MORTALITY IN TYPE 1 DIABETES

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SUMMARY

Despite major advances in management and care, type 1 diabetes remains associated with considerable premature mortality. Although significant improvements in life expectancy have been observed in those diagnosed since 1965, mortality rates among patients with type 1 diabetes remain significantly higher than the general population, a finding confirmed by several studies in the United States and internationally, with standardized mortality ratios revealing that patients with type 1 diabetes have mortality rates that are 3–18 times higher than would be expected in their respective countries. There is marked geographic variation in mortality, and further notable differences between males and females, compared to the general population.

Deaths due to diabetes-related acute and chronic complications appear to account for nearly all of the excess premature mortality in patients with type 1 diabetes compared to the general population. Diabetes-related chronic complications, particularly cardiovascular and renal disease, are now the predominant causes of death in type 1 diabetes, in contrast to the high rates of death due to diabetes-related acute complications (i.e., glycemic-related events) observed during earlier years (i.e., the pre-insulin era). End-stage renal disease (ESRD), historically, is the leading cause of death in the mid-years of diabetes duration (up to 35 years), accounting for more than half of deaths. After 35 years duration, however, cardiovascular disease (CVD) is the leading cause of death, accounting for two-thirds of deaths. With the decline (or delay) in developing ESRD due to improvements in diabetes management, this pattern may be changing.

Several risk factors for type 1 diabetes mortality have been investigated. Females with type 1 diabetes continue to have a greater increase in mortality compared to females in the general population than is found for males. This pattern is consistent for all causes of death, particularly CVD, where the standardized mortality ratio for females (24.7) is nearly three times that for males (8.6), primarily resulting from the lower rates of mortality in the female general population. In addition, African Americans remain at increased risk of premature mortality compared to Caucasians, consistently having mortality rates 2.5 higher than their Caucasian counterparts over the past 30 years. Onset of type 1 diabetes after puberty also appears to be associated with 1.5–2.0-fold higher mortality than prepubertal onset. Several other factors are associated with type 1 diabetes mortality, including lower socioeconomic status, hypertension, smoking, and renal failure. Some risk factors, such as glycemic control and insulin resistance, have not consistently shown direct associations with type 1 diabetes mortality but are associated with diabetes-related chronic complications and are likely contributing factors. Indeed, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study suggests that even 6 years of more intensive therapy may lead to a lower mortality over 20 years of further follow-up.

Finally, type 1 diabetes has a greater impact on mortality rates in U.S. populations than seen in many European countries, with U.S. standardized mortality ratios of 6.9–7.5 compared to European standardized mortality ratios of 3.3–4.2. These geographic differences indicate an urgent need to improve disease management and access to care in the United States.

INTRODUCTION

Historically, type 1 diabetes has been associated with a greatly increased risk of early mortality. Fortunately, this is no longer necessarily the case, and many individuals with type 1 diabetes can expect a normal lifespan. This chapter reviews type 1 diabetes mortality from a variety of perspectives, including improvements in mortality and life expectancy over time and comparisons to the general U.S. population, as well as international type 1 diabetes populations. Major studies and registries are described, and data are presented regarding causes of death and predictors/risk factors for mortality.

HISTORICAL DATA (PRE-1980 ERA)

Prior to the availability of insulin in bovine form in 1922, dietary restrictions and supportive therapies could usually only delay mortality for 1–2 years after onset of type 1 diabetes. Based on mortality data from the Joslin Clinic in Boston, Massachusetts, the mortality rate for type 1 diabetes patients dying within the first 10 years of life improved dramatically from 824 per 1,000 in 1897–1914 to 386 per 1,000 in 1914–1922 down to 61 per 1,000 in 1922–1926, a sixfold reduction immediately after bovine insulin became available (Figure 35.1) (1). As more standardized treatment plans were developed, these mortality rates continued to decline to 1 per 1,000 in 1950–1961 (1).

Other diabetes clinics reported that their type 1 diabetes mortality rates during the 1920s and 1930s ranged from 30% to 50% for patients diagnosed in the 1920s and followed for at least 20 years, with little difference observed by sex (2,3). Acute diabetes complications like ketoacidosis or hypoglycemia were relatively common, accounting for 15%–40% of all type 1 diabetes deaths during the 1920s at various clinics (1,2,4). With improvements in diagnosis and care, acute complications quickly became rare at these clinics, accounting for <5% of all type 1 diabetes deaths by 1943 (1,2). By the 1950s and 1960s, Joslin Clinic was reporting that diabetic comas accounted for 1% or less of all deaths in its patients, with the proportion of deaths due to diabetic coma declining by age (Figure 35.2) (1,5,6).

Prior to the discovery of antibiotics in the 1940s, infections accounted for a substantial proportion (10%–20%) of all deaths, but this figure dropped to 5%–6% after antibiotic use became widespread (1). In the 1950s, the role of long-term diabetic complications (i.e., renal disease, cardiovascular disease [CVD], hypertension, and neuropathy) on mortality became apparent, as data from long-term follow-up studies began to accumulate on patients with ≥30 years duration of diabetes (1,7,8). Although many patients with type 1 diabetes were now surviving well into adulthood with insulin therapy,

FIGURE 35.1. Mortality Prior to Age 10 Years Among Patients With Type 1 Diabetes, Joslin Clinic, Boston, Massachusetts, 1897–1961
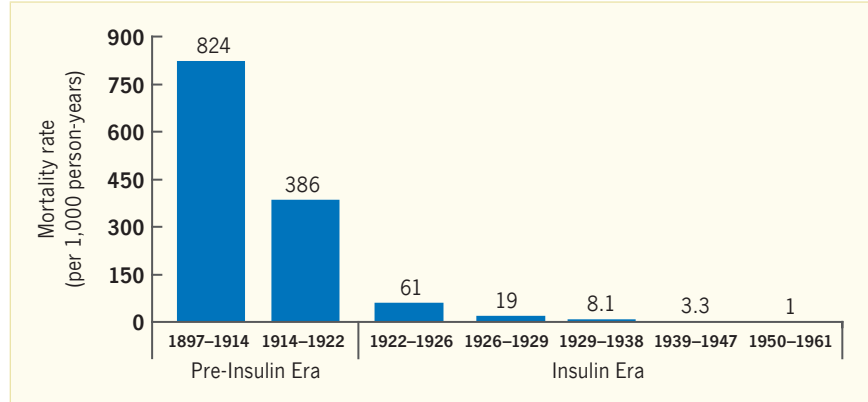
SOURCE: Reference 1

FIGURE 35.2. Cause-Specific Mortality in Type 1 Diabetes by Age at Death, Joslin Clinic, Boston, Massachusetts, 1956–1962
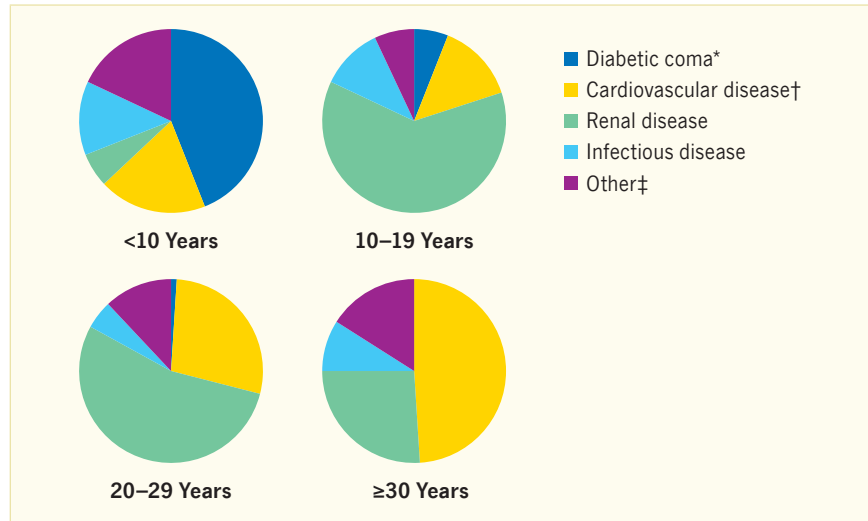
Type 1 diabetes is defined as diagnosis prior to age 20 years.
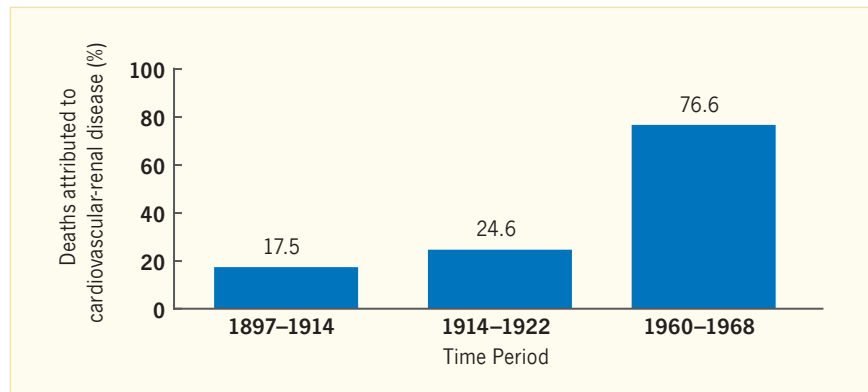* Includes diabetic ketoacidosis or hypoglycemia.
† Includes cerebrovascular disease and diabetic gangrene.
‡ Includes cancer, violence, other, and unknown.
SOURCE: Reference 1

FIGURE 35.3. Proportional Mortality Due to Cardiovascular-Renal Disease in Type 1 Diabetes, Joslin Clinic, Boston, Massachusetts, 1897–1968

SOURCE: Reference 10

their lifespans remained significantly shorter than the general population due to frequent diabetes-related complications (1). A Joslin Clinic study found that after 35 years of diabetes duration, CVD was the leading cause of death (9) and accounted for nearly 65% of all type 1 diabetes deaths by the early 1960s (1). Another Joslin report showed that the proportion of deaths caused by combined CVD and renal disease tripled by the 1960s compared to the pre-insulin era (76.6% vs. 24.6%) (Figure 35.3) (10).

During this pre-1980 era, cohorts of individuals who purchased or applied for life insurance policies were used to explore type 1 diabetes mortality. A 1967 study did not differentiate type 1 from type 2 diabetes; however, looking only at those diagnosed by age 30 years between 1935 and 1963, a sixfold greater mortality existed compared to that expected based on the nondiabetic population of policyholders, with excess mortality largely due to CVD (11). Using life insurance applicants between 1950 and 1971, those diagnosed with diabetes prior to

age 15 years had an elevenfold increase in mortality compared to that expected based on nondiabetic applicants, with a calculated life expectancy of 32 years for those with type 1 diabetes (12,13).

Joslin Clinic was an early leader in type 1 diabetes mortality research in the United States due to its large clinic population. However, as a world-renowned clinic, the clinic population was not representative of type 1 diabetes in the United States. To decrease selection bias, Joslin Clinic studies limited inclusion to Massachusetts residents seen at the clinic within 1 year of diagnosis and estimated mortality rates at 2–14 times higher than the general population, with extremely high mortality rates after age 35 years (1,5,14,15). These mortality rates may still be subject to patient selection bias and a failure to distinguish between type 1 and type 2 diabetes in the older age groups.

Population-based early type 1 diabetes mortality data first came from Erie County (Buffalo), New York (16). In an analysis of all major childhood diseases, these

researchers examined hospital, specialist, vital, and school records to ascertain childhood diseases, including type 1 diabetes, in all persons age <16 years diagnosed between 1946 and 1961. They found 389 persons with type 1 diabetes. Only seven deaths occurred during the study period, with higher case-fatality rates in females, low income, and nonwhite type 1 diabetic persons. The overall mortality rate was 4.1 per 1,000 patient-years (16). Compared to other childhood diseases in the same population, diabetes mortality was fourfold higher than that of asthma (1.0 per 1,000 person-years), but significantly lower than that of cystic fibrosis (139.4 per 1,000 person-years).

In summary, the findings of these early studies showed dramatic improvements in overall type 1 diabetes mortality with the pattern shifting from mostly acute complications in the 1920s and 1930s to mostly chronic diabetes complications since the 1940s.

CURRENT (POST-1980) ERA

During the 1980s, a major shift in type 1 diabetes research occurred. A number of large, population-based type 1 diabetes registries and cohort studies were developed to assess geographic variations in type 1 diabetes incidence both within the United States and internationally. These registry and cohort populations, as well as key mortality-related research findings, are summarized below.

KEY FINDINGS
Pittsburgh Registries
Two early efforts to obtain representative cohorts came from the Pittsburgh, Pennsylvania, area in the 1980s, specifically the Children's Hospital of Pittsburgh (CHP)-based type 1 diabetes registry and the population-based Allegheny County Type 1 Diabetes Registry (ACR) (17,18,19). The former was the source of the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, while the latter was the U.S. cohort in the Diabetes

FIGURE 35.4. Observed Deaths of Type 1 Diabetes Patients Diagnosed (Age ≤16 Years) at Children's Hospital of Pittsburgh Between 1950 and 1981 Compared to That Expected in the General U.S. Population
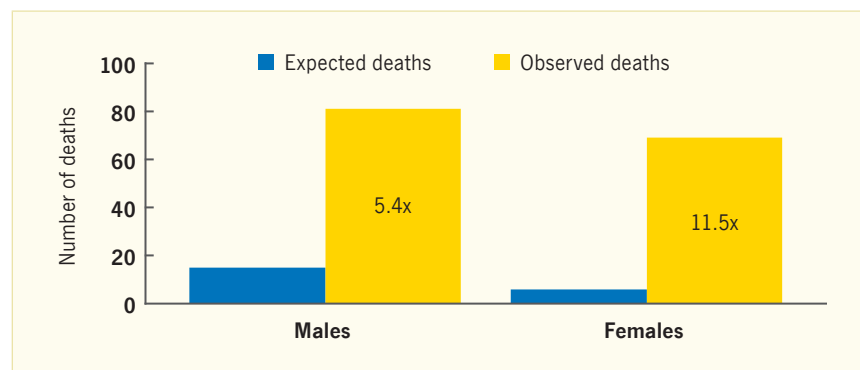
SOURCE: Reference 17, copyright © 1984 American Diabetes Association, reprinted with permission

Epidemiology Research International (DERI) study. Demographic characteristics between the registries were similar (18,19). Based on 1,966 individuals diagnosed with type 1 diabetes at CHP between 1950 and 1981, mortality among type 1 diabetes 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 males with type 1 diabetes to 11.5 times higher for females with type 1 diabetes (Figure 35.4) (17). Mortality rates were most dramatic in type 1 diabetic persons age >25 years,

where >2% died annually, which translated into a mortality rate approximately 20 times higher than the general U.S. population (20). Early ACR findings also showed that although Caucasian children with type 1 diabetes had mortality rates 1.5 times higher than African American children without diabetes, African Americans with diabetes had 2.4 times the risk of early type 1 diabetes mortality compared to Caucasians (21). The EDC study, derived from the CHP registry, reported a remarkable decline in mortality and renal disease between those diagnosed in the 1950s and 1960s compared to those diagnosed in the in 1970s and 1980s (22). These and more recent data from the ACR are discussed in the Causes of Death in Type 1 Diabetes section.

Wisconsin Study

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) began in 1979 with diabetic individuals being identified in 11 counties in southern Wisconsin (23). This cohort included 996 individuals with presumed type 1 diabetes (defined as age of diagnosis <30 years and on insulin therapy). In a 20-year follow-up report, 64% of deaths involved heart disease, and retinopathy and nephropathy status significantly predicted cardiovascular mortality (24). A separate analysis showed a significant association between mortality and hyperglycemia. Compared to the lowest quartile, participants in the highest glycosylated hemoglobin (A1c) quartile had a higher risk of overall mortality (relative risk 2.4, 95% confidence interval [CI] 1.5–3.8) (25).

Joslin Studies

The Joslin Clinic in Boston has long been a leader in diabetes epidemiology using its large database of diabetes patients. Early reports from Joslin are described in the Historical Data section. In 2008, a study from Joslin Clinic described an association between mortality and self-reported insulin restriction in women with type 1 diabetes, in an effort to lose weight, often due to eating disorder problems. There was a threefold increase in mortality in type 1 diabetic women reporting self-induced insulin restriction (50% of

TABLE 35.1. Death Rate for Deaths Coded to Diabetes on U.S. Death Certificates, by Age of Death, 1950–2009

YEAR	AGE (YEARS)					
	<5	5–9	10–14	15–19	20–24	25–29
1950–1954	4.0	3.6	6.6	10.0	12.6	19.8
1955–1959	3.0	2.5	5.0	7.0	12.5	20.1
1960–1964	2.6	2.2	4.2	5.8	10.7	21.4
1965–1969	2.2	1.8	3.4	4.1	9.9	19.8
1970–1974	2.0	1.5	2.5	3.7	7.8	15.9
1975–1979	1.0	0.9	1.5	2.2	5.6	11.9
1980–1984	0.9	0.8	1.3	1.7	4.5	10.5
1985–1989	0.7	0.7	1.1	1.8	4.6	10.4
1990–1994	0.5	0.5	0.9	1.8	4.9	11.2
1995–1999	0.4	0.4	0.8	2.3	5.4	10.8
2000–2004	0.4	0.4	1.2	2.4	5.6	11.0
2005–2009	0.4	0.4	1.1	2.4	6.1	10.8

Death rates per 1,000,000 people.
SOURCE: National Vital Statistics Reports, 1950–2009

FIGURE 35.5. Annual Death Rates in Childhood From Diabetes Per 1 Million Persons Age ≤19 Years, U.S., 1968–2009
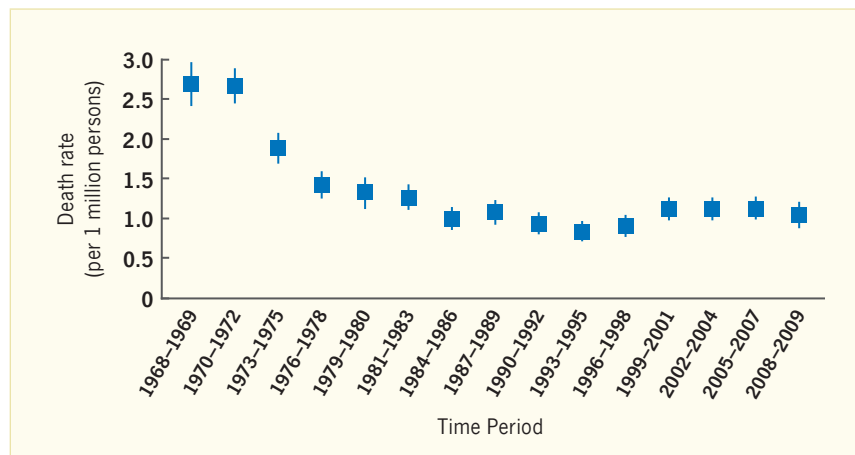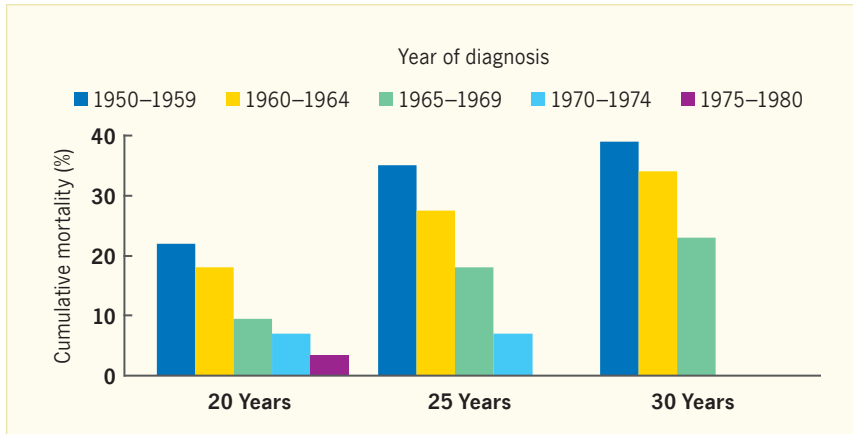

Error bars represent 95% confidence intervals.
SOURCE: Reference 31

the population studied), after adjusting for age, body mass index (BMI), and A1c level, highlighting an understudied area of dramatically higher mortality in women with type 1 diabetes suffering from eating disorders (26). Women with type 1 diabetes and concomitant anorexia nervosa have remarkably higher risks of mortality (standardized mortality ratio ≥14.5) (27,28). Eating disorders in women are discussed in more detail in Chapter 33 *Psychiatric and Psychosocial Issues Among Individuals Living With Diabetes*.

New Jersey 725

The New Jersey 725 Study examined mortality rates in 725 African Americans with a mean type 1 diabetes duration of 8 years. Participants were randomly selected from a population of hospitalized African Americans with a discharge diagnosis of diabetes, who were diagnosed prior to age 30 years and treated with insulin. Three-year mortality rates were 7.1% for women and 10.6% for men (29). More data from this study are presented in the Mortality by Race section.

FIGURE 35.6. Cumulative Mortality by Diagnosis Year and Duration of Type 1 Diabetes: The Pittsburgh Epidemiology of Diabetes Complications Study

SOURCE: Reference 22, copyright © 2006 American Diabetes Association, reprinted with permission

FIGURE 35.7. Life Expectancy at Birth by Diagnosis Cohort Based on Pittsburgh Type 1 Diabetes Registries
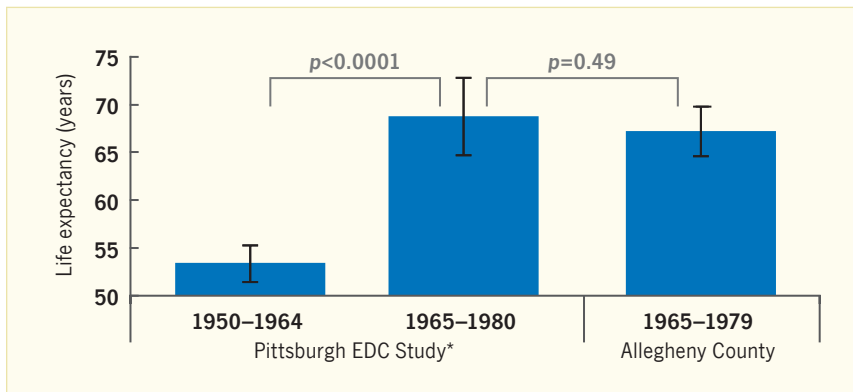
Error bars represent 95% confidence intervals.
* Pittsburgh Epidemiology of Diabetes Complications Study
SOURCE: Reference 36, copyright © 2012 American Diabetes Association, reprinted with permission

TEMPORAL TRENDS IN MORTALITY

Analyses conducted for *Diabetes in America, 3rd edition,* based on U.S. death certificates with diabetes listed as the underlying cause of death yielded diabetes-specific death rates (per 1,000,000 population) (Table 35.1). Between 1950 and 2009, there has been a marked downward trend in type 1 diabetes mortality, which appears to have leveled off during the 1990s. This trend likely reflects improvements in type 1 diabetes care, as incidence of type 1 diabetes is increasing in the United States (30). A Centers for Disease Control and Prevention analysis of diabetes-related mortality prior to age 20 years showed a decrease of 61% (2.7 deaths per million per year in 1968–1969 vs. 1.0 deaths per million per year in 2008–2009) (Figure 35.5) (31). Children age <10 years with type 1 diabetes showed a more significant decline in mortality than those age 10–19 years (78% vs. 52%, respectively).

In the Pittsburgh EDC study, at 25 years duration of type 1 diabetes, cumulative mortality declined by 80% from 35% for those diagnosed in the 1950s to 7% for those diagnosed in the early 1970s (Figure 35.6) (22).

Improvements in Life Expectancy

As discussed, life expectancy for type 1 diabetes improved dramatically after the discovery of insulin as an effective therapy in the 1920s. Both the Joslin Clinic and the Steno Clinic showed type 1 diabetes

life expectancy to increase by 15 years between 1933 and 1972 (1,32,33,34).

Despite these improvements in treatment, a report from 1975 using a life insurance cohort still found life expectancy in type 1 diabetes (diagnosis age <15 years) to be reduced 27 years compared to individuals without diabetes (13). Data from the National Health Interview Surveys from 1984–2000 showed that U.S. children diagnosed with diabetes at age 10 years lose approximately 19 years of life (35).

Based on 30 years of longitudinal data, the Pittsburgh EDC study showed that life expectancy (from birth) increased by approximately 15 years for those diagnosed in 1965–1980 compared to those diagnosed in 1950–1964 (68.8 years vs. 53.4 years, respectively, p<0.0001) (36). Over the same time interval, life expectancy for the comparable cohort of the general U.S. population increased by <1 year (36). Life expectancy for the ACR (diagnosed 1965–1979) was 67.2 years, which was comparable to the 1965–1980 EDC diagnosis subcohort (Figure 35.7).

COMPARISONS TO THE GENERAL POPULATION

Standardized mortality ratios, which compare the observed number of deaths in a specific cohort (e.g., individuals with type 1 diabetes) to that expected (usually a local general population over the same time period), are uniformly increased in type 1 diabetes. An early report, examining only black type 1 diabetes patients at two U.S. diabetes clinics (Memphis, Tennessee, and Atlanta, Georgia), found a twofold excess in mortality compared to the general black population in 1970–1971 (37). In Wisconsin, type 1 diabetic males and females had a sevenfold and ninefold greater mortality risk compared to the general Wisconsin population, respectively (38). African American males and females with type 1 diabetes in New Jersey had a sixfold and twelvefold greater risk, respectively, compared to the general New Jersey population (29). Standardized mortality ratios that have been age- and sex-standardized have been calculated periodically in the ACR. In the early 1980s,

the standardized mortality ratios for those diagnosed prior to 1975 was significantly higher than for those diagnosed in the late 1970s (39). A 2008 follow-up of the same cohort showed that males and females with type 1 diabetes had fivefold and thirteenfold higher numbers of deaths, respectively, than would be expected in the general Allegheny County population (40). The same analysis showed a significant temporal improvement in standardized mortality ratios by diagnosis year (Figure 35.8).

KEY DEMOGRAPHIC VARIABLES
Mortality by Age at Onset

The effect of prepubertal (age <11 years in girls and <12 years in boys) or peri-pubertal age of onset of type 1 diabetes was noted in early studies in the CHP cohort (41). This effect was also noted in studies in Finland and Japan, where Cox proportional hazard models indicated that individuals diagnosed during or after puberty were at higher risk of death than those diagnosed at a prepubertal age (Table 35.2) (40,42). However, the effect diminishes after adjusting for the mortality rates of the general population. Similarly, a modest effect was noted in the ACR cohort; however, there were no clear patterns in the standardized mortality ratios estimated by age at onset (40). This phenomenon of later age of diagnosis conferring increased risk for mortality supports earlier suggestions that the prepubertal years are relatively benign (43,44). This may also, in part, be explained by who manages type 1 diabetes: the parent in childhood and the individual with type 1 diabetes during the teenage and young adult years.

Mortality by Sex

Sex-specific differences in type 1 diabetes mortality are clear. Females with type 1 diabetes consistently have higher standardized mortality ratios than their male counterparts (Figure 35.9) (38,40,42,45,46,47). The magnitude of the sex difference in mortality is marked and confirms that any sex advantage for mortality seen for women in the general population is lost in type 1 diabetes (48,49). Cause-specific analyses found

FIGURE 35.8. Standardized Mortality Ratios Assessed in 1980 and 2008, Allegheny County Type 1 Diabetes Registry
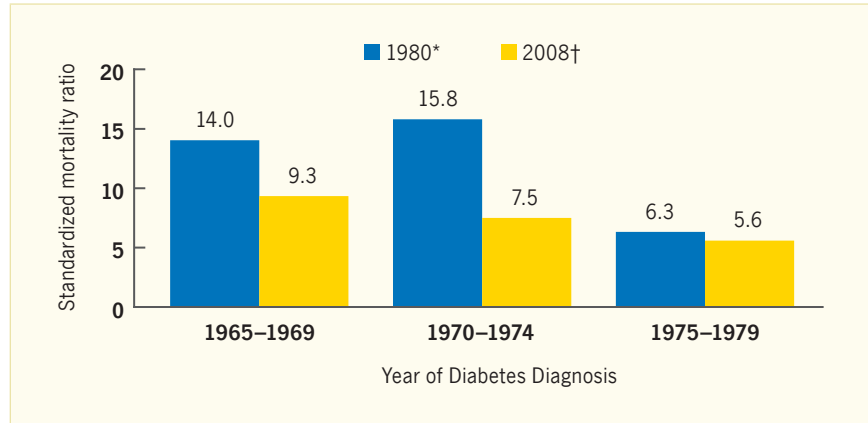

* Life-tables for comparison are based on general U.S. mortality data.
† Life-tables for comparison are based on general Allegheny County mortality data.
SOURCE: References 39 and 40

TABLE 35.2. Comparison of Mortality Rates by Age at Onset in Different Type 1 Diabetes Populations

POPULATION, YEARS (REF.)	FOLLOW-UP (YEARS)	MORTALITY RATE PER 100,000 PERSON-YEARS (95% CONFIDENCE INTERVAL)	
		Prepubertal (Males <12 years | Females <11 years)	Pubertal (Males ≥12 years | Females ≥11 years)
Allegheny County, 1965–2007 (41)	30	685 (564–805)	954 (803–1,104)
Japan, 1965–1994 (43)	15	456 (356–576)	941 (728–1,197)
Finland, 1965–1994 (43)	15	278 (234–328)	446 (383–516)

SOURCE: References are listed within the table.

FIGURE 35.9. Standardized Mortality Ratios in Type 1 Diabetes Studies
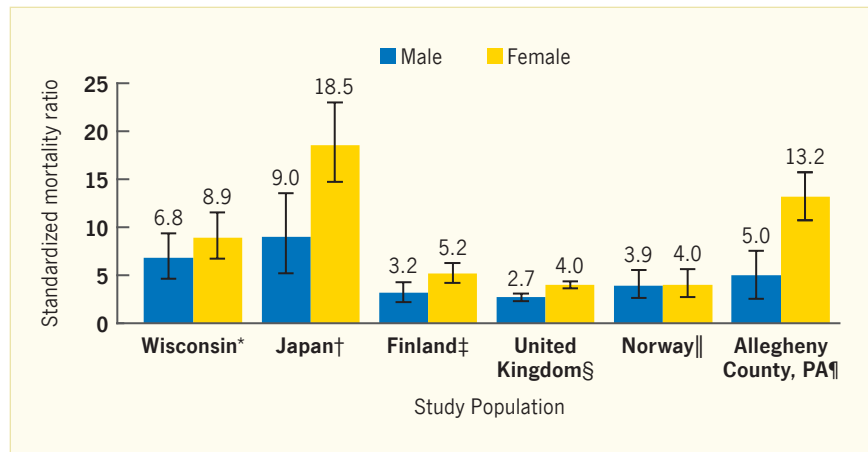
Error bars represent 95% confidence intervals.
* Based on 8.5 years of follow-up (1980–1988).
† Based on 16.3 mean years of follow-up (1965–1994).
‡ Based on 17.8 mean years of follow-up (1965–1994).
§ Based on 29 years of follow-up (1972–2000).
‖ Based on 24.2 mean years of follow-up (1973–2002).
¶ Based on 28 years of follow-up (1965–2007).
SOURCE: References 38, 40, 42, 45, 46, and 47

that sex-specific standardized mortality ratios for CVD deaths in the ACR cohort were 8.6 for males and 24.7 for females. In fact, females have higher standardized mortality ratios for all diabetes-related causes of death (acute complications, CVD, renal disease, and infections) compared to males. The reasons for

TABLE 35.3. Mortality Rates by Race, Allegheny County Type 1 Diabetes Registry Cohort and Chicago Type 1 Diabetes Registry Cohort

STUDY NAME, YEARS (REF.)	DEATH RATES PER 100,000 PERSON-YEARS (95% CONFIDENCE INTERVAL)	
	Caucasians	African Americans
Allegheny County Registry, 1965–1989 (53)	380 (240–480)	910 (340–1,480)
Allegheny County Registry, 1965–1998 (54)	571 (478–672)	1,388 (895–2,012)
Allegheny County Registry, 1965–1999 (48)	492 (412–573)	1,318 (1,168–1,469)
Chicago Registry, 1985–2000 (55)	48 (6–174)	448 (284–672)
Allegheny County Registry, 1965–2007 (40)	742 (648–836)	1,851 (1,278–2,425)

SOURCE: References are listed within the table.

FIGURE 35.10. Standardized Mortality Ratios in African Americans With Type 1 Diabetes
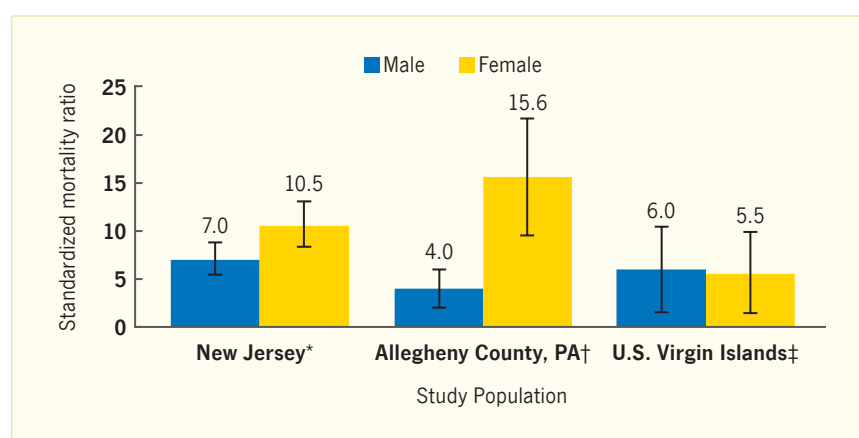
Error bars represent 95% confidence intervals.
* Based on 3 years of follow-up (1999–2001).
† Based on 28 years of follow-up (1965–2007).
‡ Based on 19 years of follow-up (1979–2010).
SOURCE: References 29, 40, and 57

these differences are unclear but probably reflect both relatively low rates of some causes (e.g., CVD) in females in the general population and higher rates of others (e.g., acute complications) in diabetic female youth (50). While males with type 1 diabetes have an accident/suicide mortality rate seven times higher than females with type 1 diabetes, the standardized mortality ratios for violent deaths were not significantly different from the general population for either sex, similar to type 1 diabetes findings in Europe (51,52).

Mortality by Race

Many studies have indicated that racial differences exist in type 1 diabetes mortality. Mortality rates in the ACR at different follow-up periods are presented by race in Table 35.3 (40,48,53,54,55). Similarly, a study of young Chicago, Illinois, patients showed that African Americans were at nearly tenfold increased risk of early mortality (age <25 years) compared to Caucasians (56). Interestingly, despite persistent 2.5-fold differences in overall mortality in the ACR by race, standardized mortality ratios were similar for African Americans with type 1 diabetes and Caucasians with type 1 diabetes (7.5 vs. 7.4, respectively) compared to the general population (40). This phenomenon may be partly explained by higher background mortality in younger African Americans in the general population due to accidental and violent causes and the surprising absence of these causes of death in African Americans with type 1 diabetes in Allegheny County. These elevated standardized mortality ratios among African Americans with type 1 diabetes compared to African Americans in the general population are seen not only in the ACR, but also in New Jersey and the U.S. Virgin Islands (Figure 35.10) (29,40,57).

Little information exists on long-term cause-specific mortality for African Americans with type 1 diabetes. A retrospective study of death certificates for Chicago residents (age 1–24 years) showed all eight acute complication deaths at onset (of 30 total type 1 diabetes deaths) occurred in either non-Hispanic black (seven) or Hispanic (one) patients (56). Caucasian type 1 diabetic patients accounted for only two deaths during this interval in Chicago, and neither was due to acute complications. African Americans with type 1 diabetes have significantly higher mortality rates for all diabetes-related complications compared to Caucasians with type 1 diabetes (50). This poorer prognosis for African Americans with type 1 diabetes reflects the ongoing racial gap in socioeconomic status or access to and utilization of health care in the United States (58).

CAUSES OF DEATH IN TYPE 1 DIABETES
Limitations of Death Certificates

Epidemiologic studies have long relied on death certificates to obtain mortality data, specifically data relating to the cause(s) of death. A notable Swedish study in 1976 used registry data to validate the cause of death listed on 1,156 death certificates and found that the death certificates were valid for most forms of cancer, stroke, and respiratory disease but *not* for diabetes (59). In the United States, misclassification, as well as substantial underreporting of mortality from diabetes, is also prevalent (60).

Only one study from Germany has specifically examined the reliability of the cause of death on death certificates in individuals with type 1 diabetes (61). A mortality review committee found that only 25% of hypoglycemic deaths were listed as such on the death certificate, and similarly, only 57% of deaths from diabetic ketoacidosis (DKA) actually listed DKA on the death certificate (61). The committee only agreed with death certificates when the cause of death was not diabetes-related (i.e., cancer, myocardial infarction, stroke, or accident). The discrepancies result both from significant overlap

between complications in type 1 diabetes (e.g., CVD and renal disease) and from the lack of formal training for physicians on death certificate completion. Thus, death certificates alone are not reliable when determining the true clinical outcome of deceased type 1 diabetes patients.
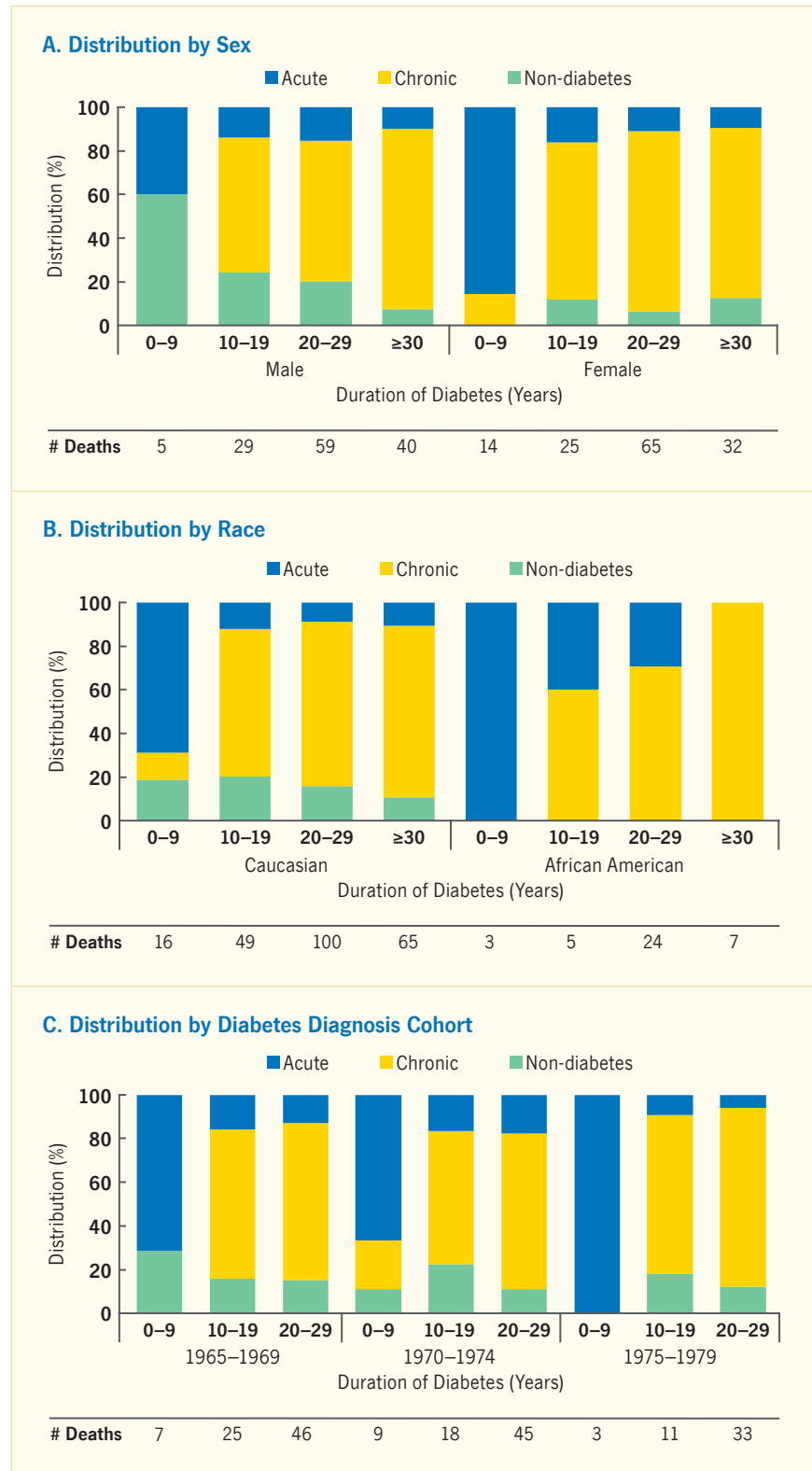
DERI Mortality Classification

Understanding the limitations of death certificates, a standardized protocol with a Mortality Classification Committee has been developed for determining underlying and secondary causes of death based not only death certificates, but also any other available data—medical records, autopsy/coroner's reports, and interviews with next-of-kin (39). Key findings from this standardized international effort are described in the United States Compared to Other Countries section. The DERI classification was used in many studies (4,28,34,46,49,50,53,54,57,62, 63,64,65,66,67,68,69), including in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study (70). Aside from the population-based cohorts in the DERI Study Group (Allegheny County, Finland, Israel, and Japan), few type 1 diabetes cohorts have examined mortality thoroughly using a physician-based review committee (47,70,71).

Complication-Specific Findings

The higher mortality seen in type 1 diabetes compared to the general population results almost exclusively from higher rates of diabetes-related acute and chronic complications. Females with type 1 diabetes in the United States have higher mortality rates for early acute complications (<10 years diabetes duration); whereas, males with type 1 diabetes have higher mortality rates for accidental or violent (non-diabetes) deaths (Figure 35.11A) (50,72). Mortality rates for all major diabetes-related complications (acute, renal, cardiovascular, and infectious) are significantly higher in African Americans with type 1 diabetes compared to Caucasians with type 1 diabetes (Figure 35.11B) (50,72). No significant changes in cause-specific distributions have

FIGURE 35.11. Distribution of Underlying Causes of Death by Duration of Diabetes and Sex (A), Race (B), and Diabetes Diagnosis Cohort (C), Allegheny County, Pennsylvania, 1965–2007

A. Distribution by Sex

| # Deaths | 5 | 29 | 59 | 40 | 14 | 25 | 65 | 32 |

B. Distribution by Race

| # Deaths | 16 | 49 | 100 | 65 | 3 | 5 | 24 | 7 |

C. Distribution by Diabetes Diagnosis Cohort

| # Deaths | 7 | 25 | 46 | 9 | 18 | 45 | 3 | 11 | 33 |

Underlying causes of death were divided into acute diabetes complications (e.g., hypoglycemia, diabetic ketoacidosis), chronic diabetes complications (e.g., cardiovascular disease, renal disease, infections), and non-diabetes (e.g., accidents, violence).
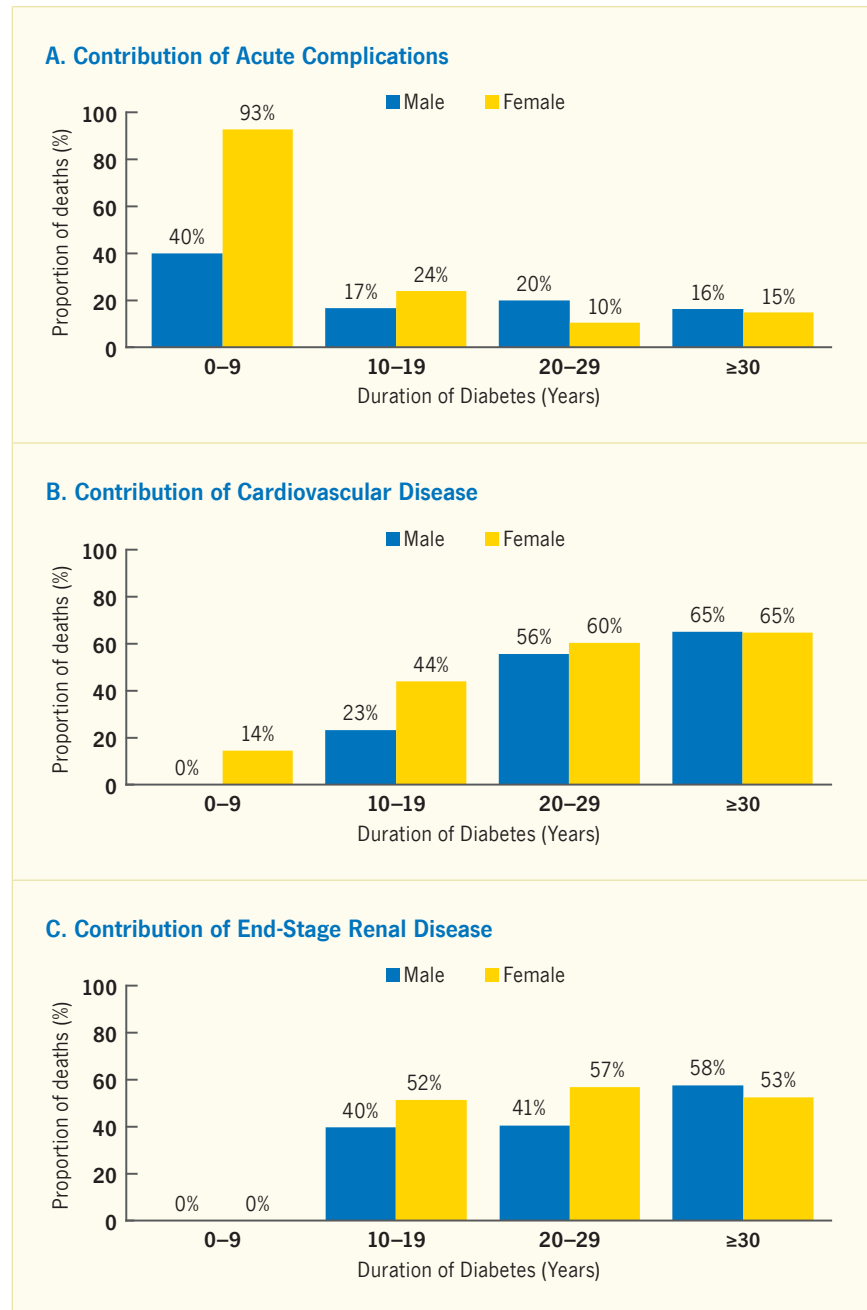
SOURCE: Reference 50, copyright © 2010 American Diabetes Association, reprinted with permission; and Reference 72

been observed in those diagnosed with diabetes more recently (1970s) compared to those diagnosed in the 1960s (Figure 35.11C) (50,72).

Causes of early type 1 diabetes mortality (<10 years diabetes duration) have been extensively studied in many cohorts. A report from the CHP cohort showed that 64% of all deaths in childhood-onset type 1 diabetes within the first 11 years after diagnosis were caused by acute complications (all DKA) (73) compared to 74% from the ACR in the first 10 years. An international study found acute complications (38%) to be the leading cause of death in the first 10 years of type 1 diabetes, followed by accident/suicide (30%), with acute deaths occurring more commonly in the United States and Japan compared to Finland and Israel (39). Acute complications contributed to 93% of deaths in females and 40% in males within the first 10 years after diabetes diagnosis, a sex difference explained at least in part by the increased risk of violent/accidental deaths in young males (Figure 35.12A) (50,72).

Only a handful of studies have evaluated cause-specific mortality in longstanding type 1 diabetes (>20 years duration). Steno Clinic tracked all individuals diagnosed with type 1 diabetes (age ≤30 years) before 1943 and followed them until death or January 1, 1984. CVD accounted for two-thirds of all deaths after 40 years of type 1 diabetes but only one-fourth of all deaths before 35 years duration. However, CVD currently contributes to more than half of all deaths after 20 years of diabetes, with many of these deaths occurring in individuals with concomitant renal disease (Figure 35.12B) (50,72). Similar findings from the Diabetes U.K. study (N=23,752) showed that acute complications accounted for 34% of all deaths prior to age 30 years, but thereafter, CVD became the leading cause (52%) (74). Conversely, end-stage renal disease (ESRD) accounted for >50% of deaths within 35 years duration of type 1 diabetes compared to only 5% of deaths after 40 years duration (75). For comparison, ESRD was the underlying cause of death in only 17% of deaths (50,

FIGURE 35.12. Total Contribution of Major Diabetes Complications to Deaths in Type 1 Diabetes, by Sex and Duration of Diabetes, Allegheny County, Pennsylvania, 1965–2007

Data represent the proportion of deaths for which the following complications either caused or contributed to death: acute complications (A), cardiovascular disease (B), and end-stage renal disease (C).

SOURCE: Reference 50, copyright © 2010 American Diabetes Association, reprinted with permission; and Reference 72

A. Secrest, T. Orchard, personal communication) but contributed to nearly 50% (i.e., including secondary causes of death, usually with CVD as the primary cause of death) of those who died after 10 years duration of type 1 diabetes in the ACR (Figure 35.12C) (50,72). Diabetes management appears to be delaying or preventing some ESRD, but there is significant room
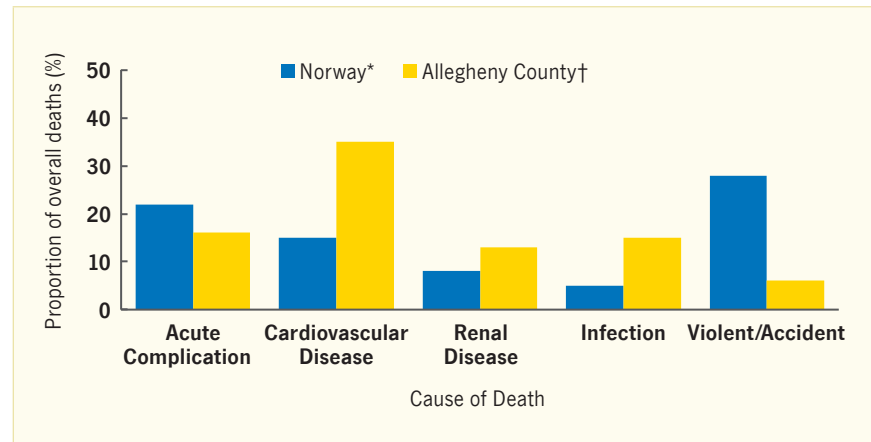
for improvement. The DCCT/EDIC findings (70) suggest intensive therapy may have a small benefit on mortality from all causes except accidents, suicides, and acute complications. The relationship to intensity of therapy and glycemic control is discussed in the Risk Factors for Mortality section.

A national Norwegian childhood-onset (age <15 years) type 1 diabetes cohort found cause-specific mortality there to be dramatically different from that in the United States. The overall proportions of death by major cause in Norway are: acute complications (22%), CVD (15%), renal disease (8%), infection (5%), and violence or accident (28%) (47). Notably, the Norwegian cohort had smaller proportions of both CVD and infections than the U.S. 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) (Figure 35.13) (47,50). While a direct comparison of rates rather than proportions would be more informative, these data are unavailable and highlight the need for additional international multi-center studies (like DERI), where more direct comparisons of type 1 diabetes mortality can be made.

"Dead-in-Bed" Syndrome

"Dead-in-bed" syndrome refers to a small subset of deaths in young (age <50 years), otherwise healthy individuals with type 1 diabetes (i.e., no diabetic complications) who are found dead in their beds without any evidence of a struggle or sweating commonly seen with a hypoglycemic event (76). Initially described in 1991 by Tattersall and Gill (77), fewer than 200 such cases have been reported worldwide. One estimate (76) suggests that "sudden unexplained death" may be increased tenfold in type 1 diabetes, although comparable data in the general population are scarce. General risk factors may include male sex, high A1c, high insulin dose, and low BMI (76). Despite the lack of clinical evidence for a hypoglycemic event at the time of death, "dead-in-bed" syndrome is believed to be associated with nocturnal hypoglycemia, which still occurs in about 50% of individuals with type 1 diabetes (78). Long-term type 1 diabetes and elevated A1c levels lead to "hypoglycemia-associated autonomic failure" (HAAF), in which the body inadequately responds to hypoglycemia. The first evidence supporting HAAF as the cause of "dead-in-bed" syndrome is a case of a 23-year-old man with a continuous glucose monitor for recurrent hypoglycemia who was found dead in bed without signs of a hypoglycemic struggle and a glucose reading of 30 mg/dL (1.67 mmol/L) around the time of death (62).

### RISK FACTORS FOR MORTALITY
Socioeconomic Factors

Low socioeconomic status (SES), both at and after onset of type 1 diabetes, is associated with a number of risk factors: poor glycemic control (63,79,80), smoking (81,82), dyslipidemia (81,83), hypertension (82,84), and multiple hospitalizations (85), all of which have been associated with increased mortality risk in type 1 diabetes. In addition, all-cause mortality rates in type 1 diabetes are significantly associated with the education and income levels attained by early adulthood, an association that was weakened by adjusting for other risk factors (86). However, a larger German study found that the SES effect on mortality persisted after adjusting for known mortality risk factors (71).

Glycemic Control

Hyperglycemia is associated with the development and progression of microvascular complications in type 1 diabetes (87). However, its relationship with macrovascular complications and mortality remains unclear (88,89), despite DCCT/EDIC trial data showing a major benefit of glycemic control for reducing rates of CVD (90). Some studies have implicated poor glycemic control in type 1 diabetes mortality (91,92), while others have found no survival advantage for improved control (71,93). The WESDR found a 2.4-fold increased risk of all-cause mortality for the highest quartile of A1c levels compared to the lowest quartile, adjusting for other diabetes-related risk factors (25). The mortality findings from the DCCT/EDIC cohort provide the most definitive data concerning this issue. A 2015 report (70) was based on 27 years of follow-up of the original DCCT cohort of 1,441 individuals who were randomized to intensive therapy (aimed at achieving A1c close to normal) or conventional therapy for a mean of 6.2 years; in the subsequent EDIC observational study, both groups largely followed intensive therapy and had similar A1c levels by 5 years of follow-up. These data showed that the intensive therapy group experienced a lower overall mortality (hazard ratio 0.67, 95% CI 0.49–0.99), although the absolute risk difference was small (109/100,000 person-years). Nonetheless, considering that the two groups were at similar levels of glycemic control during so much of the follow-up period, these data clearly underscore another major benefit of intensive therapy and better glycemic control (Figure 35.14).

FIGURE 35.13. Proportion of Deaths by Underlying Cause, Norway Type 1 Diabetes Cohort, 1973–2002, and Allegheny County Type 1 Diabetes Cohort, 1965–2007

* Diagnosis age <15 years
† Diagnosis age <18 years
SOURCE: References 47 and 50

FIGURE 35.14. Cumulative Incidence of Mortality From the Date of Randomization in the DCCT (starting in 1983) to December 31, 2012 for Intensive Versus Conventional Treatment Groups (Intent-to-Treat Analysis)
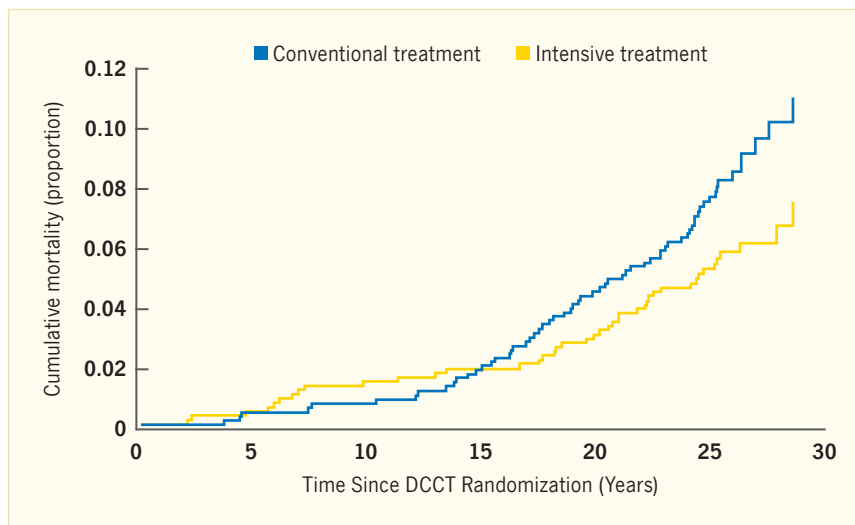
DCCT, Diabetes Control and Complications Trial.
SOURCE: Reference 70

FIGURE 35.15. Standardized Mortality Ratios in Type 1 Diabetes Compared to the General Population by Level of Albuminuria, FinnDiane Study Versus Pittsburgh Epidemiology of Diabetes Complications Study
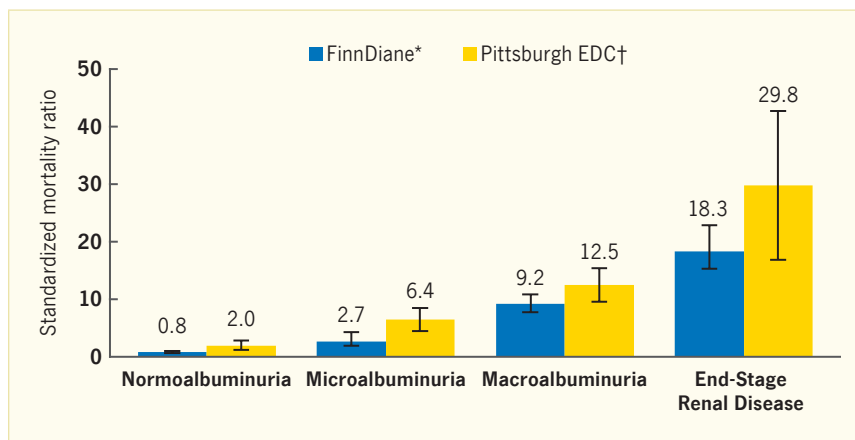
Albuminuria status is based on urinary albumin excretion rate (AER) – normoalbuminuria: AER <20 μg/min; micro-albuminuria: AER 20-200 μg/min; macroalbuminuria: AER >200 μg/min. End-stage renal disease is defined as renal failure on dialysis or transplantation. Error bars represent 95% confidence intervals. EDC, Epidemiology of Diabetes Complications Study; FinnDiane, Finnish Diabetic Nephropathy study.
* Based on 7 years of follow-up (1997–2007).
† Based on 20 years of follow-up (1986–2008).
SOURCE: Reference 100, copyright © 2009 American Diabetes Association, reprinted with permission; and Reference 101, copyright © 2010 Springer, reprinted with permission

Other Cardiovascular Risk Factors

Hypertension. Studies conducted in the 1980s indicated that higher blood pressure was associated with type 1 diabetes mortality (64,94). The New Jersey 725 Study showed that hypertension was a strong independent predictor for all-cause mortality at 3 years of follow-up (29). Given the well-established relationship between hypertension and both CVD (65,89) and nephropathy (66,95,96) in type 1 diabetes, it is likely that the association between hypertension and mortality results from the impact of hypertension on these complications.

Smoking. A prospective study examining the relationship between mortality and smoking in the CHP cohort diagnosed during 1950–1964 found that heavy smoking was a significant independent predictor of all-cause mortality among females but not males (67). These data also showed an excess mortality in females that was explained by an excess risk of coronary heart disease mortality. Contemporary studies have not further examined smoking as an independent risk factor for mortality in type 1 diabetes, although smoking was not independently associated with increased mortality in the New Jersey 725 Study (29).

Renal Failure. The development of macroalbuminuria in type 1 diabetes is known to bear excess mortality risk (39). The importance of microalbuminuria *per se* has been less clear, due to its often transient nature and its debatable prediction of those at risk of more serious renal disease (68,69,97,98). Although renal damage (albuminuria) is a risk factor for CVD, the relationship between the two conditions remains unclear (99). Landmark findings from the Finnish Diabetic Nephropathy (FinnDiane) Study showed that in the absence of microalbuminuria, individuals with type 1 diabetes appear to have mortality rates similar to those in the general population over a 7-year period (Figure 35.15) (100). The Pittsburgh EDC Study confirmed these findings and extended them to 20 years of follow-up (Figure 35.15) (101). These intriguing findings suggest that while microalbuminuria is a strong marker for mortality risk, it is likely to reflect mechanisms beyond renal disease *per se*, as only a minority die in renal failure.

Dyslipidemia. While dyslipidemia has been associated with other risk factors, such as SES (81,83), it was only in 2010 that it was found to be independently associated with mortality. As with both type 2 diabetes and the general population, mortality risk in type 1 diabetes increases with higher triglyceride and low-density lipoprotein (LDL) cholesterol levels and lower high-density lipoprotein (HDL) cholesterol levels (102,103).

Insulin Resistance

Type 1 diabetes is less commonly associated with insulin resistance than type 2 diabetes. No data exist relating insulin resistance independently to mortality in type 1 diabetes. However, insulin resistance is a risk factor for major complications in type 1 diabetes, including nephropathy and CVD (89). In fact, insulin resistance-related factors are more strongly associated with cardiovascular outcomes than is glycemic control (89).

UNITED STATES COMPARED TO OTHER COUNTRIES

Prior to the 1970s, few studies differentiated participants as having type 1 or type 2 diabetes, and fewer still used standardized methodologies to compare type 1 diabetes both nationally and internationally. A study from Cincinnati, Ohio, in 1971, was the first real attempt to standardize type 1 diabetes cohorts (diagnosed at age <17 years) and compare cumulative mortality at different clinics. At 25 years diabetes duration, cumulative mortality in Cincinnati was 20%, compared to 19% in Boston and 22% in Stockholm, Sweden (104).

During the 1980s and 1990s, DERI produced a series of type 1 diabetes mortality studies in four countries—nationwide cohorts in Finland, Israel, and Japan, as well as a U.S. cohort, represented by Allegheny County (Table 35.4) (39,40,42,48,72,105). Participants were diagnosed with diabetes between 1965 and 1979 before their 18th birthday and treated with insulin (39,105,106). These reports showed that Japan had a much higher mortality rate than the other countries, despite (or perhaps due to) having the lowest incidence of type 1 diabetes. Thus, physicians were less likely to diagnose and treat type 1 diabetes as effectively, as evidenced by Japan's excess mortality attributable to acute complications and renal disease (39,105). Renal failure-related mortality rates in Japan were twice as high as in Allegheny County (107). Finland had an excess in number of violent deaths (often suicide) in young males, and internationally, males with type 1 diabetes tended to have higher

TABLE 35.4. Age-Adjusted Mortality Rates by Country in the Diabetes Epidemiology Research International Study

FOLLOW-UP THROUGH (REF.)	DEATH RATES PER 100,000 PERSON-YEARS (95% CONFIDENCE INTERVAL)			
	United States*	Finland	Israel	Japan
1/1/1985 (39)	238	171	159	681
1/1/1990 (105)	408	250	158	760
12/31/1994 (42)		352 (315–393)		607 (510–718)
1/1/1999 (48)	627 (532–728)			
1/1/2008 (40)	812 (717–907)			

* Allegheny County Type 1 Diabetes Registry cohort
SOURCE: Reference 72 and references listed within the table.

TABLE 35.5. Comparison of Sex-Specific Mortality Rates in Different Type 1 Diabetes Populations

POPULATION, YEAR (REF.)	FOLLOW-UP (YEARS)	DEATHS	N	MALE/FEMALE MORTALITY RATE*	MALE:FEMALE RATE RATIO
Allegheny County, Pennsylvania, 1965-2007 (40)	30	202	1,075	601 / 751	0.80
Finland, 1965–1994 (42)	15	319	5,126	448 / 238	1.88
Japan, 1965–1994 (42)	15	137	1,408	617 / 601	1.03
New Zealand, 1984–2003 (45)	20	115	430	29% / 24%†	1.23
United Kingdom, 1972–2000 (46)	13	949	23,752	336 / 257	1.29
Norway, 1973–2002 (47)	20	103	1,906	300 / 130	2.26

* Mortality rate per 100,000 person-years
† Mortality rate is calculated as the percentage of deaths in participants who were age <30 years at diagnosis during the 20-year follow-up.
SOURCE: Reference 72 and references listed within the table.

rates of mortality than females (Table 35.5) (40,42,45,46,47,72). Looking specifically at diabetes-related deaths among individuals with type 1 diabetes, diabetes contributed to only 64% of deaths in Finland, compared to 96% in Japan, 83% in Israel, and 75% in the United States (39).

Over time, overall mortality rates in Finland and the United States continued to rise, as would be expected, with increasing age and type 1 diabetes duration, whereas Japan's overall mortality rates decreased for type 1 diabetes, indicating dramatic improvements in type 1 diabetes care in Japan (Table 35.4) (42,72). If the United States had the same type 1 diabetes mortality rates as Finland, more than half of the type 1 diabetes deaths each year in the United States would not occur (106). A larger, more recent study using multiple registries confirmed that

Japan, along with Russia and Eastern Europe, had the highest type 1 diabetes mortality rates and that mortality rates varied tenfold between countries in the World Health Organization DIAMOND Project Group (108).

CONCLUSION

Despite significant advances in diabetes management and care, persons with type 1 diabetes remain at increased risk of death, though the absence of microalbuminuria appears to minimize this risk and such individuals may have a normal life expectancy. Few studies have accurately quantified modern mortality risk in large, representative samples of individuals with type 1 diabetes. The research reported herein speaks to the continuing necessity for monitoring type 1 diabetes morbidity and mortality in the United States and improving diabetes health care in the United States, where mortality is higher than in many other countries. The full effect of modern management of type 1 diabetes on mortality is still unknown; however, the long-awaited data from the DCCT/EDIC study (70) suggest reduced mortality is another benefit of intensive therapy.

LIST OF ABBREVIATIONS

A1c . . . . .glycosylated hemoglobin
ACR . . . . .Allegheny County Type 1 Diabetes Registry
BMI . . . . .body mass index
CHP . . . . .Children's Hospital of Pittsburgh
CI . . . . .confidence interval
CVD . . . . .cardiovascular disease
DCCT/EDIC . . .Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study
DERI . . . . .Diabetes Epidemiology Research International
DKA . . . . .diabetic ketoacidosis
EDC . . . . .Epidemiology of Diabetes Complications study
ESRD . . . . .end-stage renal disease
HAAF . . . . .hypoglycemia-associated autonomic failure
SES . . . . .socioeconomic status
WESDR . . . . . .Wisconsin Epidemiologic Study of Diabetic Retinopathy

CONVERSIONS

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions.*

DUALITY OF INTEREST

Drs. Secrest, Washington, and Orchard reported no conflicts of interest.

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