Chapter 11

Mortality in Non-Insulin-Dependent Diabetes

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SUMMARY

Based on a followback survey of a sample of U.S. deaths in 1986, it is estimated that deaths of persons with non-insulin-dependent diabetes mellitus (NIDDM) account for 17.2% of all deaths in the United States for those age ≥25 years. Age-specific death rates for people with diabetes in 1986 were 1.0% for those age 25-44 years, 2.8% for age 45-64 years, 5.8% for age 65-74 years, 13.7% for age ≥75 years, and 5.4% for all diabetic persons age ≥25 years.

As in the general population, mortality in persons with NIDDM increases with age. However, overall age-adjusted mortality in the NIDDM population is approximately twice that of persons who do not have diabetes. Although persons with diabetes possess more and higher levels of risk factors for mortality, this increased level of risk factors cannot fully explain the excess risk of mortality in persons with diabetes compared with persons without diabetes. In some studies, the excess risk of mortality in NIDDM populations declines with increasing age and age at onset of diabetes, indicating that those who develop NIDDM at younger ages are at greater risk of excess mortality, compared with nondiabetic persons. The excess risk of mortality is also higher for those using insulin, which may be an indicator of more severe disease, and for women with diabetes.

Among middle-aged populations with NIDDM, life expectancy is reduced by 5-10 years. Reduction in life expectancy is greater for diabetic women than men and for those with complications, and decreases with increasing age at diagnosis.

The four leading causes of death in persons with NIDDM are diseases of the heart/cardiovascular disease, diabetes, malignant neoplasms, and cerebrovascular disease. The majority of deaths are due to heart disease, primarily ischemic heart disease which accounts for ~40% of deaths of persons with diabetes. The risk of heart disease and ischemic heart disease mortality is ~2-4 times higher for diabetic than nondiabetic persons. Similar to the excess risk due to all-cause mortality, the excess risk of mortality due to heart disease and ischemic heart disease is greater in those using insulin and in women and cannot be fully explained by higher levels of risk factors in persons with diabetes.

Research is needed on the impact of diabetes on mortality in racial and ethnic minority groups. Most of what is known about diabetes mortality in these groups has been derived from U.S. death certificate data, which have serious limitations and inaccuracies. Overall, diabetes was listed as the underlying cause of death in 9.6% of diabetic deaths in 1986 and as any listed cause in 38.2%, with variation by age, sex, and race. Death certificate data do not allow valid examination of the risk of mortality in persons with diabetes, compared with those without diabetes; nor do they allow examination of most risk factors for mortality. However, they indicate that diabetes ranks higher as a cause of death in racial and ethnic minority populations than in whites and that rates of death attributed to diabetes in these populations are higher than rates in the general population of the United States.

Although not all studies of persons with diabetes identify the same risk factors for mortality, these risk factors include age, age at onset of diabetes, sex, duration of diabetes, and cardiovascular disease risk factors, including smoking, hypertension or elevated systolic blood pressure, abnormal lipid levels, and physical inactivity. Risk factors for mortality may also include central obesity, insulin use, and lack of glycemic control. In addition, persons with NIDDM who have clinical risk markers and complications (e.g., microalbuminuria, retinopathy) appear to be at particularly high risk for mortality, compared with those without.

Although there have been no long-term clinical trials of the effect of risk factor reduction on the mortality

of populations with NIDDM, it is likely that NIDDM mortality rates can be reduced. Modifying or preventing risk factors (primarily cardiovascular risk factors) through the promotion of healthy lifestyles, including weight reduction/obesity prevention, glycemic control, increased physical activity, hypertension control, smoking cessation/prevention, and cholesterol-lowering therapy, could decrease NIDDM mortality rates.

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METHODOLOGICAL PROBLEMS IN ASSESSING DIABETES MORTALITY

There are a number of methodological problems in assessing NIDDM mortality. These include limitations of death certificate data and the wide variability in design and methodology of cohort studies, which follow persons with diabetes over time and which usually incorporate death certificate data in analyses of mortality. Since cause-of-death information from death certificates is the cornerstone of most diabetes mortality analyses, it is important to understand how these data are collected and the limitations of their use.

DEATH CERTIFICATE DATA

In the United States, mortality data are collected by a cooperative effort between states and the federal government in accordance with World Health Organization (WHO) regulations, as specified in the ninth revision of the Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-9)[1]. To achieve uniformity of the information collected, a model or "standard" death certificate is periodically developed and issued. The current U.S. standard death certificate was revised in 1989 (Figure 11.1).

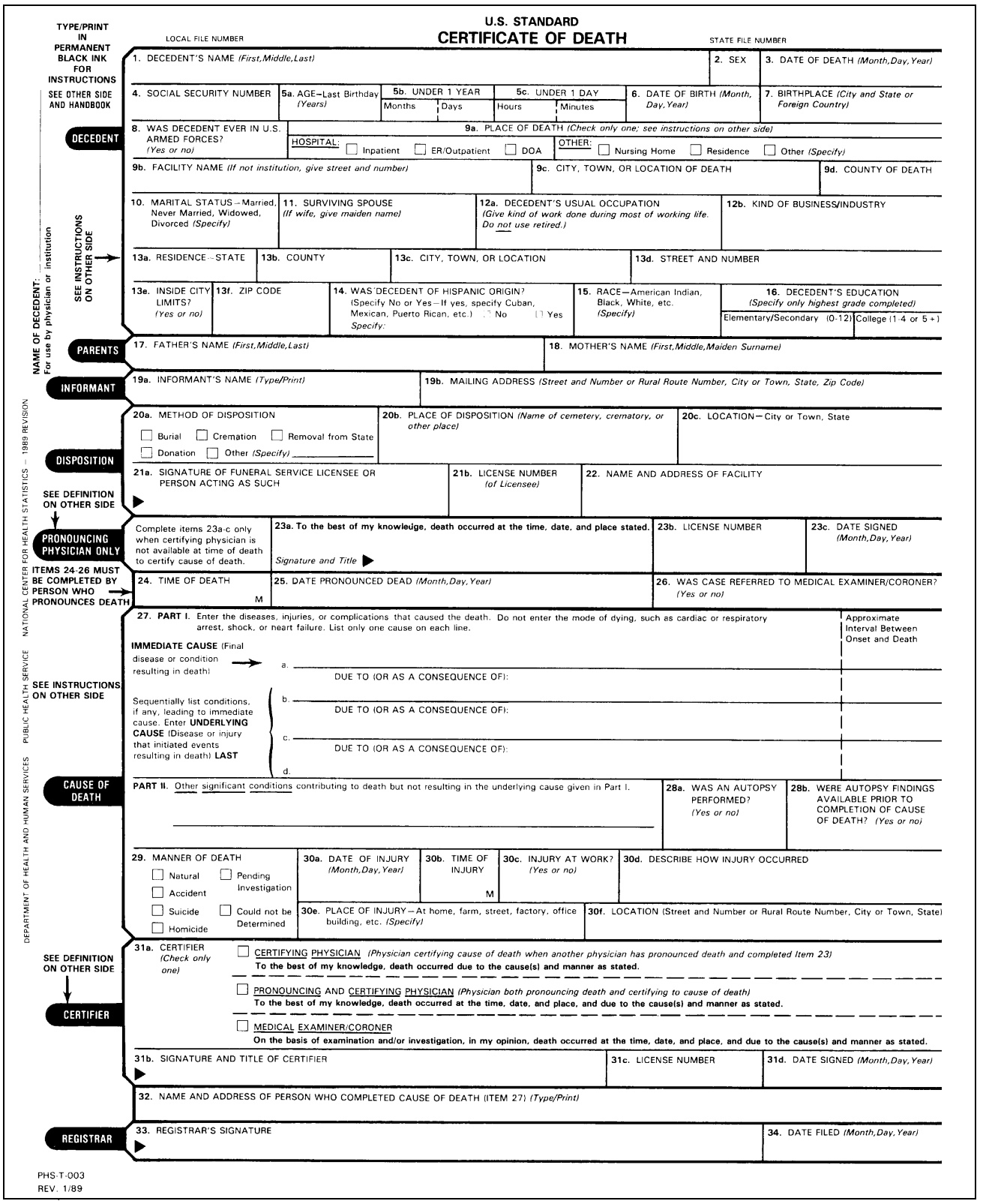
Both demographic and cause-of-death information are recorded on the death certificate. Information on cause of death in item 27 is divided into two parts. Part I contains information on conditions leading directly to death; Part II contains information on conditions that contribute to death but do not lead directly to death. The conditions listed in Part I should follow a causal sequence, beginning with the immediate cause of death (the final condition resulting in the death), then any intermediate causes (those intervening between immediate and underlying cause), and ending with the underlying cause of death (the disease or injury initiating the sequence of events leading to death) as the final line in Part I. The 1989 Standard Death Certificate contains, on the reverse of the certificate, instructions and examples for completing the cause-of-death section.

The underlying cause of death is the cause most commonly reported in national and international cause-of-death statistics. Determining the causal sequence leading to death is the responsibility of the physician(s), medical examiner, coroner, or nosologist who completes the cause-of-death sections of the death certificate.

There are a number of problems related to the reliability and validity of cause-of-death data on death certificates. These problems include improper completion of death certificates[2-4], inaccuracy of diagnoses[5,6], physician variation in interpreting causal sequences and conditions that may have contributed to death[7-9], changing perceptions of the causal role of diseases[7], variation in nosological coding[10], and underreporting of American Indian[11] and other racial/ethnic heritage. Further, selection of a single underlying cause of death in decedents with multiple chronic diseases may be difficult, because a single disease may not adequately describe the cause of death and the etiologic sequence of the diseases may be unclear[7-8,12].

Several problems in using death certificate data are more specific to analyses of diabetes mortality. First, these data do not distinguish between insulin-dependent diabetes mellitus (IDDM) and NIDDM. Second, diabetes is under-reported on death certificates. Among decedents known to have diabetes, diabetes is not listed anywhere on the death certificate in ~60% of deaths[11,13,14](see the sections later in this chapter on diabetes as an underlying cause of death and as any listed cause of death). Thus, death certificate data should not be used as the sole source of information to examine mortality in persons with diabetes. Third, decedents who do have diabetes recorded as a cause of death do not represent all decedents known to have diabetes[13,14]. Fourth, the causal role of diabetes in mortality is often unrecognized[15,16]. It is often difficult for physicians to decide whether diabetes was the cause of the death process or even if it had a contributing role[6].

Figure 11.1
U.S. Standard Certificate of Death



U.S. STANDARD
CERTIFICATE OF DEATH

TYPE/PRINT IN PERMANENT BLACK INK FOR INSTRUCTIONS SEE OTHER SIDE AND HANDBOOK

LOCAL FILE NUMBER

STATE FILE NUMBER

NAME OF DECEDENT: For use by physician or institution

SEE INSTRUCTIONS ON OTHER SIDE

DECEDENT

1. DECEDENT'S NAME (First, Middle, Last)
2. SEX
3. DATE OF DEATH (Month, Day, Year)
4. SOCIAL SECURITY NUMBER
5a. AGE—Last Birthday (Years)
5b. UNDER 1 YEAR — Months / Days
5c. UNDER 1 DAY — Hours / Minutes
6. DATE OF BIRTH (Month, Day, Year)
7. BIRTHPLACE (City and State or Foreign Country)
8. WAS DECEDENT EVER IN U.S. ARMED FORCES? (Yes or no)
9a. PLACE OF DEATH (Check only one; see instructions on other side)
HOSPITAL: ☐ Inpatient ☐ ER/Outpatient ☐ DOA
OTHER: ☐ Nursing Home ☐ Residence ☐ Other (Specify)
9b. FACILITY NAME (If not institution, give street and number)
9c. CITY, TOWN, OR LOCATION OF DEATH
9d. COUNTY OF DEATH
10. MARITAL STATUS—Married, Never Married, Widowed, Divorced (Specify)
11. SURVIVING SPOUSE (If wife, give maiden name)
12a. DECEDENT'S USUAL OCCUPATION (Give kind of work done during most of working life. Do not use retired.)
12b. KIND OF BUSINESS/INDUSTRY
13a. RESIDENCE—STATE
13b. COUNTY
13c. CITY, TOWN, OR LOCATION
13d. STREET AND NUMBER
13e. INSIDE CITY LIMITS? (Yes or no)
13f. ZIP CODE
14. WAS DECEDENT OF HISPANIC ORIGIN? (Specify No or Yes—If yes, specify Cuban, Mexican, Puerto Rican, etc.) ☐ No ☐ Yes Specify:
15. RACE—American Indian, Black, White, etc. (Specify)
16. DECEDENT'S EDUCATION (Specify only highest grade completed)
Elementary/Secondary (0-12) / College (1-4 or 5+)

PARENTS

17. FATHER'S NAME (First, Middle, Last)
18. MOTHER'S NAME (First, Middle, Maiden Surname)

INFORMANT

19a. INFORMANT'S NAME (Type/Print)
19b. MAILING ADDRESS (Street and Number or Rural Route Number, City or Town, State, Zip Code)

DISPOSITION

20a. METHOD OF DISPOSITION
☐ Burial ☐ Cremation ☐ Removal from State
☐ Donation ☐ Other (Specify) _____
20b. PLACE OF DISPOSITION (Name of cemetery, crematory, or other place)
20c. LOCATION—City or Town, State

SEE DEFINITION ON OTHER SIDE

21a. SIGNATURE OF FUNERAL SERVICE LICENSEE OR PERSON ACTING AS SUCH ▶
21b. LICENSE NUMBER (of Licensee)
22. NAME AND ADDRESS OF FACILITY

PRONOUNCING PHYSICIAN ONLY

Complete items 23a-c only when certifying physician is not available at time of death to certify cause of death.

23a. To the best of my knowledge, death occurred at the time, date, and place stated.
Signature and Title ▶
23b. LICENSE NUMBER
23c. DATE SIGNED (Month, Day, Year)

ITEMS 24-26 MUST BE COMPLETED BY PERSON WHO PRONOUNCES DEATH

24. TIME OF DEATH M
25. DATE PRONOUNCED DEAD (Month, Day, Year)
26. WAS CASE REFERRED TO MEDICAL EXAMINER/CORONER? (Yes or no)

CAUSE OF DEATH

27. PART I. Enter the diseases, injuries, or complications that caused the death. Do not enter the mode of dying, such as cardiac or respiratory arrest, shock, or heart failure. List only one cause on each line.

		Approximate Interval Between Onset and Death
IMMEDIATE CAUSE (Final disease or condition resulting in death) →	a.	
	DUE TO (OR AS A CONSEQUENCE OF):	
Sequentially list conditions, if any, leading to immediate cause. Enter UNDERLYING CAUSE (Disease or injury that initiated events resulting in death) LAST	b.	
	DUE TO (OR AS A CONSEQUENCE OF):	
	c.	
	DUE TO (OR AS A CONSEQUENCE OF):	
	d.	

SEE INSTRUCTIONS ON OTHER SIDE

PART II. Other significant conditions contributing to death but not resulting in the underlying cause given in Part I.

28a. WAS AN AUTOPSY PERFORMED? (Yes or no)
28b. WERE AUTOPSY FINDINGS AVAILABLE PRIOR TO COMPLETION OF CAUSE OF DEATH? (Yes or no)

29. MANNER OF DEATH
☐ Natural ☐ Pending Investigation
☐ Accident
☐ Suicide ☐ Could not be Determined
☐ Homicide
30a. DATE OF INJURY (Month, Day, Year)
30b. TIME OF INJURY M
30c. INJURY AT WORK? (Yes or no)
30d. DESCRIBE HOW INJURY OCCURRED
30e. PLACE OF INJURY—At home, farm, street, factory, office building, etc. (Specify)
30f. LOCATION (Street and Number or Rural Route Number, City or Town, State)

CERTIFIER

SEE DEFINITION ON OTHER SIDE

31a. CERTIFIER (Check only one)

☐ CERTIFYING PHYSICIAN (Physician certifying cause of death when another physician has pronounced death and completed Item 23)
To the best of my knowledge, death occurred due to the cause(s) and manner as stated.

☐ PRONOUNCING AND CERTIFYING PHYSICIAN (Physician both pronouncing death and certifying to cause of death)
To the best of my knowledge, death occurred at the time, date, and place, and due to the cause(s) and manner as stated.

☐ MEDICAL EXAMINER/CORONER
On the basis of examination and/or investigation, in my opinion, death occurred at the time, date, and place, and due to the cause(s) and manner as stated.

31b. SIGNATURE AND TITLE OF CERTIFIER ▶
31c. LICENSE NUMBER
31d. DATE SIGNED (Month, Day, Year)

REGISTRAR

32. NAME AND ADDRESS OF PERSON WHO COMPLETED CAUSE OF DEATH (ITEM 27) (Type/Print)
33. REGISTRAR'S SIGNATURE ▶
34. DATE FILED (Month, Day, Year)

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COHORT STUDIES OF DIABETES MORTALITY

Cohort studies, which follow people over time, have several advantages over studies that rely exclusively on death certificate data. These include the ability to: 1) describe the mortality experience of all persons with diabetes who die (not just those who have diabetes listed as a cause of death); 2) examine the risk of mortality in diabetic versus nondiabetic persons; and 3) examine risk factors for mortality not available in death certificate data, including duration of diabetes, age at onset of diabetes, glycemic control, smoking behavior, hypertension, cholesterol, and other variables.

Data from cohort studies also have limitations, however. Most cohort studies of diabetes mortality cited in this chapter do not distinguish between IDDM and NIDDM. The inclusion of IDDM deaths with NIDDM deaths will overestimate death rates of those with NIDDM and may result in inaccurate assessment of risk factors for mortality. However, most of these studies examine mortality in persons with diabetes in populations in which NIDDM is the predominant form of diabetes, i.e., older populations, minorities, and diabetic persons diagnosed at age ≥30 years. A second limitation of cohort studies is that most contain small numbers of persons with diabetes, thereby limiting the degree to which the data can be examined for factors that may influence mortality (e.g., type and duration of diabetes, age, sex, race) and limiting the detection of significant differences among subgroups. A third limitation is that some studies have identified diabetes status only at the beginning of the study, and persons developing diabetes during followup have not been classified as having diabetes. This misclassification may result in underestimating the impact of diabetes on mortality.

Cohort studies may be either population-based (i.e., studies of people with diabetes in geographically defined communities) or based on membership in a group such as patient or employee groups. Data from population-based studies are generally considered more reliable than data from selected groups within the population because the latter may not represent the community with respect to factors such as age and health status. However, even data from community-based studies may not represent the experience of the entire U.S. diabetic population because most are limited to people with diabetes residing in small geographic areas.

The cohort studies cited in this chapter differ in methodology, including study design, characteristics of the studied population (e.g., age, race, sex), years in which studies were conducted, definitions used (e.g., differences in definition of diabetes, type of diabetes, and classification of causes of death), and length of followup. Because of these differences among studies, summary statements about the mortality experience of persons with diabetes are sometimes difficult. Additional discussion of these problems can be found in other reviews[18,19].

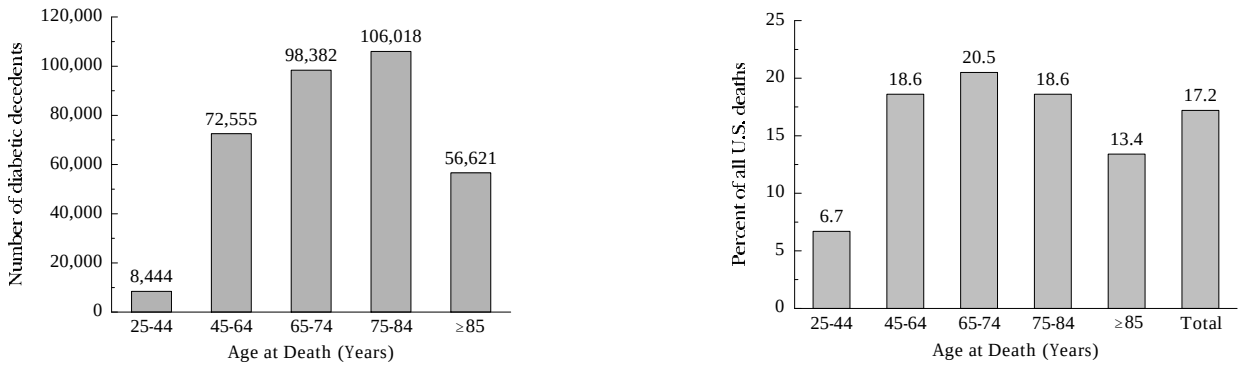
MORTALITY OF PERSONS WITH NIDDM

Most studies of mortality in persons with diabetes compare the death rates of diabetic and nondiabetic persons, and age-specific mortality data for those with diabetes are often not presented separately. A few studies, however, have published data that can be used to calculate the actual mortality experience of persons with diabetes. The 1986 National Mortality Followback Survey (NMFS) collected death certificate information and information about decedents from personal informants (including whether the decedent had diabetes) for a national sample of U.S. decedents age ≥25 years[13,20]. Based on the NMFS, the number of deaths of persons with diabetes in 1986 was estimated to be 342,020. The distribution of these deaths by age is shown in Figure 11.2. These deaths accounted for 17.2% of all deaths of U.S. residents age ≥25 years. The proportion varied from 6.7% at age 25-44 years to 20.5% at age 65-74 years (Figure 11.2).

Using NMFS data on the number of diabetic decedents[20] and U.S. diabetic population estimates for 1986[21], the death rate for persons with diabetes in the United States in 1986 was estimated to be 1.0% for those age 25-44 years, 2.8% for age 45-64 years, 5.8% for age 65-74 years, 13.7% for age ≥75 years, and 5.4% for all diabetic persons age ≥25 years (Figure 11.3).

Mortality in persons with diabetes can also be calculated from published data[22] on the mortality experience of a national sample of white men and women age 40-77 years in 1971-75 whose mortality through 1982-84 was determined in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Followup Survey (NHEFS). Using data on the number of deaths and person-years at risk for death[22], the average annual death rate for diabetic white men and women age 40-77 years is estimated to be 5.2% (Figure 11.3). Data on the mortality experience of a primarily white diabetic population in southern Wisconsin during 1980-88[23] yield an annual death rate of 5.7% for persons with diabetes diagnosed at age ≥30 years (Figure 11.3). The consistency of

Figure 11.2
Number of Decedents with Diabetes and Percent of All U.S. Deaths, 1986



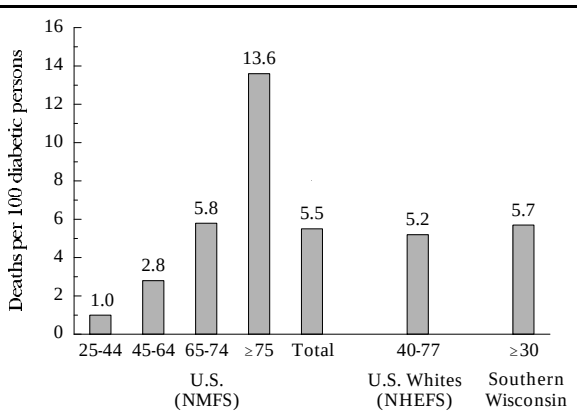
Data are based on the 1986 National Mortality Followback Survey.

Source: References 13 and 20

findings across these three studies lends credence to the estimate of an average annual death rate for NIDDM of ~5.4%.

In a 10-year followup of male Dupont employees age 17-64 years at study entry, the annual death rate for men with diabetes was 2.5%[24]. In a 12-year follow-up study of men age 35-57 years recruited from employee groups and communities in 18 cities for the Multiple Risk Factor Intervention Trial (MRFIT), an annual death rate of 1.6% was found for men with diabetes[25]. The lower death rate in these two studies compared with the population-based data presented above is likely due to the "healthy worker" effect (i.e., employed populations are younger and healthier than the general population).

Figure 11.3
Death Rates by Age for Persons with Diabetes in U.S. Studies



NMFS, 1986 National Mortality Followback Survey; NHEFS, 1974-82 National NHANES I Epidemiologic Followup Survey; data from southern Wisconsin were for a sample of diabetic patients with diabetes diagnosed at age ≥30 years.

Source: References 13, 20-23

Death rates for diabetes based on death certificates in which diabetes is mentioned as a cause of death greatly underestimate the actual mortality experience of people with diabetes. The overall death rate of 5.5% in U.S. diabetic persons age ≥25 years (Figure 11.3) is 2.3 times the death rate calculated using 1986 U.S. death certificates with diabetes mentioned as any cause and estimates of the number of people in the United States who are known to have diabetes[21]. Similarly, in Rochester, MN, the death rate during 1965-74 for persons with diabetes was 2.6 times the death rate estimated from death certificate data with diabetes mentioned as any cause of death[14].

In summary, deaths of persons with NIDDM account for ~17.2% of all deaths in the United States. The annual death rate for persons with NIDDM in the U.S. population was ~5.4% in the mid-1980s. This rate is 2.3 times the rate derived from analyses that rely on any mention of diabetes on death certificates to identify decedents with diabetes.

EXCESS MORTALITY IN PERSONS WITH NIDDM

Table 11.1 contains the results of studies published since 1970 that evaluate excess mortality, defined as the risk of death in diabetic versus nondiabetic persons[13,19-53]. When available, age-specific risks, age-adjusted risks, and risks adjusted for multiple risk factors for mortality are presented. Age-specific risks allow comparison of the risk of death in defined age groups, leading to conclusions about whether the risk

Table 11.1

Excess Risk of Mortality Among Persons with Diabetes Compared with Persons Without Diabetes

Ref.	Population	Race	Age at study entry* (years)	Risk of death among persons with diabetes relative to those without diabetes: Total	Sex: Men	Sex: Women	Notes
Population-Based Studies: U.S.							
22	U.S.	White	40-77		2.2	2.1	RR, age-adjusted
			40-64		2.8	2.3	Adjusted for age, SBP, cholesterol, BMI, and smoking
			65-69		1.9	1.6	
			70-77		2.6	2.5	
			40-77		2.3	2.0	
26	U.S.	Total	25-74	1.8			RR, age-adjusted; calculated from mortality data in Reference 26.
			25-39	2.9			
			40-49	2.5			
			50-59	2.1			
			60-69	1.6			
			70-74	1.6			
	U.S.	Total	25-44	6.3	5.7	8.1	RR, calculated from data presented by (20) and unpublished data, CDC
			45-64	3.9	3.4	4.6	
			65-74	2.4	2.0	3.1	
			≥75	1.8	1.6	2.0	
			≥25	2.6	2.3	3.0	RR, age-adjusted
		White	25-64	6.6	6.2	7.2	
			65-74	2.5	2.1	3.1	
			≥75	1.9	1.6	2.2	
			≥25	3.2	2.8	3.5	RR, age-adjusted
		Black	25-64	5.2	3.8	7.9	
			65-74	1.8	1.3	2.6	
			≥75	1.1	1.3	1.2	
			≥25	2.6	2.1	3.3	RR, age-adjusted
27	Gila River Indian Community, AZ	Pima Indians	≥15	1.6	1.4	2.1	RR, age-adjusted for each sex; total is age- and sex-adjusted
28	Oahu, HI	Japanese ancestry	45-68		2.0		RR, age-adjusted; calculated from presented data
29	Tecumseh, MI	Primarily white	≥35	1.4	1.2	1.6	SMR, cases matched by age and sex
30	Rancho Bernardo, CA	White	40-79		1.5	2.3	RR, age-adjusted
31	Framingham, MA	Primarily white	52-85	2.0			RR, adjusted for age, sex, and lens changes
23	11 counties in southern Wisconsin	Primarily white	Age at diagnosis: ≥30	2.0	1.9	2.2	SMR
32	Wadena, Marshall, and Grand Rapids, MN	Primarily white	Total, age range not stated		1.3	1.4	SMR
Hospital, Clinic, and Worksite Studies: U.S.							
25	Employees and community residents of 18 cities	Total	35-57		3.0		RR, age-adjusted
					2.5		RR, adjusted for age, race, income, cholesterol, smoking
35	Employees of 84 companies, Chicago, IL	White	25-64		1.8		RR, age-adjusted; persons with hyperglycemia included among persons with diabetes
		Black			1.5		
33	Life insurance applicants from 50 states	Not stated	Age at diagnosis:				SMR
			<15	11.3			
			15-19	9.3			
			20-29	4.4			
			30-39	3.4			
			40-49	3.0			
			50-59	2.1			
			60-74	2.3			
			Total	3.4			

Table 11.1—Continued next page

Table 11.1 Continued

Ref.	Population	Race	Age at study entry* (years)	Risk of death among persons with diabetes relative to those without diabetes: Total	Sex: Men	Sex: Women	Notes
24	Dupont employees	Not stated	Age at diagnosis:				
			17-45		6.7		SMR
			45-54		2.7		
			55-64		2.0		
			17-64		2.6		
24	Dupont employees	Not stated	Age at diagnosis:				
			25-34		3.4		SMR
			35-44		4.4		
			45-54		2.8		
			55-64		1.7		
34	Nurses from 11 states	Primarily white	30-55			3.0	RR, age-adjusted; free of CHD, stroke, and cancer at baseline
						2.3	Model 1. Adjusted for age, smoking, menopausal status, hormone use, parental history of myocardial infarction at ≤60 years, follow-up period
						2.2	Model 2. Same as Model I plus BMI
						1.9	Model 3. Same as Model 2 plus history of hypertension and high serum cholesterol
Population-Based Studies: International Populations							
36	Finland	Not stated	65-74		2.3		Odds ratio, adjusted for age, BMI, hypertension, smoking, total- and HDL cholesterol and functional capacity
			75-84		1.8		
			65-84		2.1		
37	Finland	Not stated	40-69		2.1	3.8	RR, age-adjusted; among previously diagnosed
					2.1	2.9	RR, age-adjusted; among newly diagnosed
38	Finland	Not stated	≥40		2.0	2.7	RR, adjusted for age and follow-up time
					2.4	2.8	RR, adjusted for age, follow-up time, blood pressure, smoking, and cholesterol
39	Western Australia (rural, nonaboriginal)	White	Age at diagnosis:				
			<50		1.7	3.0	SMR
			50-59		1.3	2.9	
			60-69		1.5	1.8	
			≥70		1.4	0.9	
			Total		1.4	1.8	
40	Bedford, UK	Not stated	Not stated		2.5	5.6	Odds ratio, calulated from presented data; newly diagnosed in 1962; controls were age- and sex-matched to persons with borderline diabetes
41	Oxford, UK	Primarily white	28-89	1.5	1.2	1.9	SMR
42	Gothenburg, Sweden	Not stated	38, 46, 50, 54, 60			7.1	RR, age-adjusted
43	Gothenburg, Sweden	Not stated	51-59		3.5		Odds ratio, age-adjusted; among men with no history of myocardial infarction
					3.2		Odds ratio, adjusted for age, cholesterol, SBP, smoking, BMI, occupation, family history of myocardial infarction, physical activity, stress score, marital status, and alcohol abuse
44	East Germany	Total	All ages	2.7			SMR; insulin-treated
				1.5			SMR; non-insulin-treated
19	Erfurt district of East Germany	Not stated	Age at diagnosis:				
			40-49		1.8	1.9	RR; diagnosed in 1966
			50-59		1.5	1.8	
			60-69		1.4	1.4	
			70-79		1.1	1.2	

Table 11.1—Continued next page

Table 11.1 Continued

Ref	Population	Race	Age at study entry* (years)	Risk of death among persons with diabetes relative to those without diabetes: Total	Sex: Men	Sex: Women	Notes
45	Warsaw, Poland	Not stated	Age at diagnosis:				
			30-49		2.1	1.6	SMR
			50-68		1.2	1.2	
			30-68		1.3	1.3	
Hospital, Clinic, and Worksite: International Populations							
46	Members of British Diabetic Association	Not stated	15-44		3.1	5.3	SMR
			45-64		2.0	2.7	
			≥65		1.4	2.0	
			Total		1.5	2.1	
47	Patients, Osaka, Japan	Japanese	<45		6.7	15.0	SMR; newly diagnosed or duration ≤5 years
			45-54		3.1	2.8	
			55-64		2.3	2.7	
			≥65		0.7	0.5	
48	Patients, Tokyo, Japan	Japanese	≤39	3.1	3.5	2.0	SMR
			40-59	2.4	2.4	2.4	
			≥60	1.3	1.3	1.5	
49	Patients, Aberdeen, UK	Not stated	15-44	2.6	1.3	5.7	SMR
			45-64	3.0	2.8	3.0	
			65-74	1.6	1.2	2.2	
			≥75	0.9	0.8	0.9	
			Total	1.2	1.0	1.2	
50	Patients, Tayside, Scotland	Not stated	15-44	5.5			RR
			45-64	2.3			
			65-74	1.7			
			≥75	1.3			
51	Civil servants and municipal employees, Israel	Total	≥40		2.3		SMR, previously diagnosed diabetes
					1.4		SMR, newly diagnosed diabetes
					2.0		SMR, both previously and newly diagnosed diabetes
52	Civil servants, London, UK	Not stated	40-64		2.1		RR, age-adjusted
53	Civil servants, Paris, France	Not stated	44-55		2.0		RR, previously diagnosed diabetes
					2.7		RR, newly diagnosed diabetes
					2.3		RR, both previously and newly diagnosed diabetes

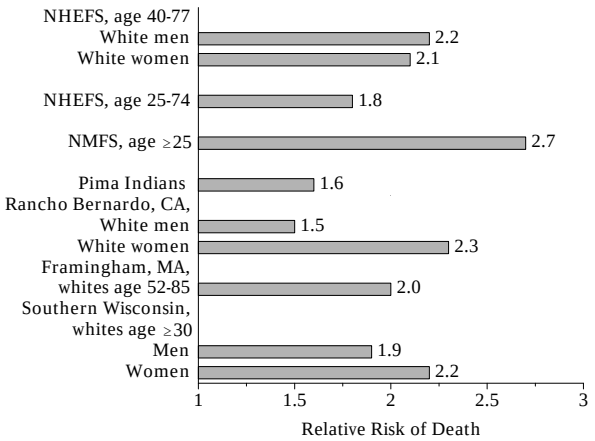
*In places indicated, age at diagnosis is shown. RR, relative risk; SBP, systolic blood pressure; BMI, body mass index; CDC, Centers for Disease Control; SMR, standardized mortality ratio, which is the ratio of observed to expected deaths; CHD, coronary heart disease.

Source: References are listed within the table

associated with diabetes varies by age or by age at onset of diabetes. Age-adjusted risks provide summary measures of risk that account for the differing age distributions of diabetic and nondiabetic populations. This is important because diabetic populations tend to be older; without age adjustment, any increased risk could be a function of older age. Mortality risks that have been adjusted for multiple risk factors (e.g., age, sex, hypertension, smoking, lipid levels) allow for examination of whether risk is a function of diabetes or higher levels in diabetic subjects of other risk factors for mortality. An excess risk in the population with diabetes that persists after adjustment for risk factors indicates that something other than these risk factors increases mortality risk.

The studies in Table 11.1 are divided according to whether they were conducted in or outside the United States and whether they were population-based studies or studies of hospital, clinic, or employee populations. Population-based studies are generally more reliable, because these studies examine whole populations or communities rather than a selected subset that may not represent the entire community with respect to factors such as age and health status. Although most of the studies fail to distinguish between IDDM and NIDDM deaths, they are likely to represent NIDDM mortality because of the older age of the

Figure 11.4
Age-Adjusted Relative Risk of Mortality for Persons with Diabetes Versus Persons Without Diabetes



NHEFS, 1974-82 National NHANES I Epidemiologic Followup Survey; NMFS, 1986 National Mortality Followback Survey; data for Pima Indians are age- and sex-adjusted; Rancho Bernardo, CA, Framingham, MA, and southern Wisconsin were predominantly white cohorts; diabetic patients in southern Wisconsin were those with diabetes diagnosed at age ≥30 years.

Source: References 13, 22, 23, 26, 27, 30, and 31

populations and the much greater prevalence of NIDDM compared with IDDM in older age groups. The studies vary greatly in methodology, including study design, population characteristics, years in which the studies were conducted, definitions used, length of followup, and statistical methods used to determine the relative risk of mortality. In cases where the populations were followed for many years and the results were published for successive follow-up periods, the results of the latest time period (i.e., longest follow-up period) are presented.

Despite differences in methodology, these studies illustrate that persons with diabetes are at increased risk of death compared with persons without diabetes. Generally, even after adjusting for the older age of the diabetic population, persons with diabetes were about twice as likely to die during the study periods as persons without diabetes (Figure 11.4). This excess risk of mortality persisted despite adjustment for other risk factors for death (e.g., hypertension, smoking, cholesterol levels), suggesting that the greater prevalence of these factors in persons with diabetes cannot entirely explain their excess risk of death. Few studies examined the excess risk of mortality due to diabetes in racial and ethnic minority populations, making similar conclusions for these populations tentative.

Most of the studies (Table 11.1) suggest that the magnitude of the excess risk of mortality in persons with diabetes declines with increasing age and increasing age at onset of diabetes. This means that persons who develop diabetes very late in life or persons with diabetes who survive to an old age have a similar or only slightly increased mortality risk compared with persons without diabetes; persons who develop diabetes at a younger age have a much higher mortality risk.

Several studies also suggest that the excess risk of death in persons with diabetes compared with persons without diabetes exists for those who are newly diagnosed[19,34,51,54], increases with duration of diabetes[22,27,33,34,55-57], is higher in those using insulin[22,24,33,39,45,47,55,57], and may be greater in diabetic women than in diabetic men (see Table 11.1 and the sections below on life expectancy and risk factors for mortality).

In summary, after adjusting for age, people with NIDDM have about twice the death rate as people without diabetes. Adjustment for risk factors does not substantially decrease this excess risk of mortality. Excess mortality risk in persons with NIDDM is higher for those using insulin (which may indicate more severe disease), is present in those newly diagnosed with diabetes, is higher in women, and declines with increasing age and increasing age at onset of diabetes.

LIFE EXPECTANCY OF PERSONS WITH NIDDM

Table 11.2, reprinted from a review of NIDDM mortality and survival[19], shows mean years of life lost by

Table 11.2
Reduction in Life Expectancy (Mean Years) in Diabetic Versus Nondiabetic Subjects

Age (years)	Marks and Krall	Goodkin	Panzram and Zabel-Langhennig
10-14	17	27	
15-19	16-17	23	
20-29	12-14	16	
30-39	10-11	11	
40-49	8-9	10	7-8
50-59	6-7	6	5-6
60-69	4-5	5	3-4
≥70			3

Age was attained age in the Marks and Krall study and age at onset of diabetes in the Goodkin and Panzram studies; in the Goodkin study, the youngest age group was <15 years and the oldest age group was 60-70 years.

Source: Reference 19

persons with diabetes in three studies that examined life expectancy of persons with and without diabetes. It was concluded in the review that the reduction in life expectancy was greater for diabetic women, averaged 5-10 years in middle-aged persons with NIDDM, and decreased with increasing age at diagnosis, with little or no reduction in years of life for those diagnosed at age ≥70 years. Appendix 11.1 shows life expectancy for the general U.S. population.

Reduction in life expectancy according to age at onset of diabetes and current age was examined in a population-based study in western Australia[39]. For men with NIDDM compared with the general population, age at onset had no effect on excess mortality and excess mortality declined with older current age (Table 11.3). For women with NIDDM compared with the general population, the effect of age at onset on excess mortality varied by current age. For diabetic persons of both sexes with age at onset ≥60 years, life expectancy was reduced by 3-4 years. However, diabetic women with age at onset <60 years experienced a much greater reduction in life expectancy than men. While the overall reduction in life expectancy averaged ~5 years for both sexes, a reduction in life expectancy was greater for those with high glycosylated hemoglobin values and several complications or risk factors, particularly in women.

Table 11.3
Reduction in Life Expectancy (Years) for NIDDM Subjects Compared with the General Population, Western Australia, 1978-86

Sex and age at onset (years)	Current age (years) 45	55	65	75
Female				
45	11.4	10.1	8.3	6.1
55		7.4	6.2	4.6
65			3.8	2.9
Male				
Any	3.5	3.1	2.5	1.9

Source: Reference 39

In summary, NIDDM is associated with a life expectancy that is reduced by ~5-10 years in middle-aged

Table 11.4
Underlying Causes of Death on Death Certificates of Diabetic Decedents

Underlying cause of death	ICD-9 Codes*	Southern Wisconsin, onset ≥30 years (23) 1980-88	Rochester, MN (14) 1965-74	U.S. sample of persons with diabetes (22) 1971-84	Wadena, Marshall, and Grand Rapids, MN (74) 1979-82	1990 U.S. death certificates with mention of diabetes, all ages 1990	1990 U.S. death certificates with mention of diabetes, age at death ≥45 years 1990
		Percent of deaths based on inclusion of diabetes in the percent distribution					
Diseases of the heart	391-398, 402, 404-429	48.8		59.9		38.5	39.0
Ischemic heart disease	410-414	38.0	38.6	40.1	41.2	28.9	29.3
Diabetes	250	15.3	10.3	12.8	12.5	29.3	28.7
Malignant neoplasms	140-208	9.9	13.8		13.8	9.5	9.7
Cerebrovascular disease	430-438	9.5	3.7		16.2	6.8	6.9
Pneumonia and influenza	480-487	3.1	4.0		5.0	2.6	2.6
		Percent of deaths based on exclusion of diabetes in the percent distribution					
Diseases of the heart	391-398, 402, 404-429	57.6		68.7		54.5	54.7
Ischemic heart disease	410-414	44.7	42.9	46.0	43.4	40.9	41.1
Malignant neoplasms	250	11.7	15.4		14.5	13.4	13.6
Cerebrovascular disease	430-438	11.3	4.2		17.1	9.6	9.7
Pneumonia and influenza	480-487	3.7	4.4		5.3	3.7	3.7

* ICD-9 codes used to classify causes of death in U.S. mortality data and Reference 23; codes for Minnesota studies were not specified; diabetic decedents in Wisconsin and the two Minnesota studies are predominantly white.

Source: References are listed within the table

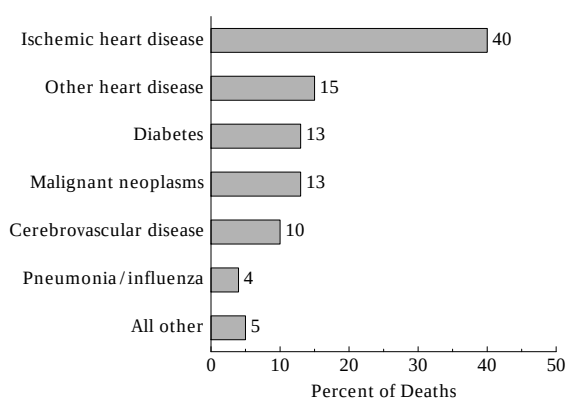
persons. The number of years of life lost, however, varies by sex, the presence of complications and risk factors, age at onset of NIDDM, and current age. Years of life lost is probably greater in women with NIDDM and in persons with complications of NIDDM, but they decrease as age and age at onset increase.

CAUSES OF DEATH

Typically, data on cause of death are based on the underlying cause of death listed on death certificates. As discussed above, there are several problems in the validity of these data. Some of the problems are particularly relevant to analyses of cause-of-death statistics for persons with NIDDM, e.g., inability to distinguish between IDDM and NIDDM, multiple conditions at death that make selection of the underlying cause of death difficult, and underestimation of the causal role of diabetes in death.

Based on the four cohort studies[14,22,23,74] shown in Table 11.4, the leading causes of death listed on death certificates of persons with diabetes are diseases of the heart/cardiovascular disease (primarily ischemic heart disease), diabetes, malignant neoplasms, and cerebrovascular disease. Despite varying techniques for classifying the underlying cause of death and differences among studies (e.g., type of population, age/sex/race differences, differences in follow-up time), the proportion of persons with diabetes dying from these causes is similar in the four studies. Also shown in Table 11.4 are data based on U.S. death certificates in 1990 in which diabetes was listed as a cause of death (underlying or contributing). The percent distribution of the underlying cause of death on these certificates, when diabetes is excluded as a cause of death, is similar to that of the four cohort studies. Figure 11.5 shows the approximate percent of deaths of diabetic decedents in the U.S. according to cause, based on the studies in Table 11.4.

Figure 11.5
Approximate Distribution of Causes of Death in Persons with Diabetes, Based on U.S. Studies



Source: Table 11.4

DISEASES OF THE HEART AND ISCHEMIC HEART DISEASE

In the United States and Western Europe, the majority of deaths and the majority of excess deaths in persons with diabetes are due to diseases of the heart or the broader classification of cardiovascular disease[14,22-25,28,33,35,46,51,54,56,58-60]. Most heart disease deaths are due to ischemic heart disease (insufficient blood and oxygen to the heart), which accounts for ~40% of all deaths of persons with diabetes (Table 11.4 and Figure 11.5).

Table 11.5 contains the results of studies published since 1970 that evaluate excess mortality due to heart disease and ischemic heart disease in diabetic versus nondiabetic persons[22-25,27,28,34-39,41,43,45-50,52,53,58,61-69]. Age-specific risks, age-adjusted risks, and risks adjusted for multiple risk factors are presented when available, and the studies have been divided according to whether they were conducted in or outside the United States and whether they are population-based or involve hospital, clinic, or employee populations. The data in Table 11.5 suggest that the risk of heart disease mortality and ischemic heart disease mortality is ~2-4 times higher in persons with diabetes than in persons without diabetes. This excess risk of dying from heart disease and ischemic heart disease is higher than the excess risk of mortality due to all causes combined. Similar to the excess risk for all causes of mortality, the excess risk of heart disease and ischemic heart disease mortality persists despite adjustment for the different age structures of the diabetic and nondiabetic populations and despite adjustment for known heart disease risk factors (e.g., hypertension, smoking, cholesterol levels, physical inactivity). This suggests that something about diabetes itself, or some unmeasured factors unique to persons with diabetes other than these risk factors, increases the risk of death. Also, similar to studies of excess mortality due to all causes, most studies examining age-specific excess risks of heart disease or ischemic heart disease mortality suggest that the amount of the increased risk of mortality in persons with diabetes compared with persons without diabetes is greater in the younger-age and younger-age-at-onset groups than in the older-age and older-age-at-onset groups.

Table 11.5

Excess Risk of Heart Disease and Ischemic Heart Mortality Among Persons with Diabetes Compared with Persons Without Diabetes

Ref.	Population	Race	Age at study entry*(years)	Risk of death among persons with diabetes relative to those without diabetes: Heart disease or cardiovascular disease — Total	Men	Women	Ischemic heart disease or coronary heart disease — Total	Men	Women	Notes
Population-Based Studies: U.S.										
22	U.S.	White	40-77		2.6	2.4		2.8	2.6	RR, adjusted for age
								2.3	2.8	RR, adjusted for age; excluding those with prior heart attack
			40-77		2.6	2.2		2.8	2.5	RR, adjusted for age, SBP, cholesterol, BMI, and smoking
								2.4	2.6	RR, adjusted for age, SBP, cholesterol, BMI, and smoking; excluding those with prior heart attack
			40-64		3.6	2.4		2.7	1.2	RR, adjusted for age, SBP, cholesterol, BMI, and smoking
			65-69		2.2	2.0		2.0	2.6	"
			70-77		2.8	2.6		2.7	3.0	"
62	U.S., 35 states	Black	Younger				6.2			Age-race specific odds ratios calculated from data in Reference 62
		White	Younger				9.4			
		Black	Older				1.5			
		White	Older				2.7			
61	U.S., 35 states	Total	25-44						18.0	Age-sex specific odds ratios calculated from data in Reference 61
		Total	45-54						6.8	
		Total	Younger				9.0	8.0	12.4	
		Total	Older				2.6	1.9	3.5	
62	U.S., 35 states	Black	Younger				12.8			Odds ratio, adjusted for age, gender, education, marital status, income, and estimated for nonsmokers of "acceptable" body mass and no history of hypertension
		White	Younger				13.9			
61	U.S., 35 states	Black	Older				1.6			Odds ratio, adjusted for age, gender, marital status, income, education, smoking history, history of hypertension, and BMI
		White	Older				2.5			
		Total	Younger					8.5	16.1	Odds ratio, adjusted for age, gender, marital status, income, education, smoking history, history of hypertension, BMI, and state of residence
		Total	Older					2.3	2.1	
27	Gila River Indian Community, AZ	Pima Indian	≥15				43.4	32.1		RR, age-adjusted for males; age- and sex-adjusted for total; risk could not be computed for females since no deaths from IHD occurred among nondiabetic females; causes of death classified through use of multiple data sources
28	Oahu, HI	Japanese ancestry	45-68		2.6			3.4		RR, age-adjusted; calculated from presented data
63	Tecumseh, MI	Primarily white	40-54					6.5	7.8	RR; excludes those with CHD at baseline
			55-69					1.9	1.0	
			≥70					1.8	3.5	
			Total					3.0	3.0	RR, age-adjusted
64	Rancho Bernado, CA	White	40-79					1.8	3.3	Relative hazard adjusted for age
								1.9	3.3	Relative hazard adjusted for age, SBP, cholesterol, BMI, smoking
65	Framingham, MA	Primarily white	45-74		2.1	4.9				RR, age-adjusted
			45-74		1.7	3.3				RR, adjusted for age, SBP, no. of cigarettes, cholesterol, ECG-LVH

Table 11.5—Continued next page

Table 11.5 Continued

Ref.	Population	Race	Age at study entry*(years)	Risk of death among persons with diabetes relative to those without diabetes: Heart disease or cardiovascular disease — Total	Men	Women	Ischemic heart disease or coronary heart disease — Total	Men	Women	Notes
58	Framingham, MA	Primarily white	30-62		1.7	7.3				SMR, by type of diabetes treatment: Insulin
			30-62		2.1	1.8				Oral agents
			30-62		2.7	2.9				Diet
			30-62		2.0	4.6				Total
23	11 counties in southern Wisconsin	Primarily white	Age at diagnosis: ≥30	2.3	2.3	2.3	2.3	2.4	2.2	SMR
32	Wadena, Marshall, Grand Rapids, MN	Primarily white	Total, age range not stated		1.5	1.5		1.4	2.0	SMR
66	Evans County, GA	White	≥40	2.1			1.3	1.0	2.8	SMR, adjusted for age, SBP, cholesterol, BMI, smoking, triglycerides; free of CHD, and stroke
Hospital, Clinic, and Worksite Studies: U.S.										
24	Dupont employees	Not stated	17-64					2.9		SMR
34	Nurses from 11 states	Primarily white	30-55			6.3			6.9	RR, age-adjusted; free of CHD, stroke, and cancer at baseline. Model 1. Adjusted for age, smoking, menopausal status, hormone use, parental history of myocardial infarction at ≤60 years, follow-up period
						4.7				
						4.4				Model 2. Same as Model 1 plus BMI
						3.0				Model 3. Same as Model 2 plus history of hypertension and high serum cholesterol
67	Employees of 84 companies, Chicago, IL	White	35-64					4.0	5.9	RR, age-adjusted; persons with hyperglycemia included among persons with diabetes; persons without history of myocardial infarction and hypertension medications at baseline
								3.8	4.7	RR, adjusted for age, cholesterol, SBP, no. of cigarettes, ECG abnormalities, education
35	Employees of 84 companies, Chicago, IL	White	25-64			2.0				RR, age-adjusted; persons with hyperglycemia included among persons with diabetes
		Black	25-64			1.4				
25	Employees and community residents of 18 cities	All races	35-57		3.7			3.9		RR, age-adjusted; calulated from data presented
		White	35-57		3.8					
		Black	35-57		2.7					"
		Hispanic	35-57		3.3					"
		Other	35-57		7.8					"
		All races	35-39		4.9					RR, age-adjusted; calulated from data presented
			40-44		4.0					
			45-49		3.3					"
			50-54		3.8					"
			55-57		3.5					"
		All races	35-57		3.0			3.2		RR, adjusted for age, race, income, cholesterol, SBP, no. of cigarettes
		White	35-57		3.2					
		Black	35-57		2.2					"
		Hispanic	35-57		1.8					"
		Other	35-57		4.1					"
		All races	35-39		3.0					RR, adjusted for race, income, cholesterol, SBP, no. of cigarettes
			40-44		3.0					
			45-49		2.4					"
			50-54		3.3					"
			55-57		3.0					"

Table 11.5—Continued next page

Table 11.5 Continued

Ref.	Population	Race	Age at study entry*(years)	Risk of death among persons with diabetes relative to those without diabetes: Heart disease or cardiovascular disease — Total	Men	Women	Ischemic heart disease or coronary heart disease — Total	Men	Women	Notes
Population-Based Studies: International Populations										
68	Puerto Rico	Not stated	45-64					4.0		RR, age-adjusted; free of CHD at baseline; diabetes includes those on treatment or blood glucose ≥140mg/dl
36	Finland	Not stated	65-74		2.4					Odds ratio, adjusted for age, BMI, hypertension, smoking, total- and HDL cholesterol and functional capacity
			75-84		1.2					
			65-84		1.6					
38	Finland	Not stated	≥40		2.5	2.9				RR, adjusted for age and follow-up time
					2.7	3.1				RR, adjusted for age, follow-up time, blood pressure, smoking, and cholesterol
37	Finland	Not stated	40-69		2.6	3.9		2.6	3.6	RR, age-adjusted, previously diagnosed
					3.1	3.6		2.0	4.1	RR, age-adjusted, newly diagnosed
39	Western Australia (rural, nonaboriginal)	White			2.1	1.9				SMR
41	Oxford, UK	Primarily white	28-89				1.7	1.3	2.3	SMR
43	Gothenburg, Sweden	Not stated	51-59		4.6			4.1		Odds ratio, age-adjusted; among men with no history of myocardial infarction
					4.1			3.4		Odds ratio, adjusted for age, cholesterol, SBP, smoking, BMI, occupation, family history of myocardial infarction, physical activity, stress score, marital status, and alcohol abuse
45	Warsaw, Poland	Not stated	Age at diagnosis:							
			30-49		4.0	3.8		3.4	3.3	SMR
			50-68		2.8	1.3		1.8	1.6	"
			30-68		3.0	1.5		2.0	1.8	"
Hospital, Clinic, and Worksite Studies: International Populations										
46	Members of British Diabetic Association	Not stated	15-44		4.6	6.3		5.0	11.5	SMR; expected based on population of England and Wales
			45-64		2.1	3.2		3.8	4.3	
			≥65		1.5	1.9		1.7	2.6	"
			Total		1.6	2.0		1.9	2.7	"
47	Patients, Osaka, Japan	Japanese	Total age range not given	1.4			2.3			SMR; newly diagnosed or duration ≤5 years
48	Patients, Tokyo, Japan	Japanese	"				2.4			SMR
49	Patients, Aberdeen, UK	Not stated	15-44				7.4	3.2		SMR; SMR not calculated for women age 15-44 years because there were no deaths due to IHD among nondiabetic women
			45-64				4.5	3.8	5.4	
			65-74				2.2	1.6	3.2	
			≥75				1.1	1.0	1.1	"
			Total				1.6	1.4	1.6	"
50	Patients, Tayside, Scotland	Not stated	45-64	3.8						RR
			65-74	2.7						"
			≥75	2.2						"
52	Civil servants, London, UK	Not stated	40-64					2.7		RR, age-adjusted
69					3.7			3.9		RR, age-adjusted; newly diagnosed
53	Civil servants, Paris, France	Not stated	44-55		2.3					RR, previously diagnosed diabetes
					2.2					RR, newly diagnosed diabetes

*In places indicated, age at diagnosis is shown. RR, relative risk; SBP, systolic blood pressure; BMI, body mass index; IHD, ischemic heart disease; ECG-LVH, electrocardiographically confirmed left ventricular hypertrophy; CHD, coronary heart disease; SMR, standardized mortality ratio, which is the ratio of observed to expected deaths. Younger— females age <55 years, males age <45 years; Older— females age ≥55 years, males age ≥45 years.

Source: References are listed within the table

Studies of excess heart disease and ischemic heart disease mortality in diabetic persons compared with nondiabetic persons also suggest that the increased risk of death exists in those newly diagnosed with diabetes[19,34,37,51] increases with duration of diabetes (although not necessarily in linear fashion)[22,34], and is higher in those using insulin[22,45,58]. There is also evidence that the risk of heart disease/ischemic heart disease mortality may be greater in women (see Table 11.5 and the section below on risk factors for mortality and excess mortality).

DIABETES

Underlying Cause of Death

In the four cohort studies of persons with diabetes in Table 11.4, diabetes was selected as the underlying cause of death in 10%-15% of deaths.

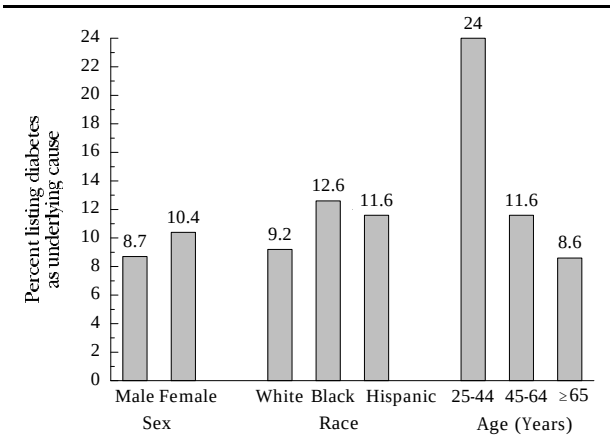
Based on the 1986 NMFS[13], the frequency of recording diabetes as the underlying cause of death is slightly higher for females than males and for blacks and Hispanics compared with all whites, although these differences were not statistically significant (Figure 11.6). In addition, decedents who develop diabetes at age <30 years, who primarily have IDDM, are twice as likely to have diabetes recorded as the underlying cause of death as those who develop diabetes at an older age (primarily NIDDM). The frequency of recording declines sharply with increasing age, from 24.0% of those dying at age 25-44 years to 8.6% of those dying at age ≥65 years (Figure 11.6). The frequency increases with increasing duration of diabetes in each age group (Figure 11.7).

In 1990, diabetes was listed on death certificates as the underlying cause of 47,664 deaths, or 2.2% of all deaths in the United States (Appendix 11.2). Only ~10% of diabetic decedents have diabetes listed as the underlying cause of death[13,14,22]. Although diabetes is thus infrequently recorded as the underlying cause of death in diabetic decedents, diabetes ranks seventh among the leading underlying causes of death in the United States, a rank it has held since 1979.

Between 1987 and 1989, age-adjusted mortality attributed to diabetes as the underlying cause of death in the United States increased 18% (Appendix 11.2). This increase was associated with use of the revised 1989 U.S. Standard Certificate of Death (Figure 11.1), designed to improve cause-of-death recording. The revision included increasing the number of lines on which to report causes of death in Part I from three to four lines and showing, on the reverse of the certificate, instructions and examples for completing the cause-of-death sections, including using diabetes as an example of a contributing cause of death.

Death rates based on diabetes listed as the underlying cause of death on death certificates, adjusted to the estimated prevalence of diabetes in the U.S. population, increase with age (Figure 11.8). In 1990, the rate for those age ≥75 years (2.07%) was ~10 times the rate of those age <45 years (0.20%).

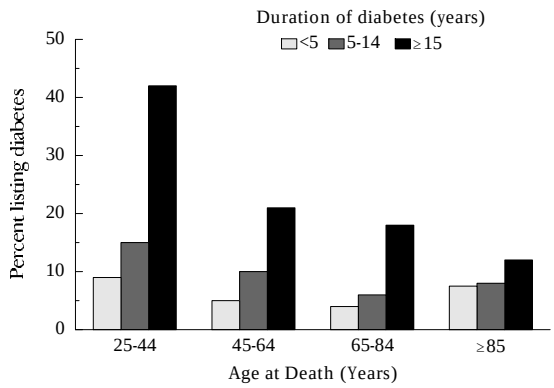
Figure 11.6
Frequency of Listing Diabetes as the Underlying Cause of Death on Death Certificates of U.S. Decedents with Diabetes, 1986



Data are from the 1986 National Mortality Followback Survey.

Source: Reference 13

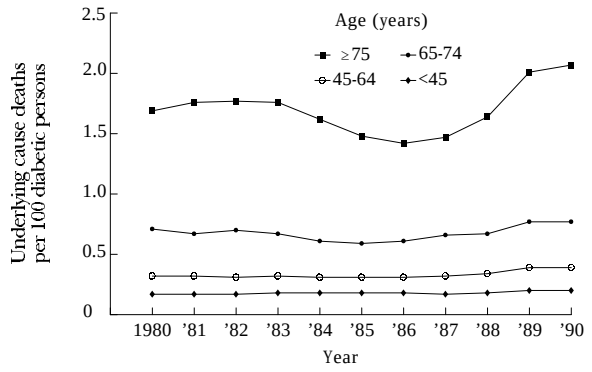
Figure 11.7
Frequency of Listing Diabetes as the Underlying Cause of Death on Death Certificates of U.S. Decedents with Diabetes, by Duration of Diabetes, 1986



Data are from the 1986 National Mortality Followback Survey.

Source: Reference 13

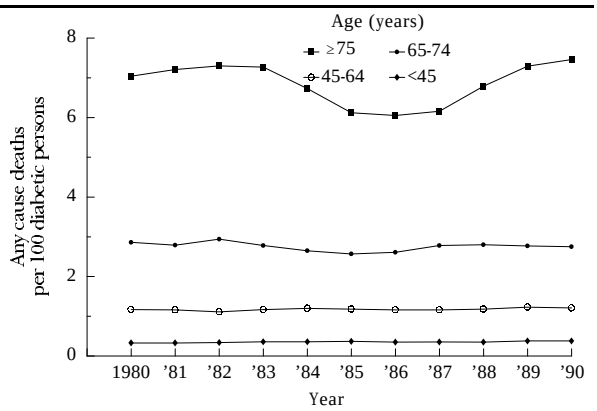
Figure 11.8
Death Rates Based on Diabetes as the Underlying Cause of Death on Death Certificates, U.S., 1980-90



Data are based on the ~10% of deaths of diabetic decedents who have diabetes listed as the underlying cause of death, although this percent varies by age (see Figure 11.6). Data are calculated from the number of U.S. death certificates that listed diabetes as the underlying cause in each year and the number of people with diabetes in the U.S. as estimated from the U.S. National Health Interview Survey in each year.

Source: Reference 21

Figure 11.10
Death Rates Based on Diabetes as Any Listed Cause of Death on Death Certificates, U.S., 1980-90



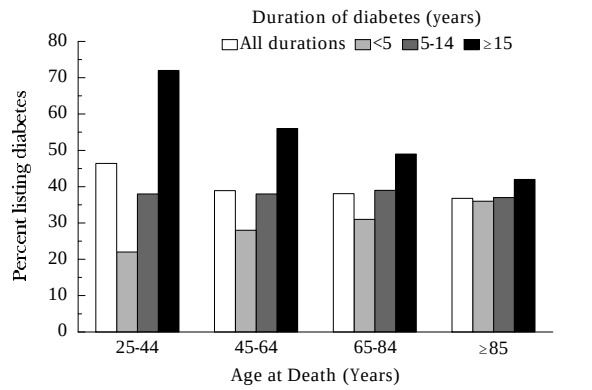
Data are shown on a log scale; data are based on the ~38% of deaths of diabetic decedents who have diabetes listed on their death certificate (Reference 13). Data are calculated from the number of U.S. death certificates that listed diabetes in each year and the number of people with diabetes in the U.S. as estimated from the U.S. National Health Interview Survey in each year.

Source: Reference 21

Any Listed Cause of Death

Among decedents with a medical history of diabetes, <40% have diabetes listed as any cause of death on the death certificate[11,13,14]. The frequency of recording diabetes as a cause of death is similar in each age group (37%-46%) but increases with longer duration of diabetes, decreases with age for those with duration ≥15 years, and increases with age for those with duration <5 years (Figure 11.9)[13]. Diabetes is more often listed when co-morbidities related to diabetes (including ischemic heart disease, hypertensive disease, cerebrovascular disease, arterial disease, and renal disease) are also listed[13]. However, diabetes is less likely to be listed as a cause of death on the death certificate when the underlying cause of death is a condition typically perceived to be unrelated to diabetes (e.g., cancer, accidents)[13,46]. In 1990, 162,567 deaths in the United States (7.5% of all deaths) had diabetes listed as a cause of death on the death certificate (Appendix 11.3). Adjusted to the estimated U.S. population with diabetes, the death rates for diabetes as any listed cause increase with age, with the highest rates in those age ≥75 years (Figure 11.10). In 1990, the rate for those age ≥75 years (7.46%) was ~20 times the rate for those age <45 years (0.38%).

Figure 11.9
Frequency of Listing Diabetes as Any Cause of Death on Death Certificates of U.S. Decedents with Diabetes, by Duration of Diabetes, 1986



Data are from the 1986 National Mortality Followback Survey.

Source: Reference 13

CEREBROVASCULAR DISEASE

In population-based studies of NIDDM mortality, between 5.7% and 16.2% of diabetic deaths are attributed to cerebrovascular disease or stroke. The proportion of deaths due to cerebrovascular disease in diabetic populations was 5.7% for Oklahoma Indians[72]; 6% for residents of Rochester, MN[73]; 7.5% for Pima Indians[27]; 8.4% for Hawaiian men of Japanese ancestry[28]; 9.5% for residents of 11 counties in southern Wisconsin[23]; 10.4% for Mexican-American residents of Starr County, TX[56]; and 16.2% for residents of three cities in Minnesota[74].

Although confidence intervals were large, two population-based studies of primarily white populations in the United States found the relative risk of cerebrovas-

cular disease mortality for persons with diabetes compared with persons without diabetes to be 1.8 and 1.7 for men and 2.2 and 2.6 for women[23,75]. This excess risk of cerebrovascular disease mortality is typically larger in studies of patients or employees. Age-adjusted excess risks of cerebrovascular disease mortality in people with diabetes compared with people without diabetes were 5.0 for female nurses[34] and 3.8 for men screened for participation in the MRFIT[25]. In a case-control study of male Dupont employees[24], an excess risk of 2.8 (not statistically significant) was found for diabetic men.

In summary, the risk of cerebrovascular mortality in persons with diabetes appears to be about twice that of persons without diabetes, and women may have a slightly greater excess risk than men.

OTHER CAUSES

Although malignant neoplasms are a major cause of death in people with diabetes (Table 11.4), people with diabetes are not at increased risk of dying from this disease, compared with people without diabetes[14,23,46,49,72-74,76].

Due to the size of populations investigated, only a few U.S. studies of mortality in people with diabetes have been able to examine causes of death less frequent than the four leading causes of death (diseases of the heart, diabetes, cerebrovascular disease, and malignant neoplasms). These studies found that 3%-6% of all diabetic decedents have pneumonia and influenza listed as the underlying cause of death[14,23,72-74]. A similar percentage is found in U.S. death certificate data for deaths with diabetes as any listed cause (Table 11.4). One study examined the relative risk of pneumonia/influenza death in diabetic versus nondiabetic persons. Among residents of southern Wisconsin, persons with diabetes with onset at age >30 years were 1.7 times more likely to die from pneumonia or influenza than the general population in southern Wisconsin[23]. In a review of mortality data related to pneumonia and influenza, it was concluded that death rates for diabetic persons may increase 5%-15% during influenza epidemics and that mortality is particularly high for persons with diabetes who have additional risk factors, particularly cardiovascular disease and age >65 years[77].

In summary, the four leading causes of death in persons with NIDDM are diseases of the heart (primarily ischemic heart disease), diabetes, malignant neoplasms, and cerebrovascular disease. About half of NIDDM deaths are due to heart disease, and most of these deaths are due to ischemic heart disease. The risk of heart disease and ischemic heart disease mortality is ~2-4 times higher in persons with NIDDM than in persons without diabetes. Similar to excess mortality from all causes, the excess risk of mortality due to heart disease and ischemic heart disease in persons with NIDDM, compared with those without diabetes is greater for those using insulin and for women and cannot be fully explained by increased levels of cardiovascular risk factors in persons with NIDDM.

ETHNIC DIFFERENCES IN NIDDM MORTALITY

Mortality in blacks, Hispanics, Asian Americans, and Native Americans with diabetes is discussed in Chapters 31-34. Based on U.S. death certificates, the rank of diabetes among leading underlying causes of death varies by race/ethnicity, age, and sex (Table 11.6). Diabetes ranks higher as an underlying cause of death in women versus men at age ≥45 years. Its highest

Table 11.6
Rank of Diabetes Listed as the Underlying Cause of Death on U.S. Death Certificates, 1990

	Males	Females
White		
All ages	8	7
<45	11	11
45-64	8	6
65-74	6	5
≥75	7	6
Black		
All ages	10	4
<45	11	11
45-64	7	4
65-74	5	4
≥75	6	5
American Indian		
All ages	9	5
45-64	5	4
65-74	5	3
≥75	6	5
Hispanic		
All ages	7	5
<45	11	11
45-64	6	3
65-74	4	3
≥75	5	6
Chinese	7	6
Filipino	9	6
Japanