County, Pennsylvania. The standardized inclusion criteria for participation in the Allegheny County T1D Registry were: 1) diagnosis with diabetes before 18 years of age; 2) placed on insulin at diagnosis; 3) diagnosis between 1 January 1965 and 31 December 1979; and 4) a resident of Allegheny County at diagnosis. Individuals were excluded if diabetes developed from a secondary cause, i.e., steroid-induced diabetes or diabetes associated with cystic fibrosis or Down's syndrome.

T1D persons in Allegheny County were identified from an incidence registry developed through the review of hospital records and validated by contacting pediatricians in the community to identify additional cases. The degree of ascertainment was well over 95%.¹⁸⁴ The initial mortality follow-up procedure (determining vital status as of 1 January 1985) consisted of seeking permission from each hospital to contact the attending or referring physician for each eligible case. With their physician's permission, patients were then contacted by phone and

letter tracing to determine vital status.⁵⁸ As of 1 January 1990, 1,075 eligible cases were identified for the Allegheny County T1D Registry cohort. The demographic characteristics of this cohort are presented in Table 2. Overall, 517 (48.1%) participants are female, and 79 (7.4%) are African-American. Vital status for this Allegheny County T1D cohort was also determined as of 1 January 1995 and as of 1 January 1999.

Table 2. Demographic characteristics of the Allegheny County T1D study population (*n* = 1075)

Characteristic	N	Percent
Year of birth		
< 1950	11	1.0
1950-1959	421	39.2
1960-1969	573	53.3
1970-1979	70	6.5
Sex		
Male	559	52.0
Female	516	48.0
Race		
Caucasian	995	92.6
African American	79	7.4
Year of T1D diagnosis		
1965-1969	354	32.9
1970-1974	391	36.4
1975-1979	330	30.7
Age at T1D diagnosis		
0-4	105	9.8
5-9	305	28.4
10-14	477	44.4
15-17	188	17.5
Vital Status (as of 1/1/99)		
Alive	802	74.6
Deceased	170	15.8
Not ascertained	103	9.6

Allegheny County is located in southwestern Pennsylvania, with the city of Pittsburgh as the county seat. In 1970, the county population was approximately 1.6 million, and the steel industry was the cornerstone of the economy. With the U.S. steel industry decline in the 1970s,

the population of Allegheny County dropped to approximately 1.3 million in 2000 with the healthcare sector becoming the largest industry in the county. Caucasians account for more than 80% of the county population.

Diabetes Epidemiology Research International (DERI) began in the 1980s as an effort to standardize the causes of death in the T1D population across countries and to compare mortality rates and causes between countries.⁸² DERI originally consisted of large population-based cohorts in four countries with vastly different T1D incidence rates – Finland, Israel, Japan, and the United States (Allegheny County cohort). Due to the domestic unrest, the Israel cohort no longer participates in DERI. T1D incidence rates in Finland are the highest in the world, approximately 40 times higher than seen in Japan.

Classification of causes of death

The primary/underlying cause of death for each decedent is determined by the DERI Mortality Classification Committee using all available data based on standardized procedures.⁵⁸

The causes are categorized into 9 major groups as follows:

- **Acute complications**, including diabetic ketoacidosis, hyperglycemia, hypoglycemia, hypokalemia, and diabetic coma unspecified.
- **Diabetic renal disease**, including diabetic nephropathy, end stage renal disease (ESRD), and dialysis-related complications.
- **Cardiovascular**, including coronary artery disease, myocardial infarction, sudden cardiac death, cerebrovascular disease, peripheral vascular disease, heart failure, arrhythmias, and cardiomyopathy.

- **Infection**, including pneumonia, bronchitis, sepsis, meningitis, encephalitis, osteomyelitis, mycosis, and endocarditis.
- **Other diabetes**, including autonomic neuropathy, angiopathy, uncontrolled diabetes, and post-transplant complications.
- **Accident or suicide**, including violent deaths, motor vehicle crashes, alcohol/drug overdose, and other accidental deaths (drowning, fall, fire).
- **Cancer**, including any form of cancer.
- **Other non-diabetes**, including other causes of death not specific to diabetes, e.g., bulimia/anorexia, sickle cell trait, lupus, septic abortion, epilepsy, gastric ulcer, and HIV.
- **Unknown**, where cause of death could not be determined based on available information.

3.2 PRELIMINARY FINDINGS

Total numbers of deceased at each time point in the Allegheny County T1D population are shown in Table 3. Confirmed deceased subjects increased 5-fold between 1985 and 1999 in this cohort. As of 1 January 2008, the surviving Allegheny County T1D population had an average age of 47 years (range = 29–59) and an average duration of T1D of approximately 36 years (range = 28–43).

Table 3: Total number of deceased Allegheny County T1D cohort participants at each follow-up time

Time point	Total Deceased (%)
As of 1/1/1985	34 (3.2%)
As of 1/1/1990	72 (6.7%)
As of 1/1/1995	111 (10.3%)
As of 1/1/1999	170 (15.8%)

The author recently explored variations in the role of diabetes in T1D deaths in the Finnish, Japanese, and U.S. DERI cohorts by country, sex, age, and duration of diabetes, and presented the findings at the 67th Annual Scientific Sessions of the American Diabetes Association in June 2007. Of 7,650 study participants diagnosed with T1D between 1965 and 1979, 449 died prior to 1 January 1995 and have been reviewed by the Mortality Classification Committee (MCC, composed of physician investigators from each country). Death certificates (and any other available information, i.e., hospital/physician records, autopsy records and interviews with next of kin) were secured for all 449 participants. Using this information, the MCC determined cause(s) of death and whether, and to what extent, diabetes played a role in each death. The role of diabetes was classified as 1) the direct cause of death, 2) a significant contributor, or 3) a marginal contributor.

Of the 449 deaths, diabetes contributed to 386 deaths (86.0%). The mortality rates for the remaining 14.0%, where diabetes did not contribute to the death, were not significantly different from those expected based on age-specific mortality rates for the general population of each country (based on international mortality figures from the WHO). While there was no difference in contribution by country, diabetes contributed significantly more to deaths in females than in males overall (91.3% vs. 81.8%, $p = 0.004$). Also, diabetes contributed to significantly fewer deaths in those diagnosed after 1970 compared to those diagnosed before 1970 (80.9% vs. 91.3%, $p = 0.007$). However, this data was unadjusted for diabetes duration. In addition, diabetes was more frequently a direct cause of death in those who died before age 30 compared to those who died later ($p < 0.001$). Thus, the role of diabetes as a contributor to death appears consistent across countries. Moreover, diabetes appears to be playing a decreasing role in the mortality of these cohorts.

We also recently explored patterns in morbidity and mortality in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. The two leading causes of death in individuals with long-standing T1D are renal and cardiovascular disease, and the former has long been considered the main driving force behind the latter. However, the EDC study has reported major declines in both mortality and renal failure but little decline in heart disease.⁷⁵ Thus, the interplay between renal and cardiovascular diabetic complications is evident but not as clear as previously thought. Using data from biennial clinical exams as well as hospital records and death certificates, we chronologically sequenced the order of cardiovascular (ischemic ECG, myocardial infarction, stroke, revascularization, or CAD death) and renal events (microalbuminuria (MA), overt nephropathy (ON), or end-stage renal disease (ESRD)). The author performed a descriptive analysis of incident CVD-related events in the subgroup of deceased individuals ($n=127$) from the EDC Study. 94.5% had at least mild kidney disease (MA, ON, or ESRD) prior to either a CVD event or death, whichever came first. However, only 70% of this group had an incident CVD event. Also, when renal status was separated into two groups – 1) no or only mild (MA) evidence of kidney disease; and 2) severe kidney disease (ON or ESRD) – patterns emerged. Comparing the two renal groups, all incident revascularizations ($n=4$), all incident non-MI CAD deaths ($n=3$), and all coincident (i.e., two or more events occurring at the same time) CVD events ($n=8$) had evidence of severe renal disease. Further data collection establishing the typical sequence of clinical events that precede adverse cardiac events in T1D persons will be necessary to draw clinically useful conclusions. However, these data indicate the need for more thorough cause-specific mortality analyses to assess changes in mortality patterns over time.

We speculate that the mortality rates in Allegheny County are likely better than seen in other areas (especially rural areas) of the United States for a few reasons. First, approximately 70% of this cohort was followed at Children's Hospital of Pittsburgh, which was an early proponent of multi-faceted and intensive diabetes care.⁵¹ Also, kidney transplants were first performed in Pittsburgh, and the success rate for these transplants were likely higher than in other areas of the United States, suggested in our previous report.⁷⁶ Finally, this cohort is predominantly Caucasian (92.7%), and Caucasians have a higher survival rate with type 1 diabetes than African-Americans.

4.0 PAPER 1: ALL-CAUSE MORTALITY TRENDS IN A LARGE POPULATION-BASED COHORT WITH LONG-STANDING CHILDHOOD-ONSET TYPE 1 DIABETES: THE ALLEGHENY COUNTY TYPE 1 DIABETES REGISTRY

To be submitted for publication

Aaron M. Secrest¹, Dorothy J. Becker², Sheryl F. Kelsey¹, Ronald E. LaPorte¹,
and Trevor J. Orchard¹

¹Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh,
Pittsburgh, Pennsylvania

²Department of Pediatrics, Children's Hospital of Pittsburgh, University of Pittsburgh School of
Medicine, Pittsburgh, Pennsylvania

4.1 ABSTRACT

INTRODUCTION: Management of type 1 diabetes dramatically improved in the 1980s, but data on long-term effects on mortality are limited. We therefore report long-term follow-up on a large contemporary population-based cohort.

METHODS: We report trends in overall mortality over a 30-year period using the Allegheny County (Pennsylvania) childhood-onset (age<18 yrs) type 1 diabetes registry ($n=1,075$) diagnosed from 1965–1979. Temporal trends were explored by dividing the cohort into three groups by year of diagnosis (1965–69, 1970–74, and 1975–79). Local (Allegheny County) mortality data were used to calculate standardized mortality ratios (SMRs).

RESULTS: As of 1 January 2008, vital status for 1,043 participants was ascertained (ascertainment rate=97.0%) when mean age (\pm SD) and duration of diabetes were 42.8 ± 8.0 and 32.0 ± 7.6 years, respectively. The 279 total deaths (26.0%) observed in this population, for a crude mortality rate of 812 per 100,000 person-yrs (95% CI 717–907), which was 7 times higher than expected (SMR=6.9, 95% CI 6.1–7.7). An improving trend in both mortality rates and in SMRs was seen by diagnosis cohort at 30 yrs diabetes duration. The SMRs were 9.3 (95% CI, 7.2–11.3), 7.5 (5.8–9.2), and 5.6 (4.0–7.2) for 1965–69, 1970–74, and 1975–79, respectively. Although within the Allegheny County type 1 diabetes registry cohort, no sex difference in mortality was observed ($p=0.27$), females with T1D were 13 times more likely to die than age-matched females in the general population (SMR=13.2, 10.7–15.7), whereas males with T1D were only 5 times more likely to die compared to the general male population (SMR=5.0, 4.0–

6.0). While life-table analyses showed survival at 30 yrs diabetes duration to be much lower in African-Americans compared to Caucasians (57.2% vs. 82.7%, respectively, $p < 0.001$), no differences in SMR were seen by race. Age at diabetes onset significantly predicted mortality, with each additional year conferring a 7% higher risk of mortality (HR 1.07, 1.04–1.10).

CONCLUSION: While survival has clearly improved, those diagnosed most recently (1975-1979) still had a mortality rate 5.6 times higher than seen in the general population, suggesting a continuing need for improvements in treatment and care.

4.2 INTRODUCTION

Type 1 diabetes is known to be associated with a higher risk of mortality compared to the general population. Type 1 diabetes (T1D) leads to hyperglycemia, which is linked to a number of acute (e.g., diabetic ketoacidosis) and chronic (e.g., diabetic nephropathy and cardiovascular disease) complications.⁹¹ With the advent of blood glucose self-monitoring, glycosylated hemoglobin (HbA_{1c}) testing, and angiotensin-converting enzyme inhibitors, treatment for T1D improved tremendously during the 1980s and 1990s.^{92, 94, 95} Despite these improvements, however, T1D complications still frequently lead to premature mortality. Recent reports from Western Europe have shown long-term mortality (≥ 15 years follow-up) in T1D to be 3-4 times the general population;^{71, 125} however, long-term population-based data on T1D mortality in the United States has been limited and ranges from 5-7 times the general population.^{51, 63}

Using a large population-based T1D cohort in Allegheny County (Pittsburgh), Pennsylvania diagnosed between 1965 and 1979, we now extend the long-term mortality trends to between 28 and 43 years of follow-up after diagnosis and explore differences in mortality rates by sex, race, and year of T1D diagnosis.

4.3 RESEARCH DESIGN AND METHODS

4.3.1 Study Population

The Allegheny County type 1 diabetes registry cohort included all individuals diagnosed with childhood-onset (age<18 years) type 1 diabetes in Allegheny County between January 1, 1965 and December 31, 1979, and placed on insulin at diagnosis. Individuals were identified through a periodic review of hospital records and validated by contacting pediatricians throughout the county, with ascertainment exceeding 95%.⁵² Individuals were excluded if diabetes developed due to a secondary cause (i.e., cystic fibrosis, Down's syndrome, or steroid-induced diabetes). A total of 1,075 eligible participants were identified and included in the Allegheny County type 1 diabetes registry cohort, which has been part of an international study (Diabetes Epidemiology Research International, DERI) comparing mortality in population-based T1D cohorts across countries.^{58, 80, 82}

Vital status was determined as of January 1, 2008, by contacting all participants initially by letter with a health update questionnaire 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.

4.3.2 Mortality Data

Deaths not identified through contacting participants were discovered by searching both the Social Security Death Index and the National Death Index (NDI). Death certificates (or NDI data) were obtained to confirm each death. In addition, the following sources of information were sought, as appropriate: 1) medical records surrounding the death; 2) autopsy/coroner's reports; and 3) interview with next-of-kin regarding the circumstances surrounding the death. The underlying cause of death, and rank order for all contributing causes, for each decedent was determined by the M.D. Mortality Classification Committee of the DERI Study.⁵⁸

4.3.3 Statistical Analysis

Distributional characteristics for each variable were assessed for normality. Student's t-test and one-way ANOVA were used to compare variables between groups, adjusting for multiple comparisons using the Bonferroni correction. Diagnosis year was categorized into three groups (1965–1969, 1970–1974, and 1975–1979) to evaluate temporal trends in overall, as well as sex- and race-specific mortality. For this analysis, age at diabetes onset was categorized as pre-pubertal (<10 yrs), peri-pubertal (10-14 yrs), and post-pubertal (>14 yrs). The χ^2 (or Fisher's exact) test was used to compare categorical variables between groups, as appropriate. Variables were then made available in multivariable Cox proportional hazards regression models using backward selection. The proportional hazards assumption was assessed visually and confirmed by testing time-dependent interaction variables.

Expected mortality was estimated using the person-years method based on general population life tables for Allegheny County, Pennsylvania.¹⁸⁵ Age-, sex-, and race-adjusted standardized mortality ratios (SMRs) were calculated as the observed divided by the expected number of deaths in each age, sex, and race category, and 95% CIs were determined with the Poisson distribution. Mortality rates and SMRs were compared using rate ratio (RR) analyses and calculating 95% CIs.¹⁸⁶ Statistical significance was considered at $p < 0.05$. All analyses were completed using SPSS 17.0 (SPSS, Chicago, IL).

4.4 RESULTS

Demographic characteristics of the Allegheny County type 1 diabetes registry cohort are presented by sex and race in Table 4. Vital status as of 1 January 2008 was verified for 1,043 participants (ascertainment rate=97.0%) providing 34,363 total person-years of follow-up. Vital status verification did not differ by sex ($p=0.11$) or by age at diabetes onset (mean \pm SD: confirmed 10.8 ± 4.2 yr vs. unconfirmed 12.2 ± 4.2 yr, $p=0.07$). However, Caucasians were more likely to be traced than African-Americans (97.7% vs. 88.6%, respectively, $p<0.001$). No differences in ascertainment rates existed by diabetes diagnosis year or age and diabetes onset.

Over a median 33.0 years of follow-up, 279 total deaths (26.0%) occurred in this population, almost evenly split between males and females (M=138 and F=141 deaths), which was 7 times higher than seen in the local general population (SMR=6.9, 95% CI 6.1–7.7). The mean age (\pm SD) and duration of diabetes at follow-up were 42.8 ± 8.0 and 32.0 ± 7.6 years, respectively. A much higher proportion of African-Americans died during follow-up compared

to Caucasians (50.6% vs. 24.0%, respectively, $p<0.001$). As a result, the mean duration of follow-up (diabetes duration) and the mean age for African-Americans in this cohort were both approximately five years less than Caucasians (Table 4). Mean follow-up duration did not differ by sex, but mean age at follow-up was significantly lower for females (F vs. M: 42.3 ± 8.4 yr vs. 43.4 ± 7.6 yr, $p=0.02$).

Overall and 30-year mortality rates by sex, race, and diabetes diagnosis cohort are presented in Table 5. The overall mortality rate was 812 per 100,000 person/yr (95% CI 717–907). African-American mortality rates were significantly higher than Caucasian rates overall and at the 30-yr follow-up time point ($p<0.001$), and while rates were higher in females compared to males, this was not significant. Individuals diagnosed before age 10 (pre-pubertal) in this T1D cohort had significantly lower mortality rates than those with peri-pubertal (age 10–14) and post-pubertal (age >14) onset both overall and at 30-yr follow-up ($p<0.01$). In addition, different cut-points for pubertal classification were selected to verify that the findings presented herein are valid (Appendix A, Table 18). We found that regardless of cut-point, individuals diagnosed in the pre-pubertal years had significantly lower mortality rates compared to those with pubertal onset. Mortality rates lowered in a stepwise manner by diabetes diagnosis cohort, with mortality in the 1965–1969 group significantly higher than the 1975–1979 group overall (rate ratio (RR) = 1.86, $p<0.001$) and at 30 years of follow-up (RR=1.51, $p=0.02$).

Results from a multivariable Cox regression model for overall mortality are shown in Table 6. Sex was not significant in the multivariable models and was not included in the final model. Race, age at onset, and year of diagnosis all significantly predicted mortality in type 1 diabetes (both categorically and continuously). Adjusted mortality risk for African-Americans was 3.2 times higher than for Caucasians. Each additional year in age at diabetes diagnosis

conferred a 7% higher mortality risk (HR 1.07, 95% CI 1.04–1.10), and risk of death decreased by 6% for each additional calendar year of diabetes diagnosis over the 15-year period of diabetes diagnosis (1965–1979) in this cohort. As pubertal onset is known to vary by sex,¹⁸⁷ an interaction term (sex × age at onset) was added to both the continuous and the categorical models, but was not significant in either model (data not shown).

Survival curves based on Kaplan-Meier life-table analyses are presented in Figure 3. Cumulative survival after diagnosis of type 1 diabetes in this cohort was 98.2% at 10 yrs, 93.1% at 20 yrs, 80.9% at 30 yrs, and 68.4% at 40 yrs (Figure 3A). Survival curves did not differ by sex (30-yr survival M vs. F: 82.6% vs. 79.0%, Figure 3B), but were significantly worse for African-Americans compared to Caucasians (30-yr survival: 57.2% vs. 82.7%, respectively, Figure 3C). Significant improvement in survival was seen across the diabetes diagnosis cohorts (Figure 3D); and, when separated by sex or race (Appendix A, Figure 8A–D), a declining trend in mortality was seen across all race and sex groups. However, only survival in males ($p=0.02$) and in Caucasians ($p=0.05$) showed a significant improvement across diagnosis cohort. A higher survival rate was also seen by in the pre-pubertal group (age<10 yrs) compared to either the peri- or post-pubertal groups.

Next, we calculated the standardized mortality ratios (SMRs) for this cohort compared to the local age-, sex- and race-matched general population (Table 7). Thirty years after diagnosis of diabetes, mortality was more than 7 times higher than seen in the local general population (SMR=7.4, 95% CI 6.4–8.4). The SMR for females is nearly three times higher than that for males (13.2 vs. 5.0, $p<0.05$), while the SMRs by race were identical (African-American vs. Caucasian: 7.5 vs. 7.4). An improving trend in SMR was seen by diagnosis cohort at 30 yrs diabetes duration: 9.3 (95% CI, 7.2–11.3), 7.5 (5.8–9.2), and 5.6 (4.0–7.2) for 1965–1969, 1970–

1974, and 1975–1979, respectively. No clear differences in SMR were seen by age at onset, with peri-pubertal onset having the highest SMR (9.2, 7.3–11.1).

The SMRs over time (5-yr follow-up intervals) are shown in Figure 4 by sex, race and diabetes diagnosis cohort. SMRs at 5-yr follow-up are very high in the Allegheny County cohort, especially in females and in the earlier diagnosis cohorts (1965–1969 and 1970–1974). Mortality within the first year of diagnosis (onset mortality) was relatively common in this cohort (10 deaths) and occurred almost exclusively in females ($n=9$), driving the extremely high female SMR at 5 years of follow-up (data not shown). Females have had SMRs of 10 or more, whereas in males SMRs range between 1.8 and 5.0 over 30 yrs of follow-up (Figure 4B). SMRs did not differ significantly by race, but were consistently lower in African-Americans over time (Figure 4C). Consistent improvements in SMRs have been seen over time between the 1965–1969 and 1975–1979 diagnosis cohorts, even after 30 years T1D duration (Figure 4D).

Finally, we explored a surrogate marker of diabetes management by stratifying the Allegheny County cohort by whether or not individuals participated in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, which included participants with childhood-onset (age<17 yrs) type 1 diabetes either diagnosed at Children’s Hospital of Pittsburgh or seen within 1 year of diagnosis. Only 271 (25.2%) individuals in the Allegheny County T1D Registry also participated in the Pittsburgh EDC Study. Compared to those only in the county registry, EDC Study participants did not differ by sex or diagnosis cohort, but were more likely to be Caucasian ($p=0.02$) and have a younger age at onset (8.8 ± 4.1 vs. 11.6 ± 3.9 yrs, $p<0.001$; Appendix A, Table 19). Also, county registry individuals who also participated in the EDC Study had a significantly lower mortality rate compared to others in the county registry (rate ratio = 1.8, $p<0.001$; Appendix A, Table 20).

4.5 DISCUSSION

These results expand on previously published reports from the Allegheny County type 1 diabetes registry cohort with an additional 9 years of follow-up.^{63, 80, 82} Of note, now with a range of 28–43 yrs of type 1 diabetes duration, the risk of dying is 7 times higher than the local general population, with significant improvements in SMR for those diagnosed most recently in this cohort. This SMR (7.4, 95% CI 6.4–8.4) is higher than Nishimura et al. reported for this cohort for the 1999 follow-up (SMR 5.2, 95% CI 4.4–6.0), perhaps reflecting an increasing effect of long-term complications, which are keeping mortality rates much higher in T1D compared to the general population.⁶³

This is the largest population-based type 1 diabetes cohort with at least 25 years of follow-up in the United States. A recent population-based study in New Zealand with 20 years of follow-up showed the highest SMRs in insulin-treated diabetic persons diagnosed at age < 30 yrs (3.3 and 4.3 for males and females, respectively).¹²⁷ A nationwide cohort of Norwegians with childhood-onset (age<15 yrs) also recently reported SMRs of 3.9 and 4.0 for males and females, respectively, after 20 years of follow-up.¹²⁵ Similar results were seen by sex in a U.K. cohort of 23,752 individuals diagnosed with diabetes prior to age 30 with a mean 13.4 years of follow-up (male SMR=2.7, female SMR=4.0).¹¹³ Other recent reports of all-cause mortality in population-based cohorts of type 1 diabetes exist, with SMRs ranging from 1.8–4.2, but their follow-up is limited (<10 yrs).^{118, 123, 129, 131, 188}

The markedly higher mortality seen in our United States type 1 diabetes cohort is clearly limited to women, for the men have very comparable SMRs to those reported in other long-term follow-up studies (New Zealand, Norway, U.K.).^{113, 125, 127} However, directly comparing SMRs across countries is not appropriate and the differences may result from either methodological or cohort differences between these studies. To what extent this reflects our different health care system and a potential lack of access in the U.S. is difficult to determine. National measures of health care performance and other national economic measures have been shown to contribute to diabetic complications in type 1 diabetes.¹⁸⁹

Compared to their respective general populations, females with T1D had an SMR nearly three times higher than males with T1D. This is partially reflective of the much lower mortality rates for young females in the general population. Long-term mortality rates do not differ by sex in type 1 diabetes, consistent with previous findings in our cohort.^{63, 81} However, these results are markedly different from the findings in New Zealand, Norway, and the U.K. The respective male/female mortality rate ratios for these studies are: 1.23 in New Zealand, 2.26 in Norway, and 1.29 in the U.K. compared to 0.80 for our study. The reason for this discrepancy is unclear, but it appears that females completely lose their general survival advantage in our diabetes population.

Despite race being a significant predictor of mortality within the Allegheny County cohort (HR=3.2), no differences in SMR were seen by race, with the African-American SMR tending to be lower than the Caucasian SMR during follow-up. This seemingly contradictory result can be explained by the extremely high mortality rates seen in young African-Americans in the general population, particularly resulting from violent deaths.^{190, 191} Thus, while mortality rates in type 1 diabetes are 2-3 times higher in African-Americans,¹²² this excess can be attributed to the background African-American mortality rates, and not to their diabetes. In a 3-

year follow-up of 725 African-Americans with a mean 9 year duration of type 1 diabetes, SMRs for males and females were 7.0 and 10.5, respectively, compared to the local general African-American population.¹²²

Temporal improvements in mortality have been reported in other type 1 diabetes studies. A report on 845 individuals diagnosed with type 1 diabetes (age<17 yrs) between 1940 and 1989 in the United Kingdom showed a four-fold decrease in SMRs between the 1940s cohort and the 1980s cohort (9.4 vs. 2.4, respectively).¹⁹² A large Danish study of mortality reported an increase of 15 years to the life expectancy of type 1 diabetic patients diagnosed over a 40-year period between 1933 and 1972.^{103, 105} A recent report in 845 individuals with childhood-onset (age < 18 yrs) type 1 diabetes in Romania showed improvements in life expectancy of 19.3 yrs between 1946 and 2005.¹⁹³ The reasons for temporal improvements in our cohort remain unclear, but an examination of cause-specific mortality is currently underway to determine whether chronic diabetes complications are being delayed or prevented in the youngest cohort (1975–1979) due to advances in care. Also, a cause-specific analysis may explain the dramatic differences in SMRs by sex.

Onset mortality (death within the first year of diagnosis) improved in this cohort. The 1975–1979 diagnosis cohort had only 1 onset death compared to 4 and 5 in the 1965–1969 and 1970–1974 cohorts, respectively. These results have been reported previously in this cohort,⁵⁸ are consistent with other studies, and correspond to improvement in diagnosis and care at onset.^{145, 194}

Finally, this cohort is part of the Diabetes Epidemiology Research International (DERI) Study group with Finland ($n=5,148$) and Japan ($n=1,410$) exploring mortality differences in childhood-onset (age<18) type 1 diabetes in three countries (all diagnosed between 1965 and 1979). The

most recent report compared mortalities in Japan and Finland after at least 15 years of follow-up.⁷¹ The SMR for Japan was significantly higher (12.9) than that of Finland (3.7). The comparable SMR for our population was 5.8, which remains consistent with previous reports from DERI showing U.S. mortality rates sandwiched between Japanese and Finnish mortality rates.^{80, 82}

A few key limitations with this follow-up study must be addressed. First, these population-based data reflect the type 1 diabetes experience of individuals diagnosed in Southwestern Pennsylvania between 1965 and 1979, and may not be representative of the entire United States, of individuals not of African-American or Caucasian ethnicity, or of those diagnosed earlier or later than this cohort. Also, 3% of the Allegheny County T1D registry cohort was lost to follow-up and vital status could not be determined for these individuals. Thus, the mortality rates might be slightly inflated. Thorough searches of both the Social Security Death Index and the National Death Index give us confidence that most (if not all) of these 32 individuals are still living. In addition, the analysis is limited to only a few key demographic variables (age at onset, race, sex), as other key socioeconomic and clinical variables could not be ascertained for all participants at study inception.⁵² Finally, as all individuals in this cohort were diagnosed prior to major modern-day advances in type 1 diabetes treatment (self-monitoring blood glucose, HbA_{1c} testing, and ACE inhibitors), the effect of these advances cannot be properly examined here.

Key strengths of this study include the size of this population-based cohort ($n=1,075$) and the 97% ascertainment rate after 25+ years of follow-up. Also, we now have sufficient follow-up data for temporal trend and other analyses in African-Americans, providing important information for this understudied type 1 diabetes population.¹²²

In summary, these results are encouraging and provide contemporary, population-based mortality figures for individuals with long-standing T1D. Females in our cohort die at a rate similar to males, a result warranting further exploration, as younger females have much lower mortality rates than younger males in the general U.S. population. These data illustrate that mortality rates are clearly decreasing in those diagnosed more recently with type 1 diabetes; however those diagnosed most recently (1975-1979) still die at rates 5 times higher than the general population. Thus, continuing improvements in treatment and care are essential.

Disclaimer

The general population mortality data were provided by the Bureau of Health Statistics and Research, Pennsylvania Department of Health. The Department specifically disclaims responsibility for any analyses, interpretations or conclusions.

4.6 TABLES

Table 4. Demographic characteristics (% (*n*) or mean \pm SD) of the Allegheny County Type 1 Diabetes Registry cohort by sex and race as of 1 January 2008.

	Male	Female	Caucasian	African American	Total
<i>n</i>	558	517	996	79	1,075
Vital status confirmed	97.8 (546)	96.1 (497)	97.7 (973)	88.6 (70)**	97.0 (1,043)
Male	---	---	52.7 (525)	43.0 (34)	52.0 (559)
Caucasian	94.1 (525)	91.1 (471)	---	---	92.7 (996)
Diagnosis: 1965–1969	32.0 (179)	34.1 (176)	32.9 (328)	34.2 (27)	33.0 (355)
Diagnosis: 1970–1974	38.1 (213)	34.4 (178)	36.7 (366)	31.6 (25)	36.4 (391)
Diagnosis: 1975–1979	29.7 (166)	31.5 (163)	30.3 (302)	34.2 (27)	30.6 (329)
Age at T1D diagnosis	11.0 \pm 4.3	10.8 \pm 4.0	10.8 \pm 4.2	11.4 \pm 4.3	10.9 \pm 4.2
Mean T1D duration^a	32.4 \pm 6.9	31.5 \pm 8.2	32.3 \pm 7.4	27.3 \pm 8.0**	31.9 \pm 7.6
Mean age^a	43.4 \pm 7.6	42.3 \pm 8.4*	43.2 \pm 7.9	38.7 \pm 8.6**	42.8 \pm 8.0
Person-years of follow-up	18,082.3	16,280.8	32,202.6	2,160.6	34,363.1

^aT1D Duration and Age at death or last follow-up

p* < 0.05; *p* < 0.01

Table 5. Overall and 30-year mortality rates by sex, race, and T1D diagnosis cohort

	Overall			30-year		
	Deaths % (<i>n</i>)	Follow-up Time (person-yrs)	Mortality rate (95% CI) (per 100,000 person-yrs)	Deaths % (<i>n</i>)	Follow-Up Time (person-yrs)	Mortality rate (95% CI) (per 100,000 person-yrs)
Overall	26.0 (279)	34,363.1	811.9 (716.6–907.2)	18.8 (202)	30,046.2	672.3 (579.6–765.0)
Sex						
Males	24.7 (138)	18,082.3	763.2 (635.8–890.5)	17.0 (95)	15,805.4	601.1 (480.2–721.9)
Females	27.3 (141)	16,280.8	866.1 (723.1–1009.0)	20.7 (107)	14,240.8	751.4 (609.0–893.7)
Race*						
Caucasian	24.0 (239)	32,202.6	742.2 (648.1–836.3)	17.1 (170)	28,016.9	606.8 (515.6–698.0)
African American	50.6 (40)	2,160.6	1,851.3 (1277.6–2425.1) [†]	40.5 (32)	2,029.3	1,576.9 (1030.5–2123.3) [†]
Age at Onset*						
<10 yrs	20.7 (84)	13,530.3	620.8 (488.1–753.6)	11.9 (48)	11,623.9	412.9 (296.1–529.8)
10–14 yrs	28.6 (112)	12,368.0	905.6 (737.8–1073.3) [†]	22.7 (89)	10,853.8	820.0 (649.6–990.4) [†]
>14 yrs	29.9 (83)	8,464.9	980.5 (769.6–1191.5) [†]	23.4 (65)	7,568.6	858.8 (650.0–1067.6) [†]
Diagnosis cohort**						
1965–1969	37.2 (132)	12,277.6	1,075.1 (891.7–1258.5)	22.3 (79)	9,877.2	799.8 (623.4–976.2)
1970–1974	23.5 (92)	12,584.8	731.0 (581.7–880.4) [†]	18.9 (74)	10,937.9	676.5 (522.4–830.7)
1975–1979	16.7 (55)	9,500.7	578.9 (425.9–731.9) [†]	14.9 (49)	9,231.1	530.8 (382.2–679.4) [†]

* $p < 0.01$ for χ^2 comparisons of deaths overall and at 30-yr follow-up

** $p < 0.01$ for χ^2 comparisons of deaths overall only

[†] $p < 0.05$ for rate ratio compared to first group within each category

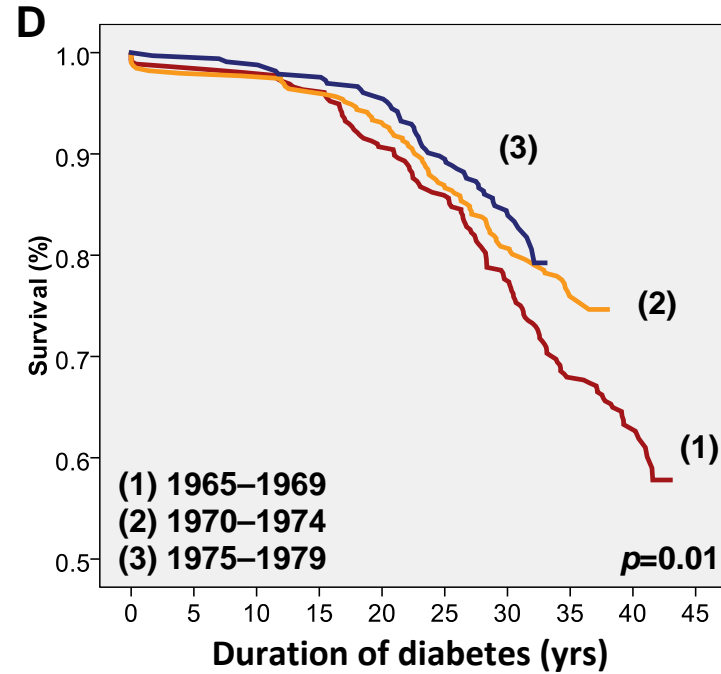
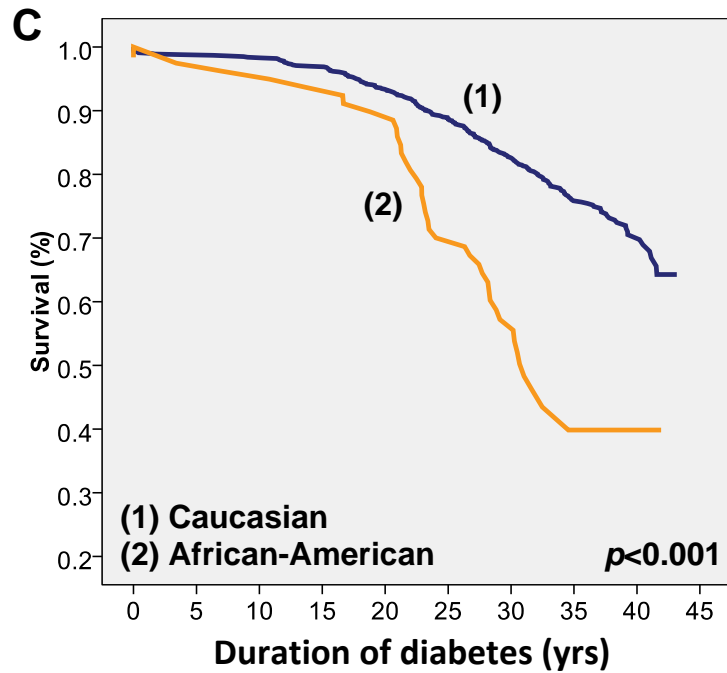
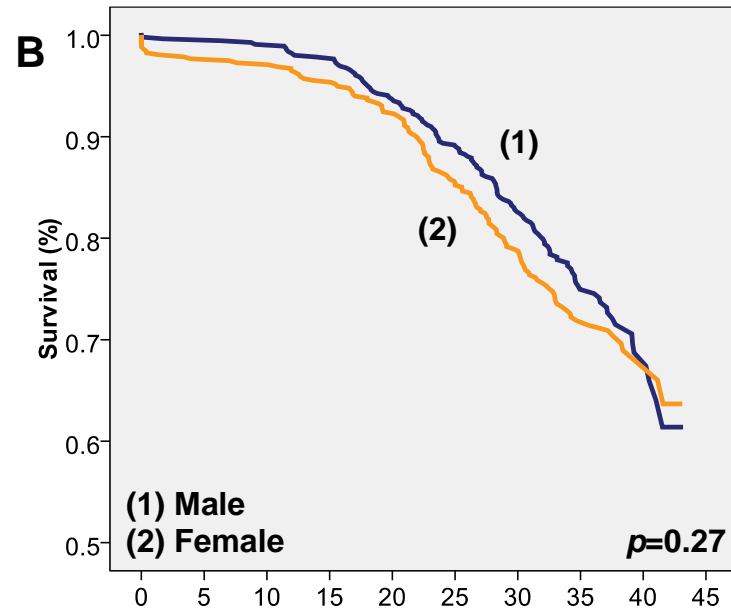
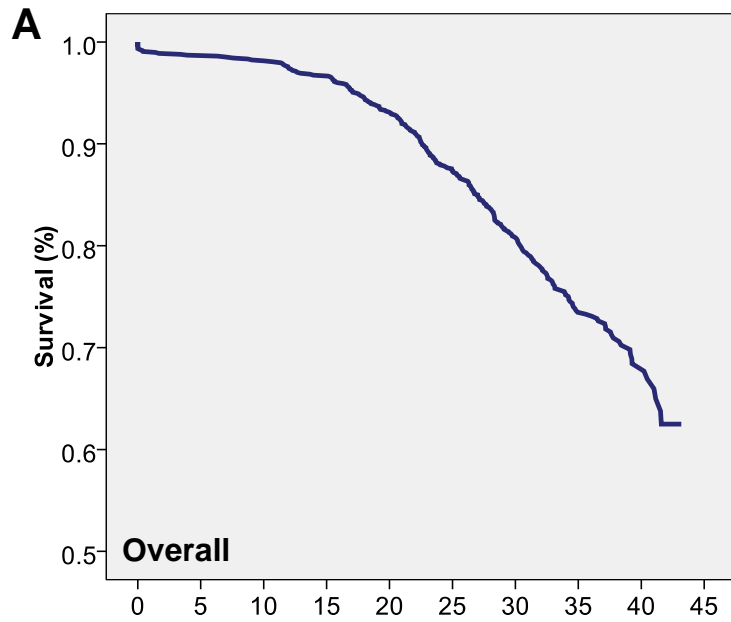
Table 6. Adjusted risk of overall mortality in the Allegheny County Type 1 Diabetes Registry cohort with age at onset and diagnosis year as categorized and continuous variables.

	Categorical		
	Adjusted HR	95% CI	<i>p</i> -value
Female	Not selected	---	---
African American	3.16	2.25–4.43	<0.001
Age at onset			0.001
<10 yrs (Ref)	1.00	---	---
10-14 yrs	1.54	1.16–2.05	0.003
>14 yrs	1.75	1.29–2.37	<0.001
Diagnosis cohort			0.003
1965-1969	1.69	1.22–2.35	0.002
1970-1974	1.20	0.86–1.69	0.29
1975-1979 (Ref)	1.00	---	---
	Continuous		
	Adjusted HR	95% CI	<i>p</i> -value
Female	Not selected	---	---
African American	3.17	2.26–4.44	<0.001
Age at onset (yr)	1.07	1.04–1.10	<0.001
Year of diagnosis (yr)	0.94	0.91–0.97	<0.001

Table 7. 30-yr standardized mortality ratios (SMRs) by sex, race, age at onset, and diagnosis cohorts

	SMR	95% CI
Overall	7.4	6.4–8.4
Sex		
Males	5.0	4.0–6.0
Females	13.2	10.7–15.7
Race		
Caucasian	7.4	6.3–8.5
African American	7.5	4.9–10.1
Age at onset		
<10 yrs	6.2	4.4–7.9
10-14 yrs	9.2	7.3–11.1
>14 yrs	6.6	5.0–8.2
Diagnosis cohort		
1965–1969	9.3	7.2–11.3
1970–1974	7.5	5.8–9.2
1975–1979	5.6	4.0–7.2

4.7 FIGURES



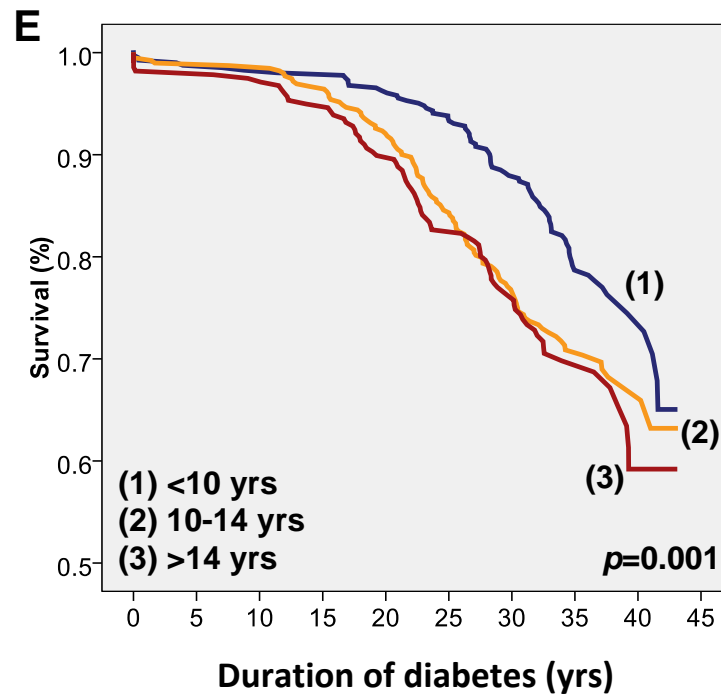
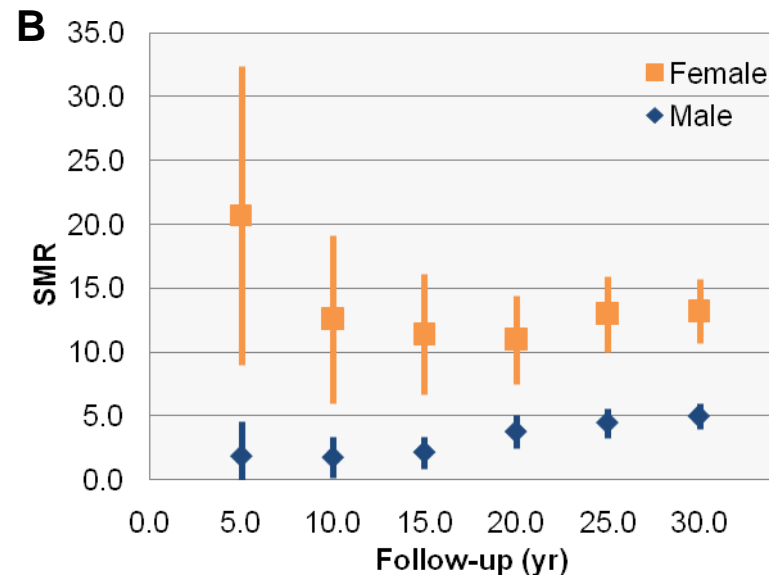
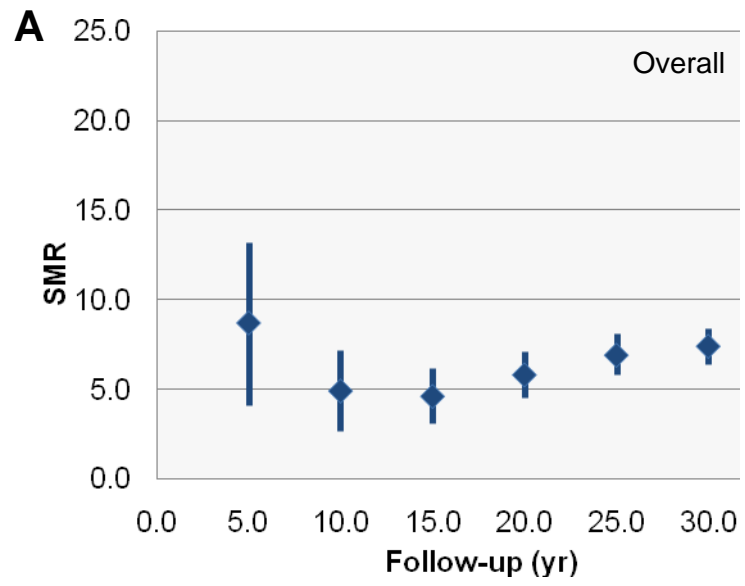


Figure 3. Life-table analyses by sex, race, diagnosis cohort, and age at onset for individuals diagnosed with type 1 diabetes between 1965 and 1979 in the Allegheny County Type 1 Diabetes Registry cohort. *P*-values calculated using the log-rank test. A) Overall; B) Sex; C) Race; D) Diagnosis cohort; E) Age at Diabetes Onset. D: 1965–69 vs. 1970–74, $p=0.02$, and 1965–69 vs. 1975–79, $p=0.02$. E: <10 vs. 10-14, $p=0.002$, and <10 vs. >14, $p<0.001$.



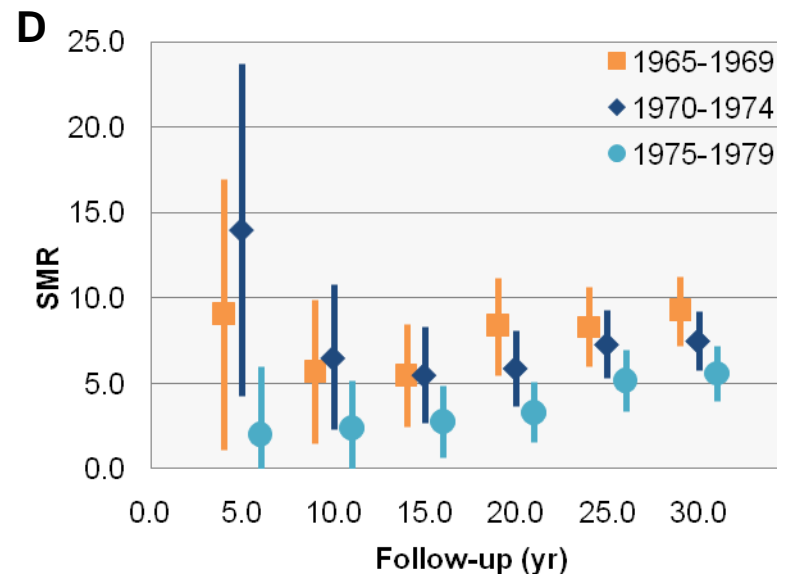
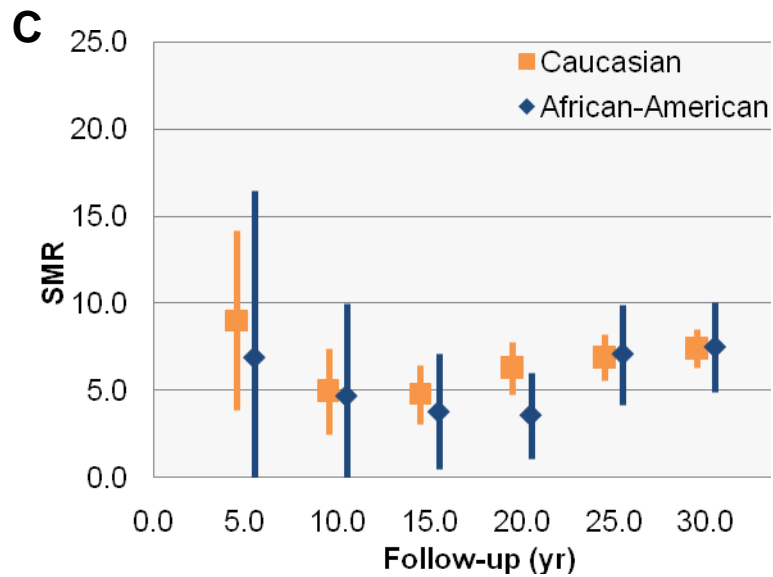


Figure 4. Standardized mortality ratios (SMRs) and 95% confidence intervals for the overall (A) Allegheny County Type 1 Diabetes Registry cohort and by sex (B), race (C), and diagnosis cohort (D) at 5-year intervals of follow-up. Panels C and D are spaced around the 5-yr intervals for visual clarity; however, all SMRs are calculated at the same 5-yr follow-up points.

**5.0 PAPER 2: CAUSE-SPECIFIC MORTALITY TRENDS IN A LARGE
POPULATION-BASED COHORT WITH LONG-STANDING CHILDHOOD-ONSET
TYPE 1 DIABETES: THE ALLEGHENY COUNTY TYPE 1 DIABETES REGISTRY**

To be submitted for publication

Aaron M. Secrest¹, Dorothy J. Becker², Sheryl F. Kelsey¹, Ronald E. LaPorte¹,
and Trevor J. Orchard¹

¹Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh,
Pittsburgh, Pennsylvania

²Department of Pediatrics, Children's Hospital of Pittsburgh, University of Pittsburgh School of
Medicine, Pittsburgh, Pennsylvania

5.1 ABSTRACT

INTRODUCTION: To address the excess mortality seen in type 1 diabetes (T1D), it is essential to understand the primary cause(s) of mortality in T1D. However, contemporary long-term data on cause-specific mortality in a population-based T1D cohort in the United States have not been reported.

METHODS: The Allegheny County (Pennsylvania) childhood-onset (age<18 yrs) type 1 diabetes registry (n=1,075) with diagnosis from 1965–1979 was used to explore patterns in cause-specific mortality. Overall, sex- and race-specific mortality rates (per person-year of follow-up) as well as standardized mortality ratios (SMRs) by underlying cause of death were calculated. Temporal patterns were examined by year of diagnosis (1965–69, 1970–74, and 1975–79).

RESULTS: Vital status for 1,043 (97%) participants was ascertained as of 1 January 2008. Over 34,363 person-years of follow-up, 279 (26.0%) deaths occurred (141 females and 138 males). Within the first 10 years after diagnosis, the leading cause of death was acute diabetes complications (73.6%). During the next 10 years of after T1D diagnosis, deaths were nearly evenly attributed to acute (15%), cardiovascular (22%), renal (20%), or infectious (18%) causes. After 20 years duration, chronic diabetes complications (cardiovascular, renal, or infectious) account for >70% of all deaths, with cardiovascular disease becoming the leading cause of death (40%). SMRs for diabetes-related complications reveal significantly higher rates than the local general population (CVD SMR=12.9, 95% CI 10.4–15.5; renal SMR=104.3, 70.7–137.9;

infection SMR=41.2, 29.3–53.1); however, SMRs for non-diabetes-related causes do not significantly differ from the general population (violent deaths: SMR=1.2, 0.6–1.8; cancer: SMR=1.2, 0.5–2.0).

CONCLUSION: The excess mortality seen in type 1 diabetes is almost entirely related to diabetes and its comorbidities, as non-diabetes-related causes are not higher in this population.

Of note, mortality rates for all diabetes-related causes appear to be decreasing, but remain high compared to the general population.

5.2 INTRODUCTION

Mortality rates for type 1 diabetes (T1D) are much higher than the general population in the United States and worldwide.^{63, 83, 195} Understanding the primary cause(s) of this excess mortality is essential for developing interventions to decrease mortality rates in T1D. This excess mortality has attributed both to acute diabetes complications as well as to chronic diabetic renal and cardiovascular disease (CVD). Previous reports have shown that renal disease is the leading cause of death in the first 20 years of T1D; subsequently, CVD predominates.^{38, 42, 51}

Only a handful of recent reports address cause-specific mortality in population-based T1D cohorts,^{112, 125, 196-199} and even fewer have long-term follow-up (>15 years).^{125, 199} A recent Norwegian report, however, addressed long-term cause-specific mortality in 1,906 childhood-onset T1D individuals followed for at least 20 years (SMR=4.0),¹²⁵ and found that before age 30, acute complications were the most common cause of death in their cohort; whereas, after age 30, cardiovascular disease was predominant, consistent with the findings of the large Diabetes U.K. study.¹¹² The Diabetes U.K. study classified T1D as insulin-treatment before age 30 (n=23,752), and based on death certificate data alone, found that acute metabolic complications accounted for 34% of all deaths prior to age 30 (leading cause), but thereafter, cardiovascular disease becomes the leading cause (52%). Aside from the current study, the Norwegian study is the only other long-term T1D study to investigate deaths with available terminal hospital records, autopsy reports and police reports.

Data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study suggest that the incidence of end-stage renal disease has declined quite markedly, while the incidence of

coronary artery disease remains relatively unchanged over 30 years in T1D persons.⁷⁵ This is of particular interest as renal disease is thought to be the major driver of cardiovascular disease in T1D.¹⁰² Herein, we explore cause-specific mortality trends by sex, race, age at diabetes onset, and calendar year of diagnosis to determine how T1D mortality is changing over time using a large population-based T1D cohort in Allegheny County (Pittsburgh), Pennsylvania diagnosed between 1965 and 1979. Apart from a race-specific analysis in a cohort combined with the Pittsburgh EDC Study, cause-specific mortality has not been formally evaluated in this population since 1985.⁵⁸ We specifically examine whether the percentage of renal-related cardiovascular deaths is changing over time as well as other cause-specific patterns.

5.3 RESEARCH DESIGN AND METHODS

5.3.1 Study Population

The Allegheny County Type 1 Diabetes Registry has been described in detail.⁸⁰ This cohort ($n=1,075$) consists of all individuals diagnosed with childhood-onset (age<18 years) type 1 diabetes in Allegheny County between January 1, 1965 and December 31, 1979, and placed on insulin at diagnosis. Individuals were identified via hospital record review and validated by contacting pediatricians throughout the county, with >95% ascertainment.⁵² Children developing diabetes from a secondary cause (i.e., cystic fibrosis, Down's syndrome, or steroid-induced diabetes) were excluded. This cohort has been part of a comparative international study (Diabetes Epidemiology Research International, DERI) of T1D mortality rates.⁸²

To determine vital status as of January 1, 2008, all participants were contacted initially by letter, then by telephone if necessary, to complete a brief health update questionnaire. The study protocol was approved by the University of Pittsburgh Institutional Review Board.

5.3.2 Mortality Classification Procedures

Deaths were identified by either: 1) participant contact, 2) the Social Security Death Index, or 3) the National Death Index (NDI), and then confirmed by death certificate. Attempts were made to obtain the following information, when appropriate: 1) medical records surrounding the death; 2) autopsy/coroner's reports; and 3) interview with next-of-kin regarding the circumstances surrounding the death. Protocols for abstracting standardized data from these records have been comprehensively detailed.⁵⁸ A Mortality Classification Committee consisting of trained internists used standardized protocols to determine 1) the underlying cause of death, and 2) the ordered contribution of all other causes of death. Causes of death were grouped as shown in Table 8.

5.3.3 Statistical Analysis

Each individual's contribution to person-years of follow-up was calculated from date of diabetes diagnosis to either 1 January 2008 or date of death or loss to follow-up. To compare continuous variables between groups, Student's *t*-test and one-way ANOVA were used, adjusting for multiple comparisons using the Bonferroni correction. The χ^2 (or Fisher's exact) test was used to compare categorical variables between groups, as appropriate. To evaluate temporal trends in

cause-specific mortality, calendar year at diagnosis was categorized into three groups (1965–1969, 1970–1974, and 1975–1979). Also, cause of deaths were grouped into four broad categories for some analyses: 1) acute diabetes complications (same as above); 2) chronic diabetes complications (including the renal, cardiovascular, infection, and other diabetes categories above); 3) non-diabetes causes (including accident or suicide, cancer, and other non-diabetes categories above); and 4) unknown cause (same as above).

Cause-specific mortality rates were calculated by dividing the number of deaths by the person-years of follow-up for those at risk during the specified duration interval. Cause-specific expected mortality was estimated using the person-years method based on general population life tables for Allegheny County, Pennsylvania, or, when deaths from a particular cause were extremely rare in the age-matched county population (i.e., renal deaths and infections), based on life tables for the state of Pennsylvania.¹⁸⁵ Cause-specific standardized mortality ratios (SMRs) adjusting for age, sex, and race were calculated as the observed divided by the expected number of deaths in each age, sex, and race category, and 95% CIs were determined with the Poisson distribution. Cause-specific mortality rates and SMRs were compared using rate ratio analyses.¹⁸⁶ Statistical significance was defined at the 5% level ($p < 0.05$). Analyses were performed using SPSS 17.0 (SPSS, Chicago, IL).

5.4 RESULTS

Demographic characteristics of the Allegheny County type 1 diabetes registry cohort are presented by year of diabetes diagnosis in Table 9. Vital status was determined as of 1 January

2008 for 1,043 participants (97.0% ascertainment rate). A total of 279 deaths (26.0%) occurred in this population over 34,363 total person-years of follow-up. Nearly half of the total deaths occurred in the 1965–69 diagnosis cohort ($n=132$), and significantly fewer deaths were observed in the 1970–74 and 1975–79 diagnosis cohorts (92 and 55 deaths, respectively). No significant differences existed in sex or race by diagnosis cohort; however, age at onset significantly increased across diagnosis cohorts from a mean of 10.5 yrs in the 1965–69 cohort to 11.4 yrs in the 1975–79 ($p=0.01$).

5.4.1 Proportions of Deaths by Cause

Figure 5 shows the proportions of deaths by underlying cause for 10-yr intervals of diabetes duration. Within the first 10 yrs of diabetes onset more than 70% of all deaths were due to acute diabetes complications. After 10 yrs of diabetes, acute complications become a minor but persistent cause of death in this population (9-15% of deaths across all diabetes duration intervals after 10 yrs, Figure 5). Also, after 10 yrs T1D duration, cardiovascular disease becomes the leading cause of death, eventually accounting for 40% of all deaths after 20 yrs duration.

By separating these data by sex, race, and diabetes duration, some patterns emerge (Appendix A, Figure 9). In females, diabetes complications caused more than 90% of all deaths in the first 30 years after diagnosis; however, in males, diabetes complications account for only 75% of all deaths during the same time period. Aside from 1 death of unknown cause, all deaths in African-American participants were due to either acute or chronic diabetes complications, whereas nearly 20% of all deaths in Caucasian participants were not related to diabetes. No clear patterns existed when the study population was separated by year of diagnosis.

5.4.2 Cause-specific Mortality Rates

Cause-specific mortality rates were stratified by sex and by race (Table 10), as well as by year of diabetes diagnosis (Table 11). Overall, females with T1D had a higher mortality rate for diabetes-related deaths (female:male mortality rate ratio (RR)=1.3, $p=0.05$), whereas males tended to have a higher mortality rate from non-diabetes-related causes (M:F RR=1.9, $p=0.06$). Specifically, of the 16 total deaths caused by accident or suicide, 14 occurred in males (M:F RR=7.2, $p=0.009$). When the mortality rates were stratified by both sex and duration of diabetes, the only significant difference was that within the first 10 years after diagnosis, 12 of 14 acute complication deaths occurred in women (F:M RR)=6.6, $p=0.01$).

When stratified by race, the overall mortality rate was significantly higher in African-American participants (RR=2.5, $p<0.001$, Table 10). Specifically, African-American T1D participants died of acute complications at much higher rates than Caucasian participants (RR=4.8, $p<0.001$). Similarly, African-American participants died at significantly higher rates of renal disease (RR=4.6, $p<0.001$), cardiovascular disease (RR=1.9, $p=0.05$), and infection (RR=2.8, $p=0.01$) than Caucasian participants. Conversely, all deaths from non-diabetes-related causes occurred in Caucasian T1D participants: all 16 accidental or violent deaths and all 10 cancer deaths, as well as all other non-diabetes-related deaths ($n=14$). Of note, all 8 suicides in this cohort occurred in Caucasian males.

Cause-specific mortality rates by diabetes diagnosis cohort were censored at 30 years of follow-up for appropriate comparisons (Table 11). Overall, the 1965–69 cohort had significantly higher mortality rates from diabetes-related causes compared to the 1975–79 cohort (RR=1.5, $p=0.05$). Mortality rates from non-diabetes related causes were also higher for the 1965–69, but

this was not significant (RR=1.7, $p=0.24$). While cause-specific mortality rates for nearly all diabetes complications were highest in the oldest cohort (1965–69) and tended to decrease stepwise to the youngest cohort (1975–79), none of the mortality rates differed significantly. Mortality rates for acute complications (RR=2.3, $p=0.08$), renal disease (RR=1.6, $p=0.32$), and cardiovascular disease (RR=1.4, $p=0.25$) were all higher in the 1965–69 cohort compared to the 1975–79 at the 30-yr follow-up, but not to a statistically significant level. In addition, further stratification by diabetes duration revealed that compared to the 1965–69 cohort, the 1975–79 cohort had a significantly lower mortality rate over the first 20 years duration of type 1 diabetes (RR=0.45, $p=0.01$) (data not shown).

5.4.3 Cause-specific Standardized Mortality Ratios

Cause-specific standardized mortality ratios (SMRs) for this cohort were calculated (Table 12). SMRs for acute complications were not calculated as these causes of death (hyperglycemia and diabetic ketoacidosis) occur almost exclusively in individuals with type 1 diabetes in the age-matched local general population. Overall, deaths from cardiovascular disease (SMR=12.9, 95% CI 10.4–15.5), renal disease (SMR=104.3, 70.7–137.9), and infection (SMR=41.2, 29.3–53.1) all occur at tremendously higher rates than seen in the comparable local population. Infectious deaths were due primarily to sepsis (52%, often with concomitant renal failure) or pneumonia (25%). However, deaths from non-diabetes related causes like accident/suicide (SMR=1.2, 0.6–1.8) or cancer (SMR=1.2, 0.5–2.0), occur at similar rates in type 1 diabetes to the age-, sex- and race-matched general population.

The CVD, renal, and infection SMRs for females in this T1D cohort were higher than the respective SMRs for males (Table 12). Most notably, the female CVD SMR was three times higher than the male CVD SMR (24.7 vs. 8.6), and the female infection SMR was 2.5 times higher than the male infection SMR (67.8 vs. 26.7). No dramatic differences in SMR were seen by race or by diabetes diagnosis cohort (Table 12) for any cause of death. However, it should be noted that over 2,161 person-years of follow-up in this young African-American cohort, 2.5 violent deaths were expected to occur based on local general population mortality rates, but none actually did occur.

5.4.4 Contribution of Major Diabetes Complications to Death in Type 1 Diabetes

Finally, most deaths (65.0%) in this T1D cohort have at least one contributing or secondary cause of death. Therefore, to determine the true contribution of each major diabetes complication (acute complications, renal disease, and cardiovascular disease) in the deaths of T1D individuals, each major complication was considered to contribute to a death if it was either the underlying cause of death or a secondary cause of death. For example, an individual develops sepsis in the hospital after a bypass surgery due to a nosocomial infection of a dialysis port. The underlying cause of death might be classified as infection; however, both renal and cardiovascular disease played a significant secondary role in this death.

The proportion of deaths to which each major diabetes complication contributed is plotted by diabetes duration in Figure 6. Acute complications contributed to 80% of all deaths within the first 10 year of type 1 diabetes, but then drop to less than 20% of all deaths thereafter (Figure 6A). Renal disease does not contribute to any deaths until after 10 years of diabetes

duration. After 10 years, renal disease contributes to about half of all type 1 diabetes deaths in this cohort (Figure 6B). Cardiovascular disease contributes to about 10% of all deaths within the first 10 year of diabetes, but dramatically increases to one-third of all deaths between 10 and 20 years duration and then contributes to 60% of all deaths after 20 years of diabetes (Figure 6C). The role of renal disease in cardiovascular deaths consistently increased over diabetes duration; renal disease contributed to 67% of all CVD deaths before 20 years duration, but the renal disease contribution increases to 85% of all CVD deaths after 30 years diabetes duration.

An exploratory analysis of the contribution of these major complications by race, sex, or diabetes duration revealed no significant patterns, except that renal disease contributed to more deaths in African-Americans than in Caucasians with type 1 diabetes (62.5% vs. 44.6%, respectively, $p=0.04$). Of note, at least one of these 3 major complications contributed to 82.5% ($n=231$) of all deaths in this cohort.

5.5 DISCUSSION

These data represent the first attempt to assess cause-specific mortality in a population-based cohort with long-standing (>20 years) type 1 diabetes in the United States. These results clearly show that the higher mortality seen in type 1 diabetes compared to the general population results almost exclusively from higher rates in diabetes-related acute and chronic complications, as cause-specific SMRs for cancer and for violent/accidental deaths do not differ from the age-, sex-, and race-matched local population. Females with type 1 diabetes had significantly higher mortality rates for acute complications within the first 10 years of after diabetes onset than

males; however, the accidental or violent mortality rate was 7 times higher for T1D males compared to T1D females. African-Americans with type 1 diabetes have significantly higher mortality rates for all major diabetes-related complications (acute, renal, cardiovascular, and infection) than T1D Caucasians. Conversely, no African-Americans died of non-diabetes-related causes in this type 1 diabetes cohort.

Causes of early mortality (<10 years diabetes duration) have been extensively studied in type 1 diabetes across many countries and cohorts. An early report from the Children's Hospital of Pittsburgh cohort diagnosed between 1950 and 1980 reported 64% ($n=35$) of all deaths within the first 11 years (compared to 74% of our cohort in the first 10 years) after diagnosis were caused by acute complications (all diabetic ketoacidosis).¹⁹⁴ Similarly, Edge et al. reported that 83 (72%) of 116 deaths in diabetic individuals under age 20 in the U.K. were diabetes-related. However, this study relied on a retrospective analysis of death certificates. The reliability of using death certificate data alone to identify diabetic individuals has been questioned.^{172, 173} An international study that included early mortality data from the present study showed that acute complications (38%) were leading cause of death in the first 10 years of T1D, followed by accident/suicide (30%), with acute deaths occurring more commonly in Japan and in Allegheny County compared to Finland and Israel.⁵⁸ Joner et al. reported that only 35% of all early deaths in all childhood-onset (age<15 yrs at diagnosis) T1D individuals in Norway were due to acute complications.²⁰⁰ This seemingly optimistic finding is tempered by the fact that 40% of the deaths in their cohort resulted from suicide or accidents (compared to 6% in our cohort) during the first 10 years of diabetes. Similarly, a more recent report from the Diabetes Incidence Study in Sweden (DISS) showed that only 31% of all early (<10 years after diagnosis) deaths were related to acute diabetes complications, in harmony with another recent Swedish study, as well as

a smaller study from Israel.^{124, 144, 201} The remaining 40 deaths were due to either suicide, alcohol/drug abuse, or mental illness. A more recent report on early mortality in type 1 diabetes from EURODIAB revealed that only 47 (35%) of 134 deaths in children diagnosed after 1989 (mean follow-up time=7.6 yrs) were due to acute diabetes complications.¹⁸⁸ Another 53% were due to non-diabetes causes (accidents, suicide, etc.), and the role of diabetes was unclear in the remaining 12%.

Cause-specific mortality in long-standing type 1 diabetes (>20 years duration) has only been explored in a handful of studies. Borch-Johnsen et al. reported cause-specific mortality findings for all individuals diagnosed with type 1 diabetes (age≤30) before 1943 at Steno Memorial Hospital (Denmark) and followed until death or 1 January 1984. More than 50% of the patients dying within 35 years of T1D onset died from renal disease, compared to only 5% of those who died after 40 years duration.¹⁰⁴ Conversely, two-thirds of all deaths after 40 years of T1D resulted from CVD compared to only one-fourth of all deaths before 35 years duration. For comparison, renal disease was determined to be the underlying cause of death in only 17.1% of those who died before 35 years T1D duration in our cohort, suggesting that significant improvements in diabetes care between the 1940s and the 1960s and 1970s have resulted in fewer renal deaths. However, on closer examination, by including deaths where renal disease was a secondary cause of death, renal disease contributed to 47.1% of all deaths in our T1D population, suggesting that improvements in care have not drastically curtailed renal disease in T1D over this time period. A 2006 report from a national Norwegian childhood-onset (age<15 yrs) type 1 diabetes cohort diagnosed between 1973 and 1982 and followed until 2002 reported findings dramatically different from the present report. The overall proportions of death by major cause are: CVD (15%), violent cause (28%), acute complications (22%), renal (8%), and

infection (5%).¹²⁵ While the authors did employ an M.D. Mortality Classification Committee to determine the underlying cause of death, the contribution of any secondary causes of death was not reported, preventing a proper comparison of renal disease (and CVD) between our cohort and their cohort. Notably, the Norwegian cohort had smaller proportions of both CVD and infections than our cohort (15% vs. 35% and 5% vs. 16%, respectively), but larger proportions of both acute complications and violent deaths (22% vs. 16% and 28% vs. 6%, respectively).

The cause-specific SMRs reported for diabetes-related complications in our cohort are comparable to other reports.^{112, 125, 199} The sex-specific SMRs for CVD deaths in Norway were 11.0 for males and 10.3 for females, compared to 8.6 for males and 24.7 for females in our cohort.¹²⁵ Still, our overall CVD SMR was 12.8. We had essentially equivalent numbers of CVD deaths by sex (50 males and 50 females), whereas more men suffered CVD deaths than women in the Norwegian cohort (10 males and 4 females), suggesting that type 1 diabetes is leading to more female CVD-related deaths in the U.S. than in Norway. Renal SMRs in Norway were 220 for males and 155 for females, compared to 82.7 in males and 140.8 in females in Allegheny County. As nearly 75% of the deaths in the Norwegian cohort occurred in males (vs. nearly 50% in our cohort), the long-term type 1 diabetes experience appears to vary by sex between the two countries. Likewise, only 5.4% of the Norwegian cohort died during follow-up compared to 12.1% of our cohort over a similar follow-up, signifying that the Norwegian cohort might be receiving better care. Cause-specific SMRs from a 20-year follow-up report from New Zealand is less directly comparable, as type 1 diabetes was defined as diagnosis prior to age 30.¹⁹⁹ Thus, CVD SMRs are higher (ages 1–39: 98.1 and age 40–59: 27.4) and renal SMRs are lower (ages 1–39: 87.0 and age 40–59: 32.9), because of an older cohort at follow-up.

Regardless, all reports are consistent in showing that SMRs for diabetes-related complications are significantly higher than the age- and sex-matched general populations in each country.

No long-term cause-specific mortality data for African-Americans with type 1 diabetes exists outside our cohort. We have previously published on the racial differences in type 1 diabetes mortality combining the present cohort with the Children’s Hospital of Pittsburgh type 1 diabetes registry cohort (diagnosed 1965–1979) for a 20-year follow-up analysis.⁶⁴ The only difference in cause of death seen at the time was a significantly higher risk of acute death in African-Americans (HR=4.9, 95% CI 2.0–11.6). These data are consistent with a retrospective study of death certificates for Chicago residents (age 1–24) from 1987–94 by Lipton et al. that showed all 8 (of 30 total T1D deaths) acute complication deaths at onset occurred in either non-Hispanic black (7) or Hispanic (1) patients.²⁰² Only 2 deaths occurred in white T1D patients during this interval in Chicago, and neither was due to acute complications. Herein we report significantly higher mortality rates for all diabetes-related complications in T1D African-Americans compared to T1D Caucasians. This likely explains the dramatically higher overall mortality rates in T1D African-Americans in our cohort.^{61, 63, 64} It should also be noted that all of the deaths (excluding one unknown cause of death) in African-Americans in this cohort were caused by either an acute or a chronic diabetes complication. Young African-Americans have the highest violent death rates in the United States, and based on our African-American follow-up time, we expected to see 2.5 deaths due to violent causes (accident/suicide/homicide); however, none were observed.^{190, 191} This suggests that young African-Americans with type 1 diabetes are “protected” from violent deaths, but are at much higher risk of diabetes-related deaths than their Caucasian counterparts. The poorer prognosis for African-Americans with T1D might reflect an underlying racial gap in socioeconomic status or access to and utilization of

health-care that is present in the general U.S. population.¹⁹¹ Regrettably, none of these known factors are available for this cohort. A cause-specific analysis of mortality in the New Jersey 725 (all African-Americans with type 1 diabetes) is forthcoming and should help understanding these racial differences in mortality.¹²²

The contribution of major diabetes complications to T1D deaths has not been fully explored in a large population-based cohort. We found that renal disease and CVD contribute to 50% and >60% of all deaths, respectively, after 20 years T1D duration. On the other hand, acute complications contribute to 80% of all early (<10 years duration) deaths, but only contribute to about 15% of deaths thereafter. This is consistent with research showing that the majority of early acute deaths in T1D result from diabetic ketoacidosis (often at diabetes onset or after an acute illness), whereas later acute deaths tend to result from hypoglycemic episodes.^{152, 203} Also, although the incidence of renal disease appears to be decreasing in the Pittsburgh EDC Study,⁷⁵ the renal effects on cardiovascular disease have yet to diminish in the EDC cohort, with renal disease contributing to only 67% of CVD deaths before 20 years duration but increasing to 85% of all CVD deaths after 30 years duration.

A key limitation of this study is that the cause-specific mortality rates may not be representative of the current type 1 diabetes experience in the United States, as study participants have now had diabetes for 30+ years. In addition, cause-specific analysis is limited to a few basic demographic variables (race, sex, year of diagnosis), since other socioeconomic and clinical variables were not ascertainable for all participants at start of the study.⁵² Finally, finalizing cause of death in this cohort is an ongoing process. To date, 219 (79%) of deaths have been finalized by the international M.D. Mortality Classification Committee (MCC). The remaining deaths have been classified based on the death certificate and all additional

information available to date. However, these deaths are often (35-40%) reclassified as we obtain additional information regarding the circumstances surrounding each death, and each death becomes finalized by the MCC.

These results offer the best picture of cause-specific mortality in long-standing (28–43 years) type 1 diabetes in the United States, as they come from a large (n=1,075) population-based cohort with near complete ascertainment (97%) of vital status. Also, we now have sufficient follow-up to determine sex, race and temporal differences in cause-specific mortality.

In summary, mortality rates for all diabetes-related chronic complications show signs of decreasing, but all remain significantly higher than seen in the age-, sex-, and race-matched local general population. Females in our cohort die at a rate similar to males for most diabetes-related causes of death, a result that merits further investigation, since younger females have much lower mortality rates than younger males in the general population. African-Americans have significantly higher mortality rates than Caucasians for all diabetes causes, supplementing our previous finding that African-Americans with T1D have higher mortality rates due to acute complications.⁶⁴ An emphasis on preventing acute complications early after diagnosis as well as preventing or delaying chronic diabetes complications would likely result in major improvements in life span for individuals with type 1 diabetes.

Disclaimer

The general population mortality data were provided by the Bureau of Health Statistics and Research, Pennsylvania Department of Health. The Department specifically disclaims responsibility for any analyses, interpretations or conclusions.

5.6 TABLES

Table 8: Cause of death groups for classification by Mortality Classification Committee

<p><u>Diabetes-Related:</u></p> <ol style="list-style-type: none">1) Acute diabetic complications: diabetic ketoacidosis, hyperglycemia, hypoglycemia, hypokalemia, and diabetic coma unspecified2) Diabetic renal disease: diabetic nephropathy, end stage renal disease, and dialysis-related complications3) Cardiovascular: coronary artery disease, myocardial infarction, sudden cardiac death, cerebrovascular disease, peripheral vascular disease, heart failure, arrhythmias, and cardiomyopathy4) Infection: pneumonia, bronchitis, sepsis, meningitis, encephalitis, osteomyelitis, mycosis, and endocarditis5) Other diabetes: autonomic neuropathy, angiopathy, uncontrolled diabetes, and post-transplant complications
<p><u>Non-Diabetes-Related:</u></p> <ol style="list-style-type: none">1) Cancer: any form of cancer2) Accident or suicide: violent deaths, motor vehicle crashes, alcohol/drug overdose, and other accidental deaths (drowning, fall, fire)3) Other non-diabetes: other causes not specific to diabetes, e.g., sickle cell trait, bulimia/anorexia, lupus, septic abortion, epilepsy, multiple sclerosis, gastric ulcer, or HIV
<p>Unknown, where cause of death could not be determined</p>

Table 9: Demographic characteristics (% (*n*) or mean \pm SD) of Allegheny County Type 1 Diabetes Registry population by diagnosis cohort as of 1 January 2008.

	Diagnosis cohort			Overall
	1965-1969	1970-1974	1975-1979	
N	355	391	329	1,075
Vital status confirmed	96.6 (343)	97.4 (381)	97.0 (319)	97.0 (1,043)
Deceased	37.2 (132)	23.5 (92)	16.7 (55)*	26.0 (279)
Male	50.4 (179)	54.5 (213)	50.5 (166)	51.9 (558)
Caucasian	92.4 (328)	93.6 (366)	91.8 (302)	92.7 (996)
Age at T1D diagnosis	10.5 \pm 4.4	10.8 \pm 4.0	11.4 \pm 4.0*	10.9 \pm 4.2
Mean T1D duration^a	34.6 \pm 9.0	32.2 \pm 7.3	28.9 \pm 4.7*	32.0 \pm 7.6
Mean age^a	45.1 \pm 9.2	42.9 \pm 7.8	40.3 \pm 5.9*	42.9 \pm 8.0
Person-years of follow-up	12,277.6	12,584.8	9,500.7	34,363.1

^aType 1 diabetes duration and age at death or last follow-up

* $p \leq 0.01$ for either χ^2 or ANOVA across diagnosis cohort groups

Table 10. Cause-specific mortality rates (per 100,000 person-yrs (95% CI)) by sex and by race in the Allegheny County Type 1 Diabetes Registry cohort.

Cause	N ^a	Sex		Race	
		Male (n=138)	Female (n=141)	Caucasian (n=239)	African-American (n=40)
Diabetes-related	239	613.9 (499.7–728.1)	786.2 (650.0–922.4)*	618.0 (532.1–703.8)	1851.3 (1277.6–2425.1)**
Acute complication	45	105.1 (57.8–152.3)	159.7 (98.3–221.1)	102.5 (67.5–137.4)	555.4 (241.2–869.6)**
Renal disease	37	88.5 (45.1–131.8)	129.0 (73.8–184.2)	86.9 (54.7–119.2)	416.6 (144.4–688.7)**
CVD ^b	100	276.5 (199.9–353.2)	307.1 (222.0–392.2)	273.3 (216.2–330.4)	555.4 (241.2–869.6)*
Infection/Other	57	143.8 (88.5–199.1)	190.4 (123.4–257.4)	155.3 (112.2–198.3)	324.0 (84.0–564.0)
Non-Diabetes-related	40	149.3 (93.0–205.6)	79.8 (36.4–123.3)	124.2 (85.7–162.7)	0.0
Accident/Violent	16	77.4 (36.9–118.0)	12.3 (0.0–29.3)*	49.7 (25.3–74.0)	0.0
Cancer	10	27.7 (3.4–51.9)	30.7 (3.8–57.6)	31.1 (11.8–50.3)	0.0
Other	14	44.2 (13.6–74.9)	36.9 (7.4–66.3)	43.5 (20.7–66.2)	0.0
Overall	279	763.2 (635.8–890.5)	866.1 (723.1–1009.0)	742.2 (648.1–836.3)	1851.3 (1277.6–2425.1)**

* $p \leq 0.05$ and ** $p \leq 0.001$ for rate ratio compared to male sex or Caucasian race

^a Observed Deaths

^b CVD: Cardiovascular disease

Table 11. Cause-specific mortality rates (per 100,000 person-yrs (95% CI)) by year of diabetes diagnosis and duration of diabetes censored at 30-years of follow-up.

Cause	N ^a	Diagnosis Cohort		
		1965–69 (n=79)	1970–74 (n=74)	1975–79 (n=49)
Diabetes-related	171	668.7 (507.4–830.1)	575.7 (433.5–717.8)	454.9 (317.3–592.5)*
Acute complication	38	152.0 (75.1–228.9)	155.3 (81.5–229.2)	65.0 (13.0–117.0)
Renal disease	26	121.6 (52.8–190.4)	64.0 (16.6–111.4)	75.8 (19.6–132.0)
CVD ^b	66	263.4 (162.2–364.7)	210.2 (124.3–296.1)	184.1 (96.6–271.6)
Infection/Other	41	131.7 (60.1–203.3)	146.2 (74.6–217.8)	130.0 (56.4–203.5)
Non-Diabetes-related	31	131.7 (60.1–203.3)	100.5 (41.1–159.9)	75.8 (19.6–132.0)
Accident/Violent	14	40.5 (0.8–80.2)	54.8 (11.0–98.7)	43.3 (0.9–85.8)
Cancer	7	40.5 (0.8–80.2)	9.1 (0.0–27.1)	21.7 (0.0–51.7)
Other	10	50.7 (6.3–95.1)	36.6 (0.7–72.4)	10.8 (0.0–32.1)
Overall	202	800.5 (624.0–977.0)	676.2 (522.1–830.2)	530.7 (382.1–679.3)*

* $p \leq 0.05$ for rate ratio of 1975–79 compared to 1965–69

^a Observed Deaths

^b CVD: Cardiovascular disease

Table 12. Cause-specific standardized mortality ratios by sex, race, and diabetes diagnosis cohort

	N	Cause-specific SMR (95% CI)				
		CVD	Renal	Infection	Violent ^a	Cancer
Sex						
Males	138	8.8 (6.3–11.2)	77.8 (39.7–116.0)	28.1 (16.1–40.1)	1.4 (0.7–2.1)	1.2 (0.1–2.2)
Females	141	24.7 (17.9–31.6)	140.8 (80.6–201.1)	67.8 (41.2–94.4)	0.7 (0.0–1.6)	1.4 (0.2–2.5)
Race						
Caucasian	239	12.4 (9.8–15.0)	103.7 (65.3–142.1)	45.0 (31.1–59.0)	1.5 (0.7–2.2)	1.3 (0.5–2.2)
African American	40	19.4 (8.4–30.3)	106.3 (36.9–175.8)	26.2 (5.2–47.2)	---	---
Diagnosis cohort						
1965–1969	132	13.9 (10.0–17.7)	137.7 (77.4–198.1)	45.9 (25.8–66.1)	1.1 (0.1–2.1)	1.6 (0.3–2.8)
1970–1974	92	10.9 (7.0–14.8)	80.1 (30.5–129.7)	39.7 (20.2–59.2)	1.2 (0.2–2.2)	0.7 (0.0–1.8)
1975–1979	55	14.7 (8.3–21.2)	82.7 (21.4–144.0)	35.8 (13.6–58.0)	1.3 (0.2–2.5)	1.3 (0.0–3.2)
Overall	279	12.9 (10.4–15.5)	104.3 (70.7–137.9)	41.2 (29.3–53.1)	1.2 (0.6–1.8)	1.2 (0.5–2.0)

^a Violent: Accident/Suicide

5.7 FIGURES

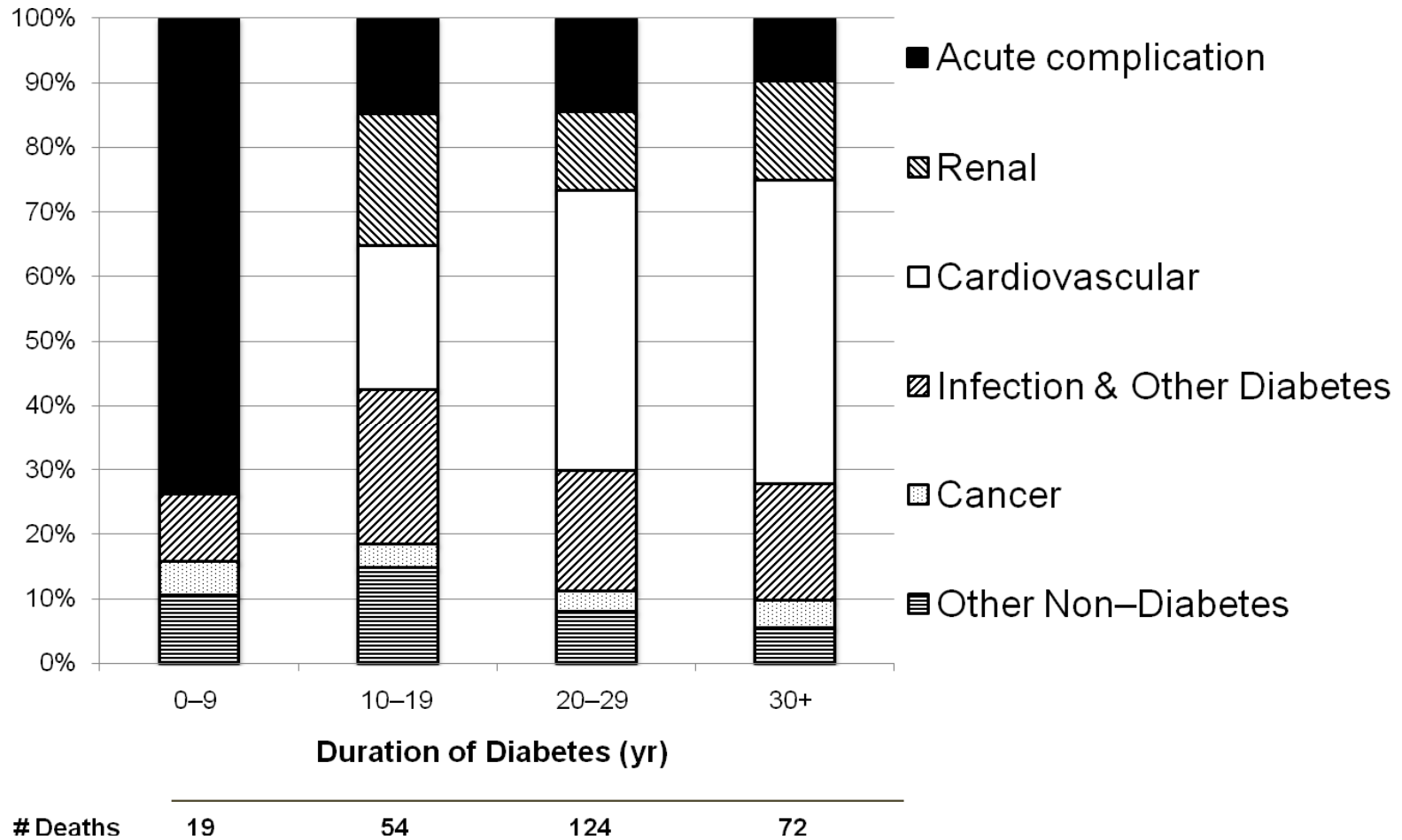
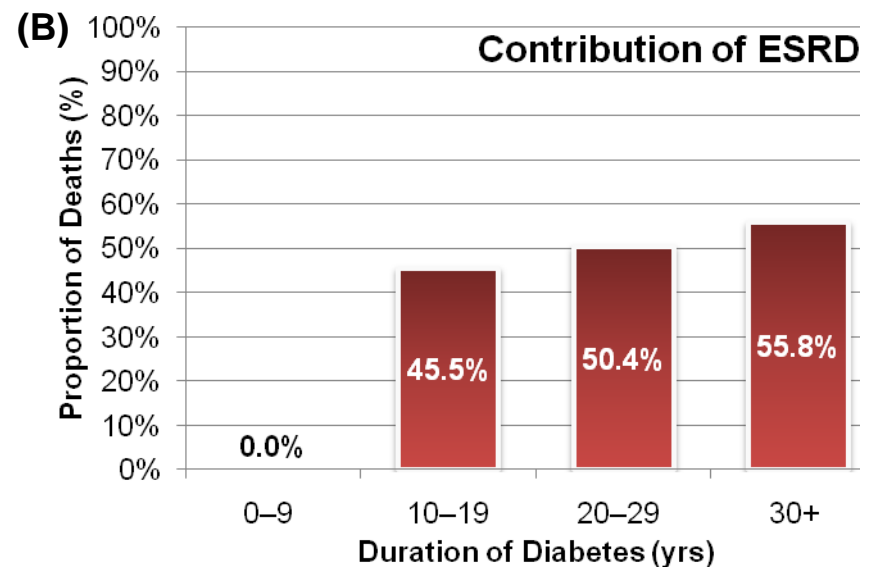
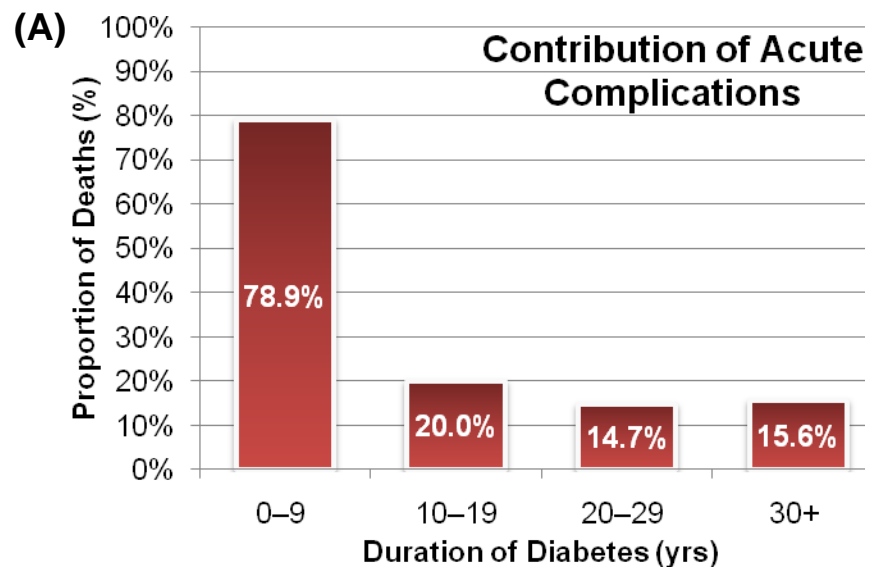


Figure 5. Distribution of underlying causes of death within 10-year intervals of type 1 diabetes duration. Ten deaths where the cause of death was unknown were excluded.



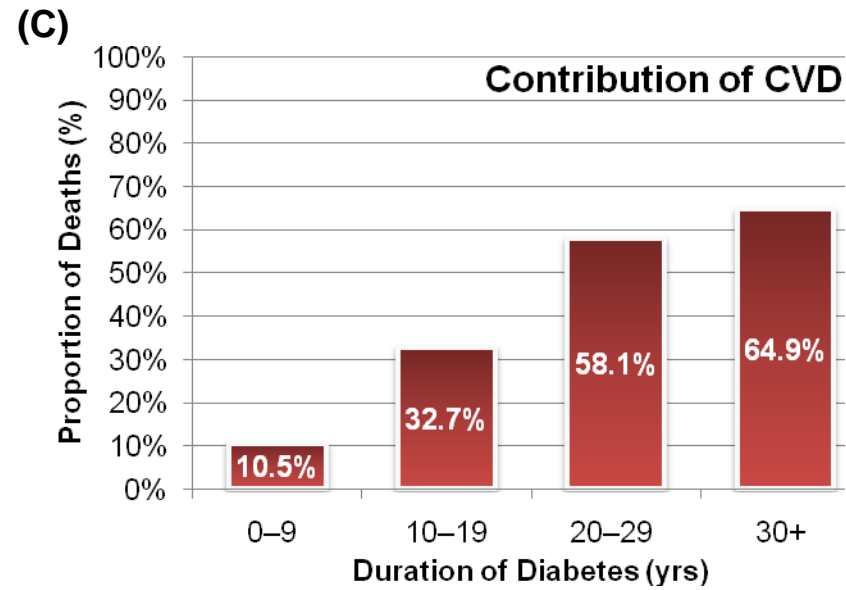


Figure 6. Total contribution (underlying and/or secondary cause of death) of major diabetes complications to deaths in type 1 diabetes. Proportion of deaths in each diabetes duration interval where the following complications either caused or contributed to death: (A) acute complications; (B) end-stage renal disease (ESRD), (C) cardiovascular disease (CVD).

**6.0 PAPER 3: CHARACTERIZING SUDDEN DEATH AND DEAD-IN-BED
SYNDROME IN TYPE 1 DIABETES: ANALYSIS FROM 2 CHILDHOOD-ONSET
TYPE 1 DIABETES REGISTRIES**

To be submitted for publication

Aaron M. Secrest¹, Dorothy J. Becker², Sheryl F. Kelsey¹, Ronald E. LaPorte¹,
and Trevor J. Orchard¹

¹Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh,
Pittsburgh, Pennsylvania

²Department of Pediatrics, Children's Hospital of Pittsburgh, University of Pittsburgh School of
Medicine, Pittsburgh, Pennsylvania

6.1 ABSTRACT

INTRODUCTION: Type 1 diabetes (T1D) is thought to increase the risk for sudden unexplained death (SUD), generating concern that diabetic processes and/or treatments underlie these deaths. Young (<50 yrs) patients, otherwise healthy the night before, and then found dead in bed, have been classified as experiencing “dead in bed” syndrome.

METHODS: To better understand dead-in-bed (DIB) syndrome and SUD in T1D, we identified all un-witnessed deaths in two incidence registries (Children’s Hospital of Pittsburgh and Allegheny County) of 1,319 persons with childhood-onset (age<18 yrs) T1D diagnosed between 1965 and 1979. Cause of death was determined by a mortality classification committee (MCC) of at least 2 physician epidemiologists, based on the death certificate and additional records surrounding the death.

RESULTS: As of 1 January 2008, 329 (25%) participants had died, of whom the MCC has so far reviewed and assigned a final cause of death to 249 (76%). Nineteen (8%) of these were SUDs (incidence density = 45/100,000 person-yrs). Seven met DIB criteria (17/100,000 person-yrs), an incidence approximately 10 times higher than reported in the general population. DIB and SUDs occurred predominantly in males. Only 3 DIB and 3 other SUDs were autopsied, at a rate similar to the other deaths in the study. The MCC adjudicated cause of death in the 7 DIB persons as: diabetic coma (diabetic ketoacidosis or hypoglycemia, $n=4$), unknown ($n=2$), and cardiomyopathy ($n=1$, found on autopsy). Clinical data was available for 8 of the 19 SUDs (3

DIB and 5 other SUDs). DIB individuals had higher HbA_{1c}, lower BMI, and higher daily insulin dose, and all had prior severe hypoglycemic episodes compared to other deaths.

CONCLUSION: SUD (and dead-in-bed syndrome) in T1D seems to be elevated 10-fold, and associated with male sex, higher HbA_{1c}, lower BMI, higher daily insulin dose, and a history of severe hypoglycemia, suggesting that poor metabolic control predisposes T1D individuals to dead-in-bed syndrome.

6.2 INTRODUCTION

In 1991, Tattersall and Gill published a report on 22 young (12-43 years old), apparently healthy individuals with type 1 diabetes (T1D) who had been found dead in their beds.¹³⁹ In nearly all cases, there was no evidence of sweating or a terminal struggle, nor was a clear cause of death found on autopsy. These characteristic features were later coined “dead in bed syndrome”. The authors postulated that the deaths were in some way associated with nocturnal hypoglycemia, possibly related to the higher incidence of hypoglycemia unawareness where transitioning from animal to synthetic “human” insulin.^{139, 140} However, a direct link between human insulin use and *dead-in-bed* syndrome was never found.^{141, 143}

Since this report, more than 100 sudden unexplained deaths (SUDs) that fit the dead in bed syndrome criteria have been reported in Sweden, Denmark, Norway, and Australia.^{124, 143-147, 204, 205} Some of these individuals were found to be taking multiple daily doses of insulin and having frequent episodes of hypoglycemia prior to death.¹⁴⁶ Two studies have reported that sudden deaths occur in >20% of all young T1D deaths (age < 50), compared to 1-5% of similar general populations.^{144, 147}

Most recently, a review of this topic estimated that 5-6% of all T1D deaths fit the criteria of dead in bed syndrome.²⁰⁴ However, the underlying cause(s) of death remain unclear. Plausible theories include hypoglycemia, malignant cardiac arrhythmias, cardiac autonomic neuropathy, hypoglycemia associated autonomic failure, or a combination of these.¹⁵⁰⁻¹⁵⁷

In addition to the defined dead in bed syndrome, reports often describe other T1D deaths where the individual is found dead and the cause of death is not determinable, yet the death does not fit the criteria for dead in bed syndrome (e.g., the person is > 50 years old or they are found dead elsewhere).^{139, 143, 147} The current report explores all SUDs occurring in two long-term observational studies of childhood-onset T1D in Allegheny County (Pittsburgh), Pennsylvania, namely, the hospital-based Children's Hospital of Pittsburgh registry and a population-based Allegheny County T1D registry. Specific objectives include: 1) determining the incidences of both SUD and its subgroup, dead in bed syndrome; 2) comparing these rates to those reported in the general literature; and 3) examining potential risk factors.

6.3 RESEARCH DESIGN AND METHODS

6.3.1 Study populations

Sudden deaths were identified from two incidence registries of childhood-onset type 1 diabetes, the Children's Hospital of Pittsburgh registry and the Allegheny County registry, which have been described previously.^{51, 58, 80} Eligibility criteria for the current investigation were: 1) a diagnosis of type 1 diabetes between 1 January 1965 and 31 December 1979; 2) receiving insulin therapy at discharge from the diagnosis admission; 3) age < 18 years old at diagnosis; and 4) residing in Allegheny County, Pennsylvania or living within 100 miles from Pittsburgh at diagnosis. These studies were approved by the University of Pittsburgh Institutional Review Board, and all participants or relatives of deceased participants provided informed consent.

Two hundred and forty-three participants came from the Children's Hospital registry alone, 805 from only the Allegheny County registry, while another 271 individuals were part of both registries, yielding a total of 1319 individuals.

6.3.2 Mortality Data

Vital status was determined as of 1 January 2008, using ascertainment methods described previously.⁶³ Deaths not identified through mail or phone contact with participants were discovered by searching both the Social Security Death Index and the National Death Index (NDI). Death certificates (or NDI data) were obtained to confirm each death. Vital status was determined for 1247 (95%) patients of whom 329 have died as of 1 January 2008. In addition, whenever appropriate, the following sources of information were sought: 1) medical records surrounding the death; 2) autopsy/coroner's reports; and 3) interview with next-of-kin. The underlying cause of death, and rank order for all contributing causes, for each decedent was determined by a Mortality Classification Committee (MCC) consisting of at least 2 trained internists using standardized protocols.⁵⁸ Only deaths that have been reviewed by the MCC and classified based on all available information are included in this analysis (255 deaths (77.5% of all deaths)).

6.3.3 Key variables

The primary variable of interest was "sudden, unexplained death" (SUD). This was defined as an unwitnessed death with no obvious cause (e.g., not a car accident or suicide) and not being

treated in the hospital for a potentially fatal condition. This is a broader definition than the Tattersall “dead-in-bed,” as it included healthy individuals with T1D over age 50, as well as individuals who were found at home in places besides their bed. Other variables of interest were obtained either from baseline survey data or from death certificates.

6.3.4 Subgroup analysis

A portion ($n=414$) of the Children’s Hospital of Pittsburgh registry participated in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, which has previously been described in detail.^{93, 206} Pittsburgh EDC Study participants, diagnosed with childhood-onset (age<17 yrs) T1D, were first evaluated between 1986 and 1988. Participants have been followed biennially by survey and for the first 10 years and again at 18 years by examination. Data from living EDC participants ($n=363$) were matched to each of these 3 DIB cases based on sex and 5-year intervals surrounding both age and diabetes duration at death for the DIB cases, for a total of 82 (22.6%) matched living participants.

EDC participants completed surveys regarding medical history and demographic information prior to a clinical examination. Blood pressure was measured in the sitting position according to the Hypertension Detection and Follow-Up Program protocol with a random-zero sphygmomanometer after a 5-min rest. Height and weight were measured for body mass index (BMI, in kg/m^2). During clinic visits, a 12-lead electrocardiogram (ECG) was obtained. The QT interval was derived from a single waveform in lead II and heart rate from an average of five R–R distances on the ECG. The QT interval was corrected for heart rate according to Hodges formula: $QT_c = QT + 1.75 \times (\text{heart rate} - 60)$.²⁰⁷

Glycosylated hemoglobin (HbA₁), lipids, and lipoproteins were measured using fasting blood samples. For analysis purposes, original HbA₁ values were converted to Diabetes Complications and Control Trial (DCCT)-aligned HbA_{1c} using the following regression equation derived from duplicate assays: DCCT HbA_{1c} = 0.14 + 0.83(EDC HbA₁). Total cholesterol was measured enzymatically, and HDL cholesterol was determined after a heparin and manganese chloride precipitation method.²⁰⁸ Non-HDL cholesterol was calculated by subtracting HDL from total cholesterol.

Hard coronary artery disease events included myocardial infarction, revascularization procedure, or angiographic stenosis $\geq 50\%$, confirmed by hospital records. Renal damage status was defined on the basis of urinary albumin excretion rates (AER) in at least two of three timed urine collections as <20 $\mu\text{g}/\text{min}$ – normoalbuminuria, $20\text{--}200$ $\mu\text{g}/\text{min}$ – microalbuminuria (MA), or >200 $\mu\text{g}/\text{min}$ – overt nephropathy (ON). Proliferative retinopathy was assessed by the University of Wisconsin-Madison Fundus Photography Reading Center using stereoscopic fundus photographs and classified based on the modified Arlie House system.²⁰⁹ Severe hypoglycemia was defined as ≥ 1 episode of unconsciousness or seizure due to hypoglycemia. Hypoglycemia was determined by an EDC-study physician as part of the physician's examination. Prolonged QTc interval was defined as $\text{QTc} \geq 440$ ms on an EDC Study ECG. An ever smoker was defined as a person who had smoked ≥ 100 cigarettes over their lifetime. Moderate alcohol use was defined as ≥ 5 drinks/week based on self-report data.

6.3.5 Statistical analysis

Distributional characteristics for each variable were assessed for normality. Univariate significance was tested using the Student's *t*-test, one-way ANOVA or the χ^2 (or Fisher's exact) test, as appropriate. Due to limited sample size, statistical significance was considered as $p < 0.10$. When comparing DIB to matched living participants, paired *t*-tests were used. All analyses were performed using either SPSS 17.0 (SPSS, Chicago, IL) or SAS 9.2 (SAS, Cary, NC).

6.4 RESULTS

As of 1 January 2008, there were 329 (24.9%) deaths in the two childhood-onset type 1 diabetes registries. Of these, 255 (77.5%) deaths have been reviewed and classified by the Mortality Classification Committee (MCC). Deaths that have yet to be classified by the MCC were more recent deaths (calendar year of death = 1999.3 ± 7.0 vs. 1993.5 ± 8.9 , $p < 0.001$) and occurred in older individuals ($p < 0.001$) with a longer diabetes duration ($p < 0.001$), and more likely occurred in African-Americans ($p = 0.06$) (Appendix A, Table 21). However, whether or not the deaths have been classified did not differ significantly by sex, age at diabetes onset, location of death (inpatient vs. other) or whether an autopsy was performed ($p > 0.10$ for all). Classified mortality cases were more likely to occur in Pennsylvania ($p = 0.01$).

6.4.1 Sudden Unexplained Deaths and Dead-in-Bed

Of the 255 MCC-classified deaths, 49 (19%) were sudden, unwitnessed deaths (Figure 7). These 49 deaths were further categorized based on whether a clear cause of death could be determined by the MCC. Nineteen (39%) of these sudden, unwitnessed deaths were further classified as “sudden unexplained deaths” (SUDs) and are summarized in Table 13. The incidence density of SUD for this study population was thus 45.4/100,000 person-yrs (95% CI 25.0–65.8) and may be even higher given the currently unclassified deaths (SUD incidence density = 47.7/100,000 person-yrs with 74 unclassified deaths excluded from denominator) (Table 14). The SUDs occurred between 1983 and 2007. SUDs in this cohort occurred primarily in males and in Caucasians. Nine (47.3%) SUDs had no history of diabetes complications, although two of these had a history of alcohol abuse. Thirteen were found dead in bed, 2 on the floor next to their bed, 1 on the floor in the living room, 1 in the bathroom, and 1 in a chair. Only 6 (31.6%) had an autopsy performed. The underlying cause of death on the death certificate was most often listed as diabetes ($n=11$). The underlying cause of death on the death certificate matched the MCC-classified underlying cause of death in just 4 cases: 2 cases of heart disease, 1 of pneumonia, and 1 of diabetic ketoacidosis. Based on the classic definition of dead-in-bed syndrome (i.e., age < 50, no major diabetes complications, and found dead in bed), only 7 (36.8%) individuals in this study can be defined as dead-in-bed (incidence density of 16.7/100,000 person-yrs, Table 14). The 12 other SUDs did not meet the dead-in-bed criteria due to: history of CVD ($n=5$), history of ESRD ($n=2$), age>50 ($n=1$), or found dead elsewhere (chair or floor near bed, $n=3$)

Comparisons between the 19 SUD individuals with the other MCC-classified deaths ($n=224$) are reported in Table 15. SUDs were divided into two groups: those who met the dead-

in-bed (DIB) criteria ($n=7$) and other SUDs ($n=12$). Compared to deaths from other causes, DIB and SUDs occurred more in males (71% and 67%, respectively, vs. 49% of other deaths) and were not as likely to attend college (17% and 36%, resp., vs. 48%) or be married at death (14% and 25%, resp., vs. 38%). Of note, diabetes was listed on the death certificate of all DIB (100%), and all but one SUD (91.7%) compared to only 72.3% of death certificates for all other deaths ($p=0.09$). Also, DIB and SUDs were no more likely to have an autopsy performed ($p=0.50$). After classification by the MCC, the DIB deaths were classified as: 4 (57.1%) from diabetic coma (DKA or hypoglycemia), 1 (14.3%) from cardiomyopathy (found on autopsy), and 2 (28.6%) from an unknown cause. Other SUDs were classified as: 2 (16.7% from diabetic coma, 6 (50.0%) from a chronic diabetes complication (3 cardiovascular deaths, 2 end-stage renal disease, and 1 infection), and 4 (33.3%) from an unknown cause.

6.4.2 Subgroup Analysis from the Pittsburgh EDC Study

In an effort to determine distinguishing characteristics of individuals who die from a SUD, an analysis of 133 participants (51 deceased and 82 living) in the Pittsburgh EDC Study was performed (Table 4). Eight (16%) of these deaths were classified as SUD, of which three (6%) met the dead-in-bed criteria. No DIB individuals and only 1 SUD person were married at death compared to nearly half of the other deaths and more than half of the matched living participants (0.0% and 12.5%, resp., vs. 48.8% and 62.0%). The mean follow-up time between the last EDC Study visit and death did not differ greatly between groups (3.0 yrs for DIB, 1.4 yrs for SUDs, and 1.5 yrs for all other deaths). Clinically, there were no differences in systolic or diastolic blood pressure, pulse, or HDL or non-HDL cholesterol. HbA_{1c} was much higher in the DIB

individuals compared to other SUDs, all other deaths, and matched living participants (11.2 ± 2.2 % vs. 8.8 ± 1.1 vs. 9.8 ± 1.9 vs. 8.5 ± 1.4 , resp.). Also, individuals with DIB had a very low BMI (19.3 ± 1.0 kg/m²) compared to other SUDs (22.3 ± 5.2), which was also much lower than all other deaths or those still alive (24.9 ± 4.9 and 25.6 ± 3.6 , resp.). Conversely, DIB were on a somewhat higher daily insulin dose (0.98 ± 0.31 IU/kg/d) compared to other SUDs (0.73 ± 0.24), to all other deaths (0.66 ± 0.25), and to match living participants (0.67 ± 0.23). Also, DIB and SUD individuals tended to have a history of severe hypoglycemia (100.0% and 80.0% vs. 55.8% in other deaths). However, no other differences between DIB and other groups were apparent regarding prevalent diabetes complications (CAD, renal disease, or retinopathy) or other contributing factors (history of smoking or moderate alcohol consumption). Of note, none of individuals with DIB or SUD had evidence of prolonged (≥ 400 ms) QTc interval.

6.5 DISCUSSION

This study identifies and characterizes the unfortunate occurrence of sudden unexplained deaths (SUDs), including dead-in-bed syndrome, in two cohorts in Southwestern Pennsylvania – a hospital-based cohort and a population-based county cohort of type 1 diabetic (T1D) individuals diagnosed between 1965 and 1979. SUDs and dead-in-bed syndrome accounted for 7.8% and 2.8% of all deaths so far classified, respectively, in this study population. These deaths were most often attributed to diabetes mellitus as the underlying cause of death; however, two-thirds of these SUDs did not have an autopsy, and an underlying cause of death could not be determined by the Mortality Classification Committee for nearly one-third of the SUDs, despite

interviews with next-of-kin and hospital or autopsy records, when appropriate. Individuals with SUDs were typically male, healthy (non-symptomatic) the night before, and then found dead the following day. It appears that individuals meeting dead-in-bed criteria have a higher HbA_{1c}, lower BMI and use a higher daily insulin dose (per kg body weight) compared to similar T1D individuals who die from other causes. Furthermore, individuals with DIB and SUDs tend to have a history of severe hypoglycemic events (often more than one), but do not have a history of prolonged QTc intervals on exam.

Although the contribution of SUDs (and dead-in-bed syndrome) to early mortality in T1D is not insignificant (5–10% of all T1D deaths),²⁰⁴ it has been unclear as to what extent SUDs (or dead-in-bed syndrome) occur more frequently in T1D than in the similarly-aged general population. Table 14 compares data from a review of the literature on the incidence density of sudden deaths, SUDs, dead-in-bed (DIB) syndrome. The incidence densities found in the present study for all SUDs and for DIB (45.4 and 16.7/100,000 person-yrs, respectively) are quite comparable to the range (20–60) reported by Koltin et al. in a recent review of dead-in-bed syndrome in T1D.²⁰⁴ However, when compared to incidence densities for all sudden deaths (including sudden cardiac deaths confirmed on autopsy) or for SUDs alone in the young (age<50) general population, SUDs appear to be up to 10 times more frequent in T1D (Table 14).

These results confirm findings from previous studies showing that SUDs and dead-in-bed syndrome tend to occur more in males (Thordarson et al¹⁴⁶: 10 M, 6 F, Tu et al¹⁴⁷: 8 M, 2 F). However, Edge et al. reported on 128 total deaths in the UK in T1D children aged 1–19, where 9 were classified as dead-in-bed, the majority of whom were female (7 F, 2 M).²⁰⁵ Although, Edge et al. did find that a significant proportion of the overall deaths in their report occurred in young males with poorly controlled T1D who died at home (often of hypo- or hyperglycemia),

suggesting that some males who met criteria for dead-in-bed syndrome might have been classified as dying from hypo- or hyperglycemia on the death certificate.

Considerable focus has been placed on the search for potential mechanisms for dead-in-bed syndrome in T1D, and a growing body of literature has addressed associations between nocturnal hypoglycemia and undiagnosed cardiac autonomic neuropathy.^{150, 151, 157, 210} A plausible theory to try to explain the etiology of dead in bed syndrome has been proposed and developed over the last decade.¹⁵⁰⁻¹⁵⁷ Although nocturnal hypoglycemia rarely itself results in sudden death,¹⁵¹ in otherwise healthy, young T1D patients, those at risk of dead in bed syndrome may have reduced parasympathetic activity (and, thus, relative sympathetic predominance), due to long-standing T1D and early stages of cardiac autonomic neuropathy.^{150, 156} This has been shown to lead to ventricular arrhythmias,¹⁵⁶ and autonomic neuropathy has also been associated with abnormal cardiac repolarization, as evidenced by prolonged corrected QT (QTc) intervals.^{155, 158} Furthermore, prolonged QTc intervals have been shown to independently predict overall and cardiovascular-related mortality in T1D.¹⁵⁹ In addition, data exists that hypoglycemia, especially severe episodes of hypoglycemia, acutely prolongs the QTc interval.¹⁵⁵ However, it is important to note that our subgroup analysis found that none of the 3 DIB or 5 other SUDs in the Pittsburgh EDC Study had any clinical evidence of prolonged QTc interval in any EDC exam visits. Nonetheless, this does not preclude the possibility that severe nocturnal hypoglycemia in this group might have caused an acute prolongation of the QT interval, as was reported recently.²¹¹ A history of multiple severe hypoglycemic events (loss of consciousness or seizures) was present in all 3 DIB and 4 of the 5 other SUDs in the EDC Study group, and they were relatively thin with higher insulin doses. DIB individuals also had much higher HbA_{1c}.

Nocturnal hypoglycemia has a higher propensity to persist for hours at night due to long-standing T1D causing “hypoglycemia-associated autonomic failure” (HAAF), where the body produces an inadequate response of glucagon and adrenaline when it senses hypoglycemia. Woodward et al. very recently confirmed that nocturnal hypoglycemia is very common in individuals with long-standing T1D.²¹² They performed overnight continuous glucose monitoring on 25 healthy T1D participants and found that nearly half (12 participants) experienced nocturnal hypoglycemia (<3.5 mmol/l), rates which have not dramatically changed in over 20 years, despite the wide usage of long-acting insulin analogs.²¹³⁻²¹⁶ An interesting case report from Tanenberg et al. appeared to link nocturnal hypoglycemia to dead-in-bed syndrome.²¹⁷ The authors were treating a 23-yr old man with recurrent severe hypoglycemia and placed a retrospective continuous glucose monitoring system (CGMS) on him. The man was found dead in an undisturbed bed the next day, after stacking his insulin before bed. The CGMS revealed that his glucose levels fell below 30 mg/dL around the time of his death with only a minimal counterregulatory response.

Regardless, it is likely that the combination of early autonomic neuropathy, nocturnal hypoglycemia, decreased counter-regulatory response to hypoglycemia at night, and HAAF (from long-standing T1D), may all predispose an individual with T1D to have prolonged QTc intervals at night, and this in turn could cause fatal ventricular arrhythmias.^{151, 152, 218}

The findings in this study are preliminary as several limitations exist. The two incidence registries combined for this study population were originally developed through retrospective review of hospital records and contacting pediatricians. As such, it is difficult to obtain information in addition to the death certificate, especially for earlier deaths (before 2000), and consequently, nearly 25% of all deaths have yet to be classified by the Mortality Classification

Committee. However, of the 80 deaths not yet classified, we have sufficient information on 40 deaths to determine whether they might have been an SUD. Of these 40, only three deaths might be SUD, pending more information regarding the circumstances of death. Classifying these 80 deaths might, then, increase the number of SUDs, and as such the incidence density of SUDs reported herein might be underestimated. Also, clinical and diabetes complication data were not obtained for the majority of the study population. The Allegheny County T1D Registry cohort has only been contacted three times since the cohort was developed, and the focus of these contacts has been ascertainment of vital status, not socioeconomic or complication status. Thus, this report is primarily descriptive in nature and analysis for the entire cohort is limited to basic demographic data collected at baseline or from the death certificate. Few associations reach statistical significance; however, there is limited sample size. Generalizing these findings to other T1D populations should be done with caution.

In conclusion, these results suggest patterns predictive of sudden unexplained deaths and dead-in-bed syndrome in type 1 diabetes. SUDs tend to occur in males with lower BMI and higher reported daily insulin doses and in those with a history of severe hypoglycemia. SUD in T1D occurs at rates much higher than seen in similarly aged general populations. However, since SUD and dead-in-bed syndrome comprise a limited proportion of all T1D deaths, large epidemiologic studies combining data from multiple centers or studies are necessary to determine predictors and work to prevent these devastating deaths in type 1 diabetes.

6.6. TABLES

Table 13. Characteristics of individuals with sudden unexplained deaths ($n=19$) in this type 1 diabetes study population.^a

Age (yr)	Race	Sex	Diabetes Duration (yr)	Major Diabetes Complications	Where Found	Autopsy Performed	Underlying Cause on DC	Underlying Cause by MCC	Dead-in-bed ^b
19	Caucasian	Female	7.6	None	Bed	Yes	Diabetes mellitus	Diabetic coma	Yes
22	Caucasian	Female	11.9	CHF, MI	Bed	No	Arteriosclerotic heart disease	Acute MI	No
33	Caucasian	Male	17.6	None	Bed	Yes	Diabetes mellitus	Diabetic cardiomyopathy	Yes
34	Caucasian	Male	23.7	ESRD, silent MI	Bathroom*	No	Diabetes mellitus	ESRD	No
23	Caucasian	Male	17.0	None	Chair*	Yes	Focal myocardial fibrosis	Presumed hypoglycemia	No
37	Caucasian	Male	24.5	None	Bed	No	Unstable diabetes mellitus	Diabetic coma	Yes
31	Caucasian	Female	21.0	CAD	Bed	No	Cardiac failure	Unknown	No
36	Caucasian	Male	26.4	CAD	Bed	No	Arteriosclerotic heart disease	Presumed CAD	No
35	Caucasian	Male	27.0	ESRD, hypoglycemic brain damage	Bed	No	Diabetes mellitus	ESRD	No
37	African-American	Male	21.6	None	Floor*	Yes	Bronchopneumonia	Pneumonia	No
37	Caucasian	Female	31.0	None	Bed	No	COPD	Unknown	Yes
36	Caucasian	Male	32.6	Brain damage	Floor near bed*	No	Diabetes mellitus	Unknown	No
29	Caucasian	Male	23.7	None	Bed	No	DKA	DKA	Yes
37	Caucasian	Male	27.0	None	Bed	No	Diabetes mellitus	Unknown	Yes
39	Caucasian	Male	33.4	ESRD, MI, PR	Floor near bed*	No	Probable insulin shock	CAD	No
26	Caucasian	Male	25.4	None	Bed	Yes	Diabetes mellitus	Hypoglycemia	Yes
52	Caucasian	Female	38.4	PR	Bed	No	Diabetes mellitus	Unknown	No
56	Caucasian	Male	39.1	CAD, PR	Bed	No	Diabetes mellitus	Unknown	No
45	Caucasian	Female	31.2	PVD, PR	Bed	Yes	Diabetes mellitus	Presumed DKA	No

* Death occurred at home

^a Cases ordered by calendar year of death (range 1983–2007)

^b Meets criteria for “dead-in-bed” classification: under age 50, no major complications, found dead in bed

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DC, death certificate; DKA, diabetic ketoacidosis; ESRD, end stage renal disease; MCC, Mortality Classification Committee; MI, myocardial infarction; PR, proliferative retinopathy; PVD, peripheral vascular disease

Table 14. Comparison of incidence densities of sudden deaths, sudden unexplained deaths (SUDs), and dead-in-bed in young type 1 diabetes and general populations

Study	Location	# of deaths (definition used)	Age Range (yr)	Incidence Density (per 100,000 person-yrs)
Type 1 Diabetes				
Current study	Allegheny County, PA	19 (SUD)	19–56	45.4 (25.0–65.8) ^a
Current study	Allegheny County, PA	7 (Dead-in-bed)	19–37	16.7 (4.3–29.1) ^a
Koltin et al, 2008 ²⁰⁴	Review of literature	Not stated (Dead-in-bed)	14–49	20–60 (estimated)
General Population				
Shen et al, 1995 ²¹⁹	Olmsted County, MN	54 (Sudden deaths ^b)	20–40	4.1 (Female); 8.7 (Male)
Eckart et al, 2004 ²²⁰	U.S. Military recruits	44 (SUD)	18–35	4.5 (calculated)
Vaartjes et al, 2009 ²²¹	Netherlands	172 (SUD)	1–40	0.2 (calculated)
Vaartjes et al, 2009 ²²¹	Netherlands	1,908 (Sudden deaths ^b)	1–40	1.2 (Female); 2.9 (Male)

^a 95% Confidence Interval

^b Includes all sudden deaths (both known and unknown causes)

Table 15. Characteristics (% (*n*) or mean ± SD) of the deceased type 1 diabetes (T1D) study population (*n*=243)^a by sudden unexplained death (SUD) classification

Variables	Dead-in-bed	Other SUD	All other deaths	Overall <i>p</i>-value
N	7	12	224	---
Male sex	71.4 (5)	66.7 (8)	49.1 (110)	0.26
African-American	0.0 (0)	8.3 (1)	12.9 (29)	0.54
Education > 12 yrs (<i>n</i>=200)	16.7 (1)	36.4 (4)	47.5 (87)	0.26
Married at Death (<i>n</i>=242)	14.3 (1)	25.0 (3)	38.1 (85)	0.30
Autopsy Performed (<i>n</i>=242)	42.9 (3)	25.0 (3)	28.7 (64)	0.84
Diabetes on Death Certificate	100.0 (7)	91.7 (11)	72.3 (162)	0.09
Age at Diabetes Onset (yr)	9.0 ± 5.1	10.8 ± 4.1	11.4 ± 3.9	0.26
Diabetes Duration at Death (yr)	22.4 ± 7.7	27.0 ± 8.4	23.1 ± 9.0	0.33
Age at Death (yr)	31.4 ± 6.9	37.7 ± 10.2	34.5 ± 9.2	0.34

* $p \leq 0.10$.

^a Of the 249 deaths classified by the Mortality Classification Committee, 6 deaths lacked sufficient data to determine whether the death was a sudden unexplained death

Table 16. Characteristics (% (*n*) or mean \pm SD) of deceased and matched living participants based on data from the most recent study visit in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study (*n*=133) by sudden unexplained death (SUD) classification

Characteristics	Dead-in-bed	Other SUD	All other deaths	Matched living ^a
N	3	5	43	82
Demographic				
Male sex	66.7 (2)	80.0 (4)	53.5 (23)	69.5 (57)
African-American	0.0 (0)	0.0 (0)	7.0 (3)	1.2 (1)
Education > 12 yrs (<i>n</i> =130)*	33.3 (1)	60.0 (3)	52.4 (22)	72.5 (58)
Married (<i>n</i> =130)*	0.0 (0)	20.0 (1)	48.8 (21)	62.0 (49)**
Autopsy Performed	33.3 (1)	40.0 (2)	32.6 (14)	---
Diabetes on Death Certificate	100.0 (3)	100.0 (5)	72.1 (31)	---
Clinical				
HbA _{1c} (%)*	11.2 \pm 2.2	8.8 \pm 1.1**	9.8 \pm 1.9	8.5 \pm 1.4**
Systolic BP (mmHg)*	126.0 \pm 26.9	130.0 \pm 19.1	126.6 \pm 20.5	114.1 \pm 14.3
Diastolic BP (mmHg)*	73.7 \pm 2.9	79.6 \pm 22.6	79.6 \pm 10.8	71.5 \pm 9.4
Pulse (bpm)	81.3 \pm 9.2	80.0 \pm 11.4	79.3 \pm 13.0	74.2 \pm 12.9
Body Mass Index (kg/m ²)*	19.3 \pm 1.0	22.3 \pm 5.2	24.9 \pm 4.9**	25.6 \pm 3.6**
HDL cholesterol (mg/dL)	48.8 \pm 3.4	52.0 \pm 13.9	47.6 \pm 16.2	52.6 \pm 15.7
Non-HDL cholesterol (mg/dL)*	148.6 \pm 39.6	169.0 \pm 70.9	161.4 \pm 45.8	133.1 \pm 28.4
Insulin dose (IU/kg/day)	0.98 \pm 0.39	0.73 \pm 0.24	0.66 \pm 0.25**	0.67 \pm 0.23**
Intensive Insulin Therapy (\geq 3 inj/d)	0.0 (0)	60.0 (3)	34.9 (15)	39.0 (32)
Last exam to death (yr)	2.99 \pm 2.89	1.37 \pm 0.66	1.47 \pm 1.64	---
Prevalent Complication				
Hard Coronary Artery Disease*	0.0 (0)	60.0 (3)	46.5 (20)	11.0 (9)
Microalbuminuria (AER \geq 20 μ g/min)*	66.7 (2)	80.0 (4)	88.4 (38)	36.6 (30)
Overt Nephropathy (AER \geq 200 μ g/min)*	33.3 (1)	60.0 (3)	72.1 (31)	14.6 (12)
Proliferative Retinopathy*	33.3 (1)	80.0 (4)	76.2 (32)	56.1 (46)
Severe Hypoglycemia	100.0 (3)	80.0 (4)	55.8 (24)	67.1 (55)
Hypoglycemia Unawareness	33.3 (1)	60.0 (3)	32.6 (14)	43.9 (36)
Prolonged QTc interval (\geq 440 ms)	0.0 (0)	0.0 (0)	7.0 (3)	0.0 (0)
Ever Smoker*	66.7 (2)	80.0 (4)	55.8 (24)	31.7 (26)
Moderate Alcohol Use (\geq 5 drinks/wk)	33.3 (1)	40.0 (2)	34.8 (15)	28.0 (23)

* $p \leq 0.10$ for overall χ^2 or ANOVA, as appropriate

** $p \leq 0.10$ compared to “Dead-in-bed”.

^a Living individuals matched to dead-in-bed cases based on sex and 5-year interval surrounding age and diabetes duration at death for cases.

Abbreviations: AER, albumin excretion rate; BP, blood pressure; QTc, corrected QT-interval

6.7 FIGURES

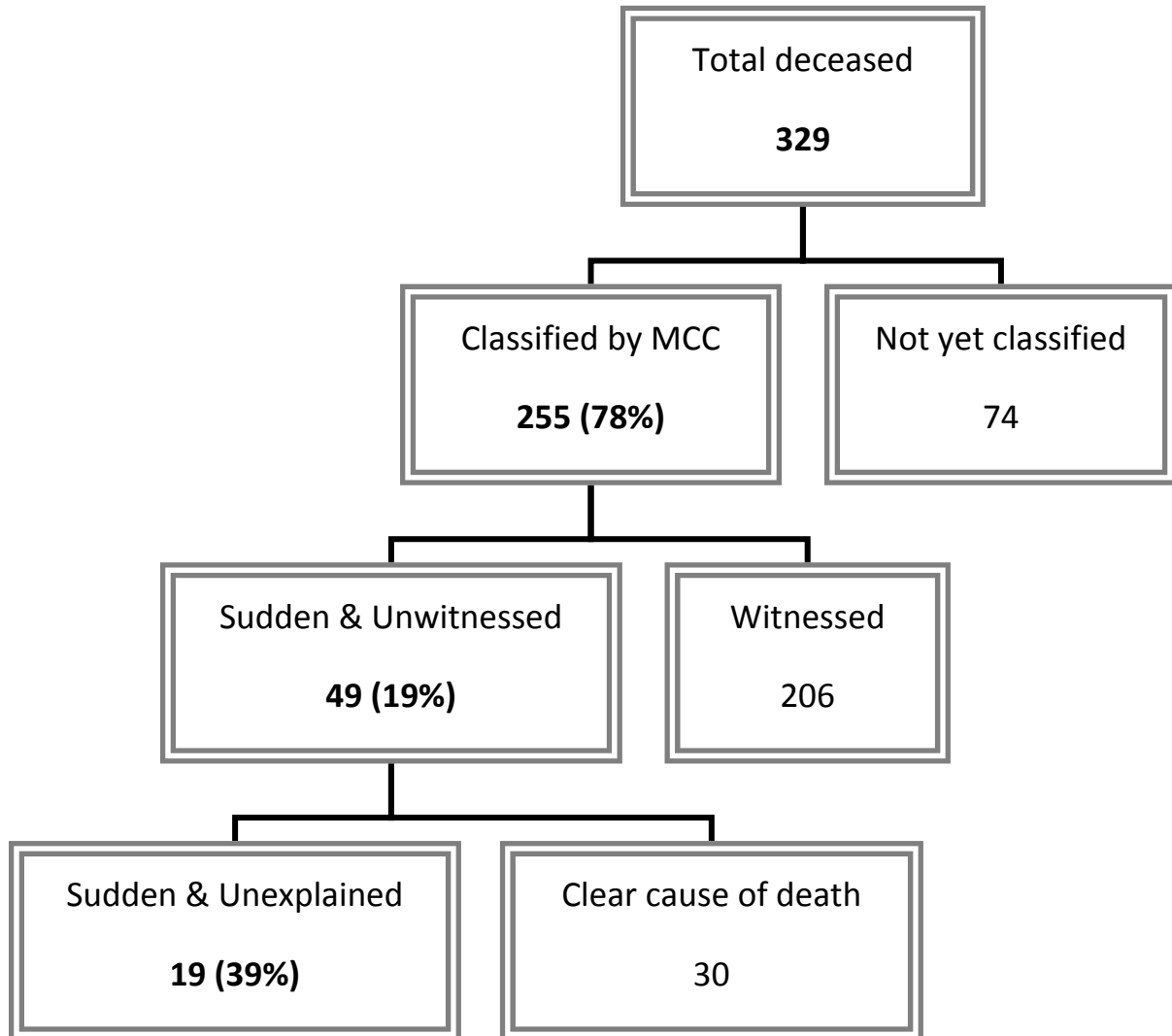


Figure 7. Flow diagram showing the breakdown by cause of death.

7.0 DISCUSSION

7.1 SUMMARY AND CONCLUSIONS

The main goal of this study was to determine whether mortality in individuals with T1D is improving over time (i.e., do individuals diagnosed with T1D more recently have a better chance at survival than those diagnosed at an earlier date?). These results are encouraging and provide contemporary, population-based mortality figures for individuals with long-standing T1D. African-Americans have significantly higher mortality rates than Caucasians for all diabetes causes, supplementing our previous finding that African-Americans with T1D have higher mortality rates due to acute complications.⁶⁴ Females in our cohort have a similar mortality to males, a result warranting further exploration, as younger females have much lower mortality rates than younger males in the general population.

These data represent the first attempt to assess cause-specific mortality in a population-based cohort of long-standing (>20 years) T1D in the United States, and clearly show that the higher mortality seen in T1D compared to the general population results almost exclusively from higher rates of diabetes-related acute and chronic complications. Cause-specific SMRs for cancer and for violent or accidental deaths do not significantly differ from the age-, sex-, and race-matched local population. These data also illustrate that mortality rates are decreasing in those diagnosed more recently with T1D, specifically for deaths from diabetes-related causes;

however, those diagnosed most recently (1975-1979) still die at rates 5 times higher than the general population. Thus, the effects of continuing improvements in treatment and care need to be assessed.

7.2 GENERAL FINDINGS

7.2.1 Overall Mortality in Type 1 Diabetes in Southwestern Pennsylvania

It is important to compare the current findings to previous findings in the two major T1D cohorts in Southwestern Pennsylvania, the Allegheny County T1D Registry Cohort and the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study cohort. With respect to mortality, these cohorts have been analyzed separately as well as combined to increase power, and early research has shown that the hospital-based EDC Study cohort was representative of the population-based county cohort.¹⁸⁴ The current data greatly extend and expand upon previous findings in the Allegheny County cohort, as an additional 109 deaths (39% of all deaths) have occurred in the nine years subsequent to the previous follow-up (as of 1 January 1999).^{63, 80, 82} For this relatively modern population with a median type 1 diabetes duration of 36 years, the overall age- and sex-adjusted SMR has increased to 7.4 from 5.2 times the general population in the 1999 follow-up by Nishimura et al.⁶³ This is remarkable in that the population is aging. As mortality increases dramatically with age in the general population,¹⁸⁵ these data therefore confirm that individuals with T1D continue to die at a much higher rate than their age-matched general population. Based on census data and a conservative annual U.S. incidence rate for childhood-onset (age<20

yr) T1D of 10/100,000,^{11, 52} it is estimated that 75,000-150,000 individuals were diagnosed with childhood-onset T1D in the U.S. between 1965 and 1979. Extrapolating our T1D mortality data to the U.S. T1D population, approximately 15,000-30,000 excess deaths have occurred in the U.S. as a result of childhood-onset T1D. This is most likely due to an increasing effect of long-term complications, which become common over time in T1D (cumulative incidence after 25 yrs duration: overt nephropathy (>30%), symptomatic autonomic neuropathy (>20%), peripheral polyneuropathy (>40%), and proliferative retinopathy (>50%)).⁷⁵ The same EDC report showed that cumulative mortality at 25 years diabetes duration has declined by 80% comparing those diagnosed 1950-59 (35%) to those diagnosed 1970-74 (7%).⁷⁵ The EDC Study included individuals diagnosed between 1950 and 1980, offering a broader range of time for assessing temporal improvements. While the Allegheny County cohort had a more narrow range of diagnosis years (1965-1979), smaller but significant improvements in cumulative mortalities at 25 year duration (15% vs. 10%) and 30-year (23% vs. 16%) when comparing the 1965-69 diagnosis cohort to the 1975-79 cohort, respectively.

One hypothesis for the consistently high overall mortality rates (even in the youngest cohort (diagnosed 1975–79) over time in the current study is based on the fact that the entire study cohort was diagnosed during the “pre-modern” era of type 1 diabetes. The advent of modern improvements in type 1 diabetes care – namely, self-monitoring of blood glucose,⁹⁴ HbA_{1c} testing,^{92, 93} widespread use of ACE inhibitors in preventative diabetes care,⁹⁵⁻⁹⁷ and intensive insulin therapy⁹⁸⁻¹⁰⁰ – began in the mid-1980s and were widely prevalent by the mid-1990s. As such, all participants in the current study had diabetes for between 5 and 20 years prior to transitioning to modern T1D care. Abundant evidence exists showing that poor metabolic control, especially hyperglycemia, leads to microvascular changes and damage.²²²⁻²²⁴

Miller et al showed that even short-term hyperglycemia (12 hrs) produced significant changes to plasma renin activity and mean arterial pressure in healthy adults with type 1 diabetes.²²⁵ They hypothesized that these changes, if persistent in the face of chronic hyperglycemia, would have deleterious micro- and macrovascular effects. We hypothesize, as have others, that significant irreversible microvascular damage occurred during the pre-modern era of T1D care in this cohort. This has phenomenon recently been termed “metabolic memory”, and has been seen in the Diabetes Control and Complications Trial (DCCT) and other observational studies.^{226, 227} Thus, the modern advances in T1D care will delay major complications in this cohort, but not prevent them entirely, as early damage likely occurred in all participants.

7.2.2 Temporal Trends in Overall and Cause-specific Mortality in Type 1 Diabetes

Temporal improvements in mortality have been reported in other type 1 diabetes studies. Studies from Joslin and Steno Clinics have shown dramatic improvements in mortality in the first 50 years after the discovery of insulin, with T1D life expectancy increasing 15 years between 1933 and 1972.^{20, 40, 103, 105} Of note, the first real attempt to standardize T1D cohorts and compare cumulative mortality at different clinics reported that at 25 years T1D duration (follow-up through 1970), cumulative mortality in Cincinnati was 20%, compared to 19% in Boston, and 22% in Stockholm, Sweden.³¹ For comparison, the cumulative mortality in the current study at 25 years T1D duration was 12.8%.

Onset mortality (death within the first year of diagnosis) improved in this cohort. The 1975–79 diagnosis cohort had only 1 onset death compared to 4 and 5 in the 1965–69 and 1970–74 cohorts, respectively. These results have been reported previously in this study and are

consistent with other studies and correspond to improvement in diagnosis and care at onset.^{145, 194} Today, death at onset (due to DKA) in type 1 diabetes has become rare in the United States and in many other countries, in part due to widespread availability of glucometers and early testing of blood sugar levels by paramedics and emergency department physicians.²²⁸⁻²³⁰

Causes of early mortality (<10 years diabetes duration) in T1D have been explored in many populations. Nearly two-thirds of all deaths within the first 11 years in the Children's Hospital of Pittsburgh cohort diagnosed between 1950 and 1980 were due to acute diabetes complications (similar to the 74% seen in the current study in the first 10 years).¹⁹⁴ A Norwegian study (diagnosed between 1973 and 1982) found that only 35% of all early (<10 yrs duration) deaths in all childhood-onset (age<15 yrs at diagnosis) T1D individuals in Norway were due to acute complications; however, another 40% of deaths were caused by suicide or accident (compared to 6% in the Allegheny County cohort).²⁰⁰ It is unclear whether the smaller proportion of acute deaths compared to our study is solely due to the dramatically higher proportion of violent deaths in Norway, or results from their cohort being diagnosed nearly a decade later than the our cohort. More recent reports from Sweden and EURODIAB showed not only lower mortality rates than the present study, but also that acute diabetes complications account for only one-third of all early (<10 years after diagnosis) deaths; however, both of these cohorts consisted of individuals diagnosed more recently than the present study.^{124, 188} The majority of the remaining deaths were not related to diabetes (accidents, suicide, etc.).

Few studies have examined cause-specific mortality in long-standing (>20 years duration) type 1 diabetes, and most report cause of death as reported on death certificates, which have been known for years to be unreliable.²³¹ A Steno Clinic report compared the underlying cause of death in T1D patients dying before 35 yrs duration to those dying after 40 yrs duration

and found the proportion of renal deaths dramatically dropped from >50% in the former group to only 5% in the latter group.¹⁰⁴ On the other hand, deaths from CVD increased from about 25% of all deaths before 35 yrs duration to ~67% of all deaths after 40 years duration. The current study found renal disease to be the underlying cause of death in 17% of all deaths, but contributory (underlying or secondary cause of death) to 47% of all deaths, which suggests that though improvements in T1D care may have delayed renal disease in T1D over this time period, it continues to play a major role in T1D mortality. However, Nishimura et al found that the cumulative incidence of end stage renal disease (ESRD) in the Allegheny County cohort by 20 years duration had significantly decreased over time from 9.1% in the 1965-69 diagnosis cohort to 3.6% in the 1975-79 cohort.⁷⁶ Again, the hypothesis proposed in Section 7.2.1 that early microvascular damage occurred in all three diagnosis cohorts prior to modern T1D advances has application here as well. The decreased incidence of ESRD by 20-yrs duration combined with the current finding that renal disease contributed to nearly half of all deaths in the Allegheny County indicate that modern T1D care is actually delaying onset of diabetes complications and not completely preventing them.

Aside from the population-based cohorts in the Diabetes Epidemiology Research International Study Group (Finland, Japan, and the current cohort), mortality in only a few type 1 diabetes cohorts have been examined thoroughly using an M.D. Mortality Classification Committee (MCC).^{125, 232} The committee uses information from other sources beside the death certificate to ascertain an accurate underlying cause of death as well as secondary causes, and the role of diabetes in each death. A Norwegian group using M.D. MCC to examine mortality in a national cohort of childhood-onset (age<15 yrs) type 1 diabetes cohort diagnosed between 1972 and 1982 with at least 20 years of follow-up had very different findings than seen in Allegheny

County cohort.¹²⁵ Although an M.D. MCC was used to determine the underlying cause of death, the contribution of any secondary causes of death was not reported, preventing an appropriate comparison of renal and cardiovascular disease between the present study cohort and their cohort. Of note, the Norwegian cohort had much smaller proportions of both CVD and infections than the present study (15% vs. 35% and 5% vs. 16%, respectively), but larger proportions of both acute complications and violent deaths (22% vs. 16% and 28% vs. 6%, respectively). These differences can be explained in part by the dramatically higher numbers of suicides in the Northern European countries (in both T1D and general populations), as similar differences have been seen in DERI when the Allegheny County T1D cohort has been directly compared to the Finnish T1D cohort.⁵⁸

Of note, the contribution of major diabetes complications to T1D deaths has not been fully explored in a large population-based cohort. In a 20-year follow-up study exploring the relationship between retinal changes and cardiovascular disease, Klein et al reported that heart disease was involved in 64% of deaths in their Wisconsin cohort, which had an age of onset of up to 30 years.⁹⁰ In the present study, acute complications contributed to 80% of all early (<10 years duration) deaths, but only to about 15% of deaths thereafter. Conversely, CVD and renal disease contribute to >60% and ~50% of all deaths, respectively, after 20 years T1D duration (Figure 5). Also, although the incidence of renal disease appears to be decreasing in both the Pittsburgh EDC Study and the Allegheny County cohort,^{75, 76} the renal effects on cardiovascular disease have yet to diminish in the Allegheny County cohort, where renal disease contributed to only 67% of CVD deaths before 20 years duration but increased to 85% of all CVD deaths after 30 years duration.

7.2.3 Sex Differences in Overall and Cause-specific Mortality in Type 1 Diabetes

Sex-specific differences in overall mortality in the present study were quite impressive with the SMR for females nearly 3 times that of males. This is partially reflective of the much lower mortality rates for young females in the general population. On the whole, more females than males died during follow-up in this cohort (141 females, 138 males), both overall and when investigated by duration of diabetes. These findings have been seen in other studies and in earlier reports from the current study, but the magnitude of the sex difference in mortality is striking and clearly confirms that any sex advantage for mortality is lost in T1D females.^{63, 81} Other recent long-term follow-up studies have shown higher (or at least equivalent) SMRs in females with T1D: New Zealand (SMR: Male=3.3, Female=4.3),¹²⁷ U.K. (Male=2.7, Female=4.0);¹¹³ and Norway (Male=3.9, Female=4.0)¹²⁵ The respective male/female mortality rate ratios for these studies are: 1.23 in New Zealand, 1.29 in the U.K, and 2.26 in Norway compared to 0.80 for the current study. However, the markedly higher relative mortality seen overall in our U.S. T1D cohort is clearly limited to females, as males have more comparable SMRs to those reported in these other long-term follow-up studies. Directly comparing SMRs across countries is often confounded by either methodological or cohort differences between studies. For example, the 20-yr cumulative mortality for Norway was only 5.4% compared to 12.1% of the Allegheny County cohort. To what extent these differences reflect differences in health care systems is difficult to determine, but national measures of health care performance and other national economic measure have been shown to correlate with diabetes complications in type 1 diabetes.¹⁸⁹

To understand what was driving the higher mortality figures for females, cause-specific analyses were performed in the present study. The sex-specific SMRs for CVD deaths in the Allegheny County cohort were 8.6 for males and 24.7 for females, compared to 11.0 for males and 10.3 for females in Norway (Table 17).¹²⁵ Cause-specific SMRs from a 20-year follow-up report from New Zealand is less directly comparable, as type 1 diabetes was defined as diagnosis prior to age 30.¹⁹⁹ Equivalent numbers of CVD deaths by sex (50 males and 50 females) were seen in the Allegheny County cohort, whereas more men than women suffered CVD deaths in the Norwegian cohort (10 males and 4 females), suggesting that type 1 diabetes leads to more female CVD-related deaths in the U.S. than in Norway. In the Diabetes U.K. Study, no sex differences in CVD mortality rates were seen in T1D, but younger T1D females (age 30-39) showed a 45-fold higher risk of CVD mortality compared to the general population (compared to SMR for males 30-39=8.0), which partly explained the higher overall mortality risks in T1D females compared to T1D males seen in the U.K.¹¹⁴ Both the U.K. General Practice Research Database and the London Cohort of the WHO Multinational Study of Vascular Disease in Diabetes showed very similar results for overall and CVD-related mortality in T1D, i.e., both seeing a greater higher risk of mortality in T1D females than males.¹¹⁷⁻¹²⁰

Table 17. Comparison of sex-specific mortality rates in different T1D populations.

Study	Follow Up	Deaths	N	Male/Female SMR	Male/Female Mortality Rate (/10 ⁵ p-yr)	M:F Rate Ratio
Current study	30-yr	202	1,075	5.0 / 13.2	601 / 751	0.80
Norway ¹²⁵	20-yr	103	1,906	3.9 / 4.0	300 / 130	2.26
U.K. ¹¹⁴	13-yr	949	23,752	2.7 / 4.0	336 / 257	1.29
New Zealand ¹⁹⁹	20-yr	115	430	3.3 / 4.3	29% / 24%	1.23
Finland ⁷¹	15-yr	319	5,126	3.2 / 5.2	448 / 238	1.88
Japan ⁷¹	15-yr	137	1,408	9.0 / 18.5	617 / 601	1.03

In addition to elevated CVD mortality, females had higher mortality rates for all diabetes-related causes of death (acute complications, renal disease, and infections) compared to males in the Allegheny County cohort. Specifically, females with T1D had significantly higher mortality

rates than males for acute complications within the first 10 years of after diabetes onset. Males, on the other hand, had a mortality rate for accidents/suicide that was 7 times higher than seen in T1D females. However, this was comparable to the sex-specific rates seen in the age- and race-matched general population, as the SMR for violent deaths were not significantly different from the general population for either sex. These findings are consistent with recent reports from EURODIAB and from Sweden, which both show slightly higher, but non-significant, rates of accident/suicide compared to their respective general populations.^{144, 188}

7.2.4 Racial Differences in Overall and Cause-specific Mortality in Type 1 Diabetes

Apart from the present cohort, no long-term follow-up of African-Americans with type 1 diabetes exists in the literature. One study examined only African-American T1D patients at two diabetes clinics in the U.S (Memphis and Atlanta). With 9 years of follow-up, the authors reported a two-fold excess in mortality at both clinics compared to the respective general African-American populations.³⁹ The only other report with SMRs for African-Americans with T1D came from the New Jersey 725 Study. African-Americans with a mean 9-yr T1D duration were followed for 3 years, and SMRs for males and females were 7.0 and 10.5, respectively, compared to the local African-American population.¹²² This is higher than the SMRs seen in our African-American population after a T1D duration of 10 years (overall SMR=4.7).

A previous report combining the present cohort with the Children's Hospital of Pittsburgh T1D cohort (diagnosed 1965–1979) examined racial differences over 20 years of follow-up.⁶⁴ At the time, the only significant difference in cause of death by race was a significantly higher (5-fold) risk of acute complications in African-Americans. These data are

consistent with a retrospective study of death certificates for early (age<25) T1D deaths in Chicago residents showing that all acute complication deaths at onset occurred in either non-Hispanic black ($n=7$) or Hispanic ($n=1$) patients.²⁰² Only 2 deaths occurred in Caucasian T1D patients during this interval in Chicago, and neither was due to acute complications.

We now expand on previous findings in this cohort and report significantly higher mortality rates for all diabetes-related complications in T1D African-Americans compared to T1D Caucasians, which accounts for the continuing dramatically higher overall mortality rates seen in African-Americans with T1D in our cohort.^{61, 63, 64} Despite race being a significant predictor of mortality within the Allegheny County cohort (HR=3.2), no differences in SMR were seen by race. This seemingly contradictory result can be explained by the extremely high mortality rates seen in young African-Americans in the general population, particularly resulting from violent deaths.^{190, 191} Thus, while mortality rates in type 1 diabetes are 2-3 times higher in African-Americans,¹²² this excess is attributable to the background African-American mortality rates, and not to their diabetes.

Excluding one unknown cause of death, all of the deaths in African-Americans with T1D in this cohort were caused by either an acute or a chronic diabetes complication. Of note, despite young African-Americans having the highest rates of violent death in the U.S., none were observed in this cohort (2.5 deaths were expected),^{190, 191} suggesting that young African-Americans with T1D are “protected” from violent deaths, but are at much higher risk of diabetes-related deaths than their Caucasian counterparts. The poorer prognosis for African-Americans with T1D might reflect an underlying racial gap in socioeconomic status or access to and utilization of health-care that is present in the general U.S. population.¹⁹¹ Regrettably, none of these known factors are available for this cohort. Cause-specific analyses for the New Jersey

725 are forthcoming and should aid in understanding racial differences in T1D mortality in the U.S., as both clinical and demographic variables have been collected from this population.¹²²

7.2.5 Age at Onset Differences in Overall and Cause-specific Mortality in Type 1 Diabetes

Although not a major focus of the current study, it should be noted that we found a significantly lower mortality in individuals with a pre-pubertal onset (defined as age<10) of T1D compared to individuals with peri-pubertal (age=10-14, mortality rate ratio=0.69) and post-pubertal onset (age>14, mortality RR=0.63) (Table 5 and Figure 3E). Pubertal status was classified this way to help ensure proper classification. Other T1D reports (including those using the Allegheny County cohort) have dichotomized pubertal status based on the classical definition (M \geq 12 yrs, F \geq 11 yrs).¹⁸⁷ These reports have consistently shown higher mortality rates in T1D individuals with pubertal onset compared to pre-pubertal onset.⁷⁰⁻⁷² Several possible mechanisms have been postulated to account for these higher rates. It has been shown that glycemic control gets worse when children with T1D reach puberty.²³³ This poorer glycemic control could be the result of hormonal changes, mental stress, or changes in self-care (as the teenager with T1D seeks independence). Kostraba et al suggested that pubertal-onset and pre-pubertal onset T1D are two different entities, with the former being a more severe variant.⁷⁰ Another theory (suggested by Dr. Harvey Knowles) is that the pre-pubertal years of exposure to diabetes are less harmful; the true damage of the disease occurring after pubertal onset.³²

7.2.6 Sudden Unexplained Deaths and Dead-in-Bed Syndrome in Type 1 Diabetes

Sudden unexplained deaths (SUDs) that meet the criteria for dead-in-bed syndrome (age < 50, healthy, but are found dead in bed in the morning) are not exclusive to type 1 diabetes.

However, rates of sudden deaths in young general populations have not frequently been calculated,^{219-221, 234} making it difficult to determine the magnitude of risk attributable to type 1 diabetes for dead-in-bed syndrome. However, our results suggest that dead-in-bed syndrome occurs at rates 5-10 times higher than seen in the general population (Table 14).

Although a major hypothesis used to explain dead-in-bed syndrome implicates autonomic neuropathy as the basis for a malignant cardiac arrhythmia, convincing data to validate this hypothesis is lacking.^{150, 151, 204} On the other hand, reasonable evidence exists linking nocturnal hypoglycemia to dead-in-bed syndrome,^{139, 146, 155} however, a causal association between the two entities has not been convincingly made. We saw that a history of severe hypoglycemic events was present in nearly all dead-in-bed events and SUDs. A recent case report confirmed hypoglycemia in a dead-in-bed death using a continuous glucose monitoring system, and reported that the individual was found in an undisturbed bed (suggesting that the hypoglycemic episode did not elicit a terminal seizure or struggle).²¹⁷

Our data suggests patterns that might be predictive of sudden unexplained deaths and dead-in-bed syndrome in type 1 diabetes. DIB syndrome tends to occur in males with lower BMI, higher HbA_{1c}, and higher daily insulin doses and in those with a history of severe hypoglycemia. If these characteristics can be confirmed in other population-based cohorts of T1D, these individuals at highest risk for DIB syndrome could be placed on a continuous glucose

monitoring system with regular follow-up with the hope that the nocturnal hypoglycemic events seen frequently in T1D do not lead to devastating consequences.²¹²

7.3 STRENGTHS AND WEAKNESSES

Several key strengths of the current study should be noted. We have confirmed vital status in 97% in a large population-based cohort ($n=1,075$) more than 25 years after diagnosis with type 1 diabetes. These results offer the best picture of both overall and cause-specific mortality in long-standing (28–43 years duration) T1D in the U.S. Also, we now have sufficient follow-up data to examine trends in mortality in African-Americans with T1D, offering important insights into this understudied type 1 diabetes population.¹²²

A few key weaknesses of this follow-up study must be addressed. First, these population-based data reflect the type 1 diabetes experience of individuals diagnosed in Southwestern Pennsylvania between 1965 and 1979, and may not be representative of the entire U.S., of individuals not of African-American or Caucasian ethnicity, or especially of those diagnosed earlier or later than this cohort. Also, 3% of this cohort was lost to follow-up and vital status could not be determined for these individuals, potentially inflating the mortality rates. Thorough searches of both the Social Security Death Index and the National Death Index give us confidence that most (if not all) of these 32 individuals are still living. In addition, the analysis is limited to only a few key demographic variables (age at onset, race, sex), as other key socioeconomic (education and income levels) and clinical (HbA_{1c}, serum creatinine, lipid levels, blood pressure, etc.) variables could not be ascertained for all participants at study inception.⁵²

As all individuals in this cohort were diagnosed prior to major modern-day advances in type 1 diabetes treatment (self-monitoring blood glucose, HbA_{1c} testing, and ACE inhibitors), the effect of these advances cannot be properly examined here. However, if a new population-based T1D cohort in Allegheny County was established (perhaps diagnosed between 1990 and 2005), data from our cohort would serve as an excellent comparison group to properly determine the role of these T1D treatment advances in decreasing mortality rates and increasing life expectancy in T1D. Finally, classifying cause of death in this cohort is an ongoing process. To date, 219 (79%) of deaths have been finalized by the international M.D. Mortality Classification Committee (MCC). The remaining deaths have been classified based on the death certificate and all additional information presently available. However, these deaths might be reclassified as each death is finalized by the MCC.

7.4 FUTURE RESEARCH

Several research questions remain unanswered regarding long-term mortality in T1D. A few of these will be explored using these data in the near future. Based on previous research, diabetes is grossly underreported on death certificates worldwide. Only one study (from Germany) has examined the reliability of death certificates for analysis in T1D mortality studies.¹⁸¹ We intend to combine mortality data from the Allegheny County T1D cohort with the Pittsburgh EDC Study, both of which utilize a standardized mortality classification system to determine the underlying causes of death, as well as the role of diabetes in each death. We will compare the results of the MCC with the information reported on death certificates alone to determine how

frequently the role of diabetes is underreported in T1D. We can then compare causes of death to determine when death certificate data might be reliable in T1D mortality studies (e.g., only for acute complications of T1D).

Also, previous attempts to contact Allegheny County T1D participants have focused almost exclusively on vital status determination. Realizing that the surviving ACIR population currently has an estimated average duration of diabetes of >35 years, we have surveyed the surviving population to obtain detailed information concerning physician-diagnosed long-term complications, diabetes treatment, health-care utilization, and demographic and socioeconomic factors. We have currently obtained completed surveys from 70% of the surviving population, and expect to obtain survey data from another 5-10% of the surviving population. To date, only 7% of the surviving cohort has declined to participate. We also have detailed complication information on 60-70% of the deceased population. Using these data, we will determine population-based estimates of incidence for each of the major diabetes complications (e.g., myocardial infarction, cerebrovascular accident, end stage renal disease, proliferative retinopathy, blindness and amputation). These data will aid in understanding the burden of type 1 diabetes and determining life expectancy in a modern T1D population.

As stated in Section 2.3.2.1, the Allegheny County T1D cohort has been part of an international collaboration (Diabetes Epidemiology Research International (DERI)) since the mid-1980s. The last multinational DERI report on T1D mortality was based on follow-up through 1994, providing mortality rates in a population with 15-30 years T1D duration, and this analysis did not include data from Allegheny County.⁷¹ The Japanese and Finnish cohorts have determined vital status for their cohort as of 1 January 2005. We will compare contemporary

T1D mortality rates in Japan, Finland, and Allegheny County to explore international variations in mortality trends in long-standing T1D (25-40 years duration).

7.5 PUBLIC HEALTH IMPLICATIONS

Despite significant advances in diabetes management and care in recent decades, T1D persons remain at a markedly increased risk of death. Few studies have accurately quantified modern mortality risk in large, representative, samples of T1D individuals. These results speak to the continuing necessity for monitoring type 1 diabetes morbidity and mortality in the U.S. and worldwide to accurately assess whether rates are improving. Most studies have either used small physician-based or hospital-based cohorts in homogeneous T1D populations or relied on death certificate data alone to determine mortality rates and cause(s) of death. The current findings add greatly to the understanding of causes of mortality in long-standing T1D in the United States and offer insights as to how mortality rates can be lowered. For example, females with T1D have a higher risk of dying from a diabetes-related cause, whereas males with T1D die more frequently from non-diabetes-related causes than do T1D females. In fact, all suicides occurred in Caucasian males in this cohort. Therefore, depression screening in Caucasian males would have the most impact at preventing suicides in this population. Similarly, race-specific analyses show that all of the African-Americans in our T1D cohort died from a diabetes-related cause. Consequently, a focus on diabetes education and self-management with tight glucose control for African-Americans, including early preventative measures (ACE inhibitors to delay/prevent renal damage) could significantly impact the long-term mortality rates in African-Americans

with T1D. Specifically, acute complications, which cause a greater proportion of deaths in African-Americans, are largely preventable through proper diabetes education. Another important area to explore is whether young African-American males with T1D are truly “protected” against violent deaths, and if so, why this occurs. Armed with these data, we hope strategies can be developed that will allow mortality rates in T1D patients to approach those of the general population.

These mortality data will serve many additional purposes. Presently, life insurance coverage for T1D persons are based on antiquated mortality estimates, greatly inflating policy premiums. These estimates do not account for recent advances in T1D treatments and concomitant increases in life expectancies.¹⁰⁵ Moreover, these data will provide insight into premature mortality and morbidity, and thus enable more effective preventative strategies to be developed, especially strategies to decrease the number of sudden unexplained deaths in T1D. Finally, previous results from this cohort have recently been included in a summary report submitted to Congress to show evidence of improvements of T1D care.¹⁸³ These current findings will aid in determining the appropriate allocation of future T1D research funding, as incidence rates for T1D are increasing in the in U.S. and worldwide.^{1, 2}

APPENDIX

SUPPLEMENTARY ANALYSES

Table 18. Comparison of overall mortality rates by various age-at-onset cut-points

	Deaths % (n)	Total n	p	Follow-up Time (p-yrs)	Mortality rate (95% CI) (per 100,000 p-yrs)
Overall	26.0 (279)	1,043		34,363.1	811.9 (716.6–907.2)
Age at Onset (Paper 1)			0.006		
<10 yrs	21.2 (84)	396		13,530.3	620.8 (488.1–753.6)
10-14 yrs	29.4 (112)	381		12,368.0	905.6 (737.8–1073.3)*
>14 yrs	31.2 (83)	266		8,464.9	980.5 (769.6–1191.5)*
Age at Onset			0.006		
Pre-pubertal (F<11, M<12)	23.1 (124)	537		18,107.8	684.8 (564.3–805.3)
Pubertal (F≥11, M≥12)	30.6 (155)	506		16,255.3	953.5 (803.4–1103.6)*
Age at Onset			0.002		
<10 yrs	21.2 (84)	396		13,530.3	620.8 (488.1–753.6)
F=10-14, M=10-15 yrs	28.4 (123)	433		14,080.1	873.6 (719.2–1028.0)*
F>14 yrs, M>15 yrs	33.6 (72)	214		6,752.7	1,066.2 (820.0–1312.5)*
Age at Onset			0.004		
<10 yrs	21.2 (84)	396		13,530.3	620.8 (488.1–753.6)
10-15 yrs	29.1 (136)	467		15,200.4	894.7 (744.3–1045.1)*
>15 yrs	32.8 (59)	180		5,632.4	1,047.5 (780.2–1314.8)*
Age at Onset			0.006		
<10 yrs	21.2 (84)	396		13,530.3	620.8 (488.1–753.6)
10-16 yrs	29.8 (158)	531		17,101.5	923.9 (779.8–1068.0)*
>16 yrs	31.9 (37)	116		3,731.4	991.6 (672.1–1311.1)*
Age at Onset			0.026		
<11 yrs	23.1 (114)	493		16,693.7	682.9 (557.5–808.3)
11-15 yrs	28.6 (106)	370		12,037.0	880.6 (713.0–1048.3)
>15 yrs	32.8 (59)	180		5,632.4	1,047.5 (780.2–1314.8)*
Age at Onset			0.038		
<11 yrs	23.1 (114)	493		16,693.7	682.9 (557.5–808.3)
11-16 yrs	29.5 (128)	434		13,938.0	918.4 (759.3–1077.5)*
>16 yrs	31.9 (37)	116		3,731.4	991.6 (672.1–1311.1)*

* $p < 0.05$ for rate ratio compared to first group within each age-at-onset category

Table 19. Characteristics (% (*n*) or mean ± SD) by study participation

Variables	Allegheny County Only	Allegheny County & EDC	<i>p</i> -value
N	804	271	---
Male sex	52.7 (424)	49.4 (134)	0.35
African-American	8.5 (68)	4.1 (11)	0.02
Diagnosis Cohort			0.63
1965-1969	33.6 (270)	31.4 (85)	
1970-1974	36.6 (294)	35.8 (97)	
1975-1979	29.9 (240)	32.8 (89)	
Age at Diabetes Onset (yr)	11.6 ± 3.9	8.8 ± 4.1	<0.001
Ascertainment as of 1/1/2008	96.0 (772)	100.0 (271)	0.001
Deceased as of 1/1/2008*	30.2 (233)	16.5 (46)	<0.001

*Percentage of those ascertained as of 1/1/2008

Table 20. Overall mortality rates by study participation

	Overall			
	Deaths % (<i>n</i>)	Total <i>n</i>	<i>p</i>	Follow-up Time (p-yrs) Mortality rate (95% CI) (per 100,000 p-yrs)
Overall	26.0 (279)	1,043		34,363.1 811.9 (716.6–907.2)
Study participation			<0.001	
Allegheny County Only	30.2 (233)	772		25,215.3 924.0 (805.4–1,042.7)
Allegheny County & EDC	16.5 (46)	271		9,147.8 502.9 (357.5–648.2)*

**p* < 0.05 for rate ratio compared to Allegheny County Only group

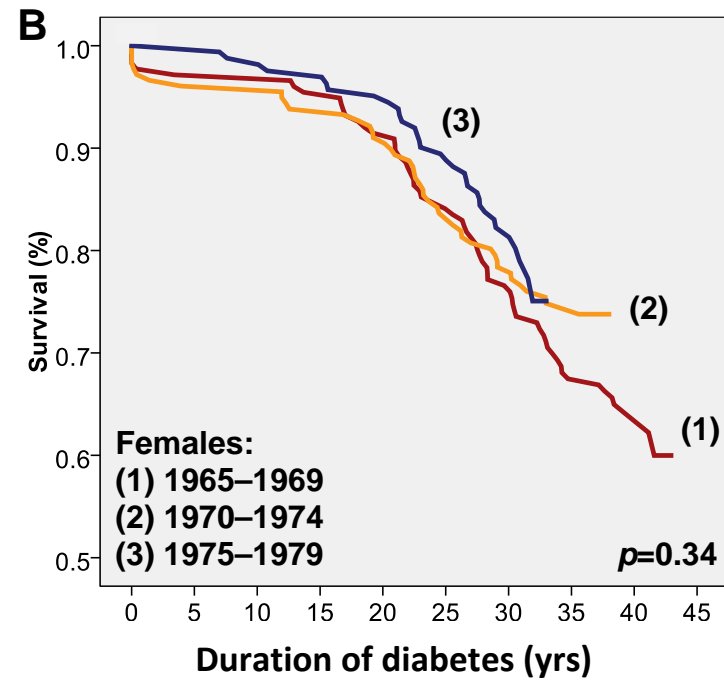
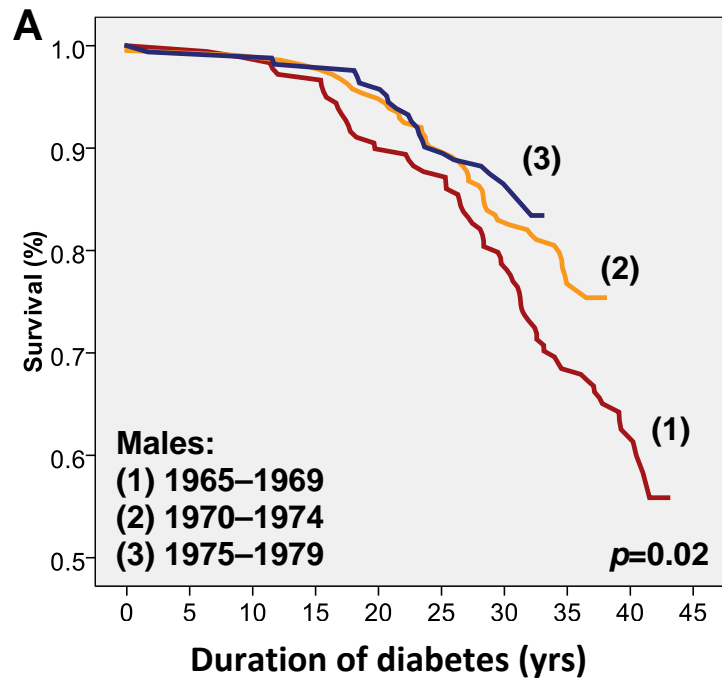
Table 21. Characteristics (% (*n*) or mean \pm SD) of the deceased type 1 diabetes study population by Mortality Classification Committee (MCC) status

Variables	Classified by MCC	Not yet classified by MCC	<i>p</i>-value
N	255	74	---
Male sex	49.4 (126)	55.4 (41)	0.36
African-American	11.8 (30)	20.3 (15)	0.06
Age at Diabetes Onset (yr)	11.3 \pm 4.0	11.1 \pm 3.9	0.76
Diabetes Duration at Death (yr)	23.6 \pm 9.0	28.2 \pm 7.0*	<0.001
Age at Death (yr)	34.9 \pm 9.1	39.3 \pm 7.3*	<0.001
Calendar Year of Death	1993.5 \pm 8.9	1999.3 \pm 7.0*	<0.001
Pennsylvania Death^a	84.7 (216)	71.6 (53)*	0.01
Inpatient at Death^b	55.6 (140)	58.3 (35)	0.70
Autopsy performed	28.2 (71)	17.9 (10)	0.11

* $p \leq 0.05$.

^a Pennsylvania Death = death occurred in the state of Pennsylvania

^b Inpatient Death = death occurred as an inpatient in the hospital



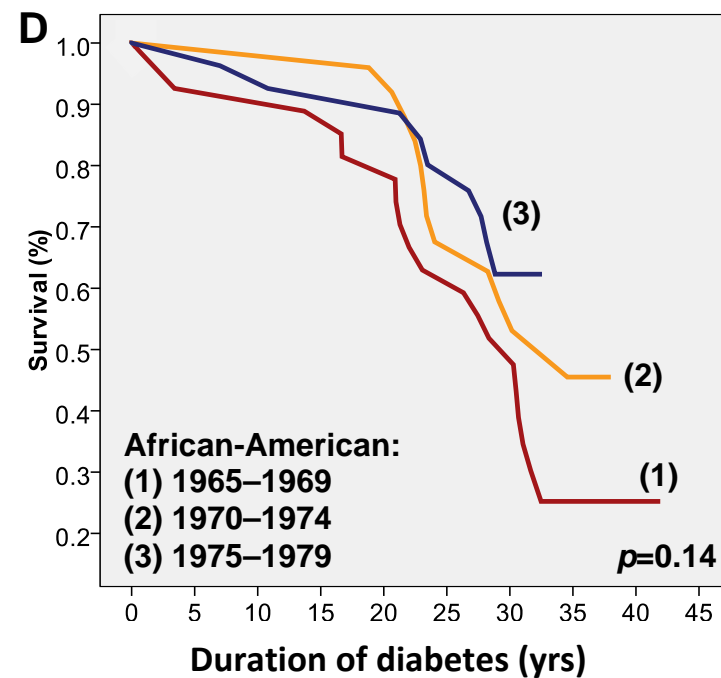
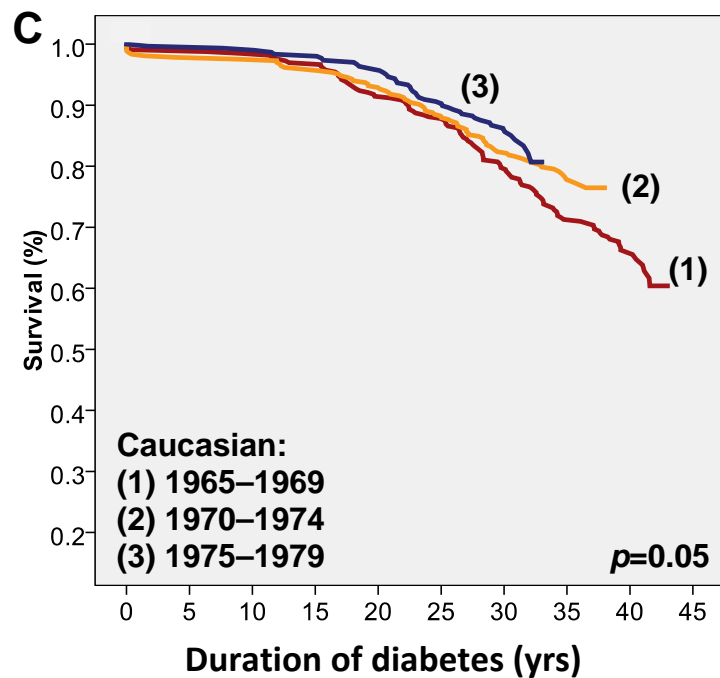
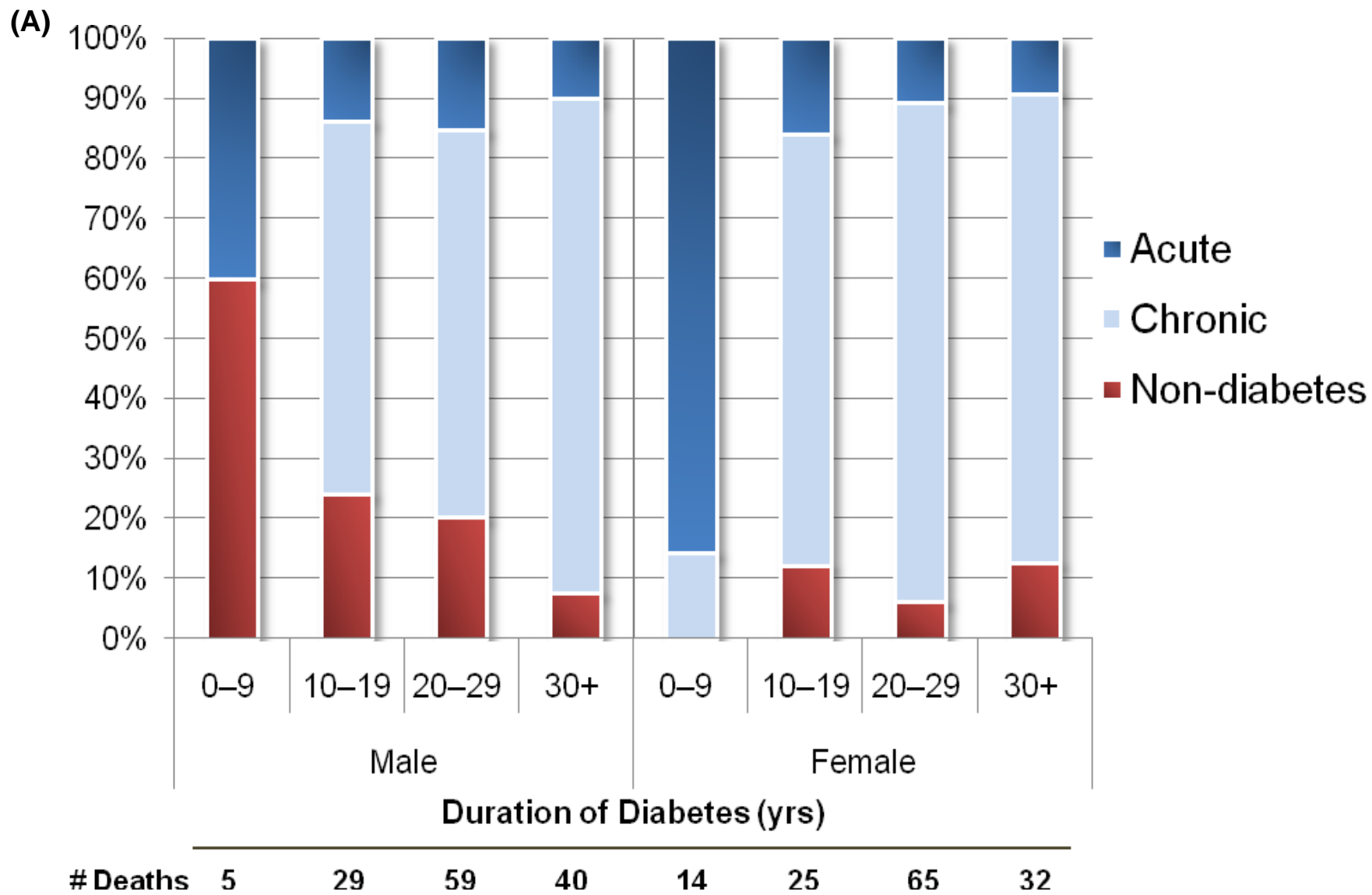
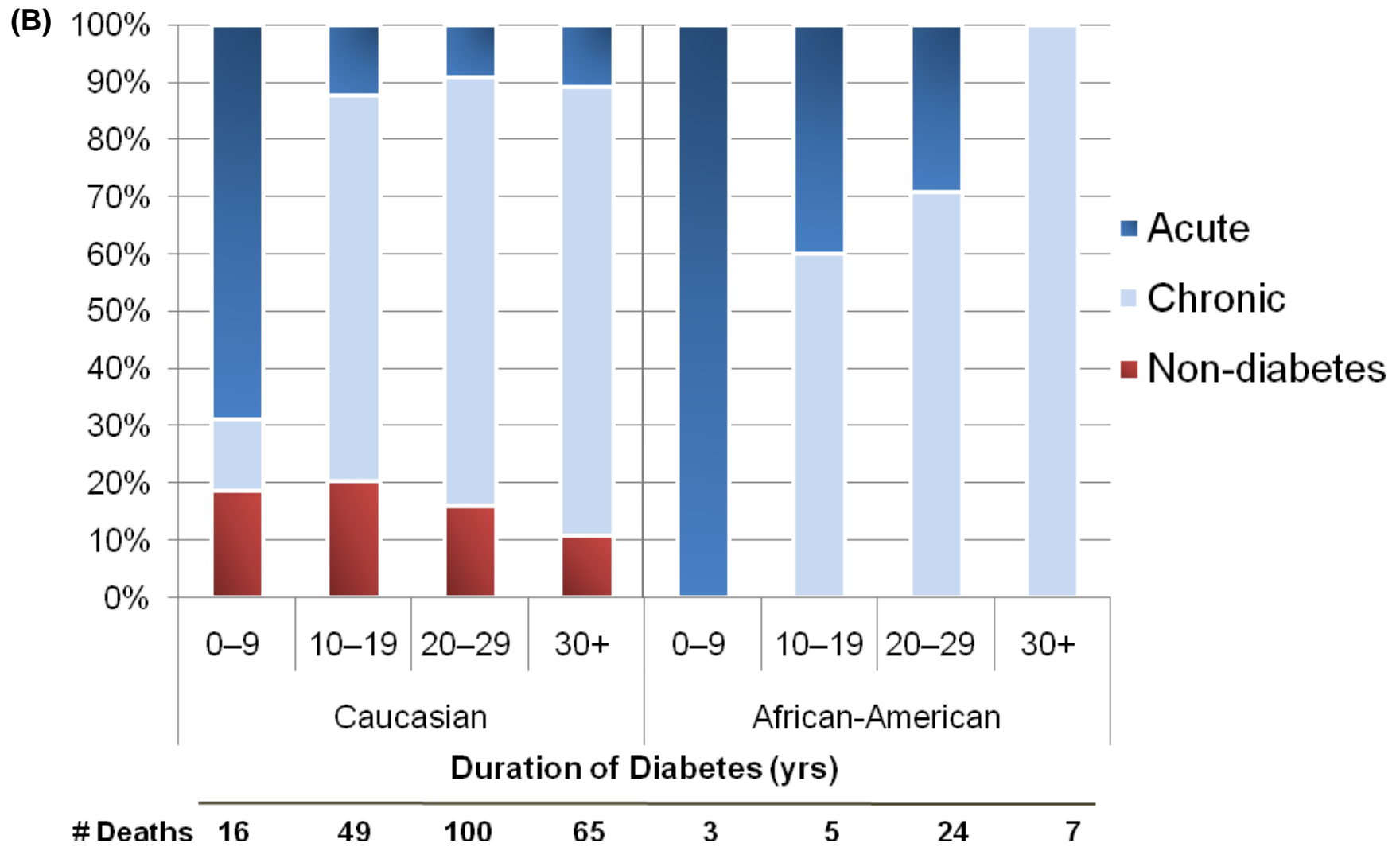


Figure 8. Life-table analyses by diagnosis cohort stratified by sex and race for individuals diagnosed with type 1 diabetes between 1965 and 1979 in the Allegheny County Type 1 Diabetes Registry cohort. *P*-values calculated using the log-rank test. A) Males by Diagnosis cohort; B) Females by Diagnosis cohort; C) Caucasian by Diagnosis cohort; D) African-American by Diagnosis cohort. A: 1965–69 vs. 1970–74, $p=0.04$, and 1965–69 vs. 1975–79, $p=0.02$. No statistical differences seen in B, C, or D.





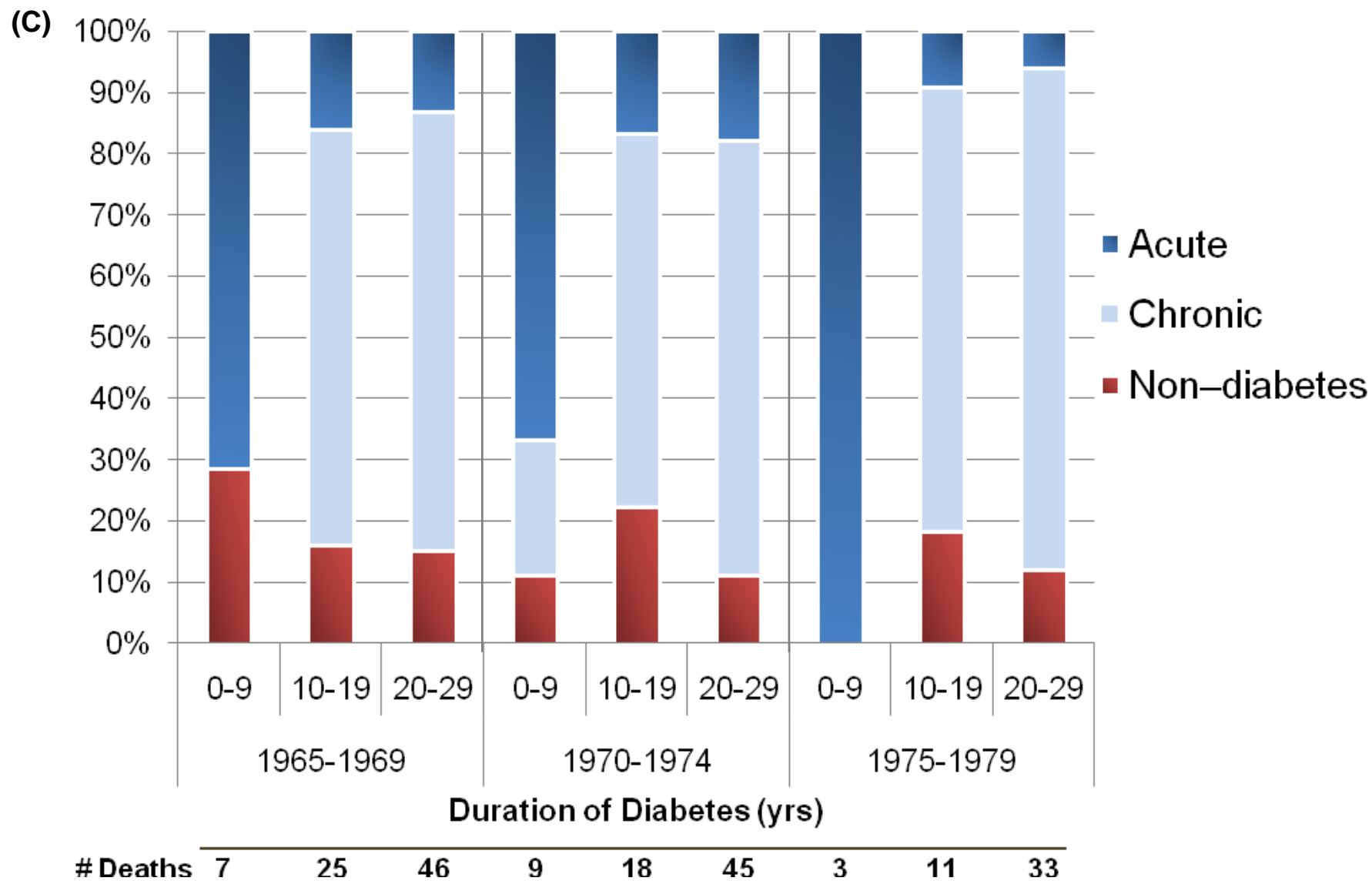


Figure 9. Distribution of underlying causes of death by duration of diabetes (10-year intervals) and (A) sex; (B) race; and (C) diabetes diagnosis cohort. Ten deaths where the cause of death was unknown were excluded.

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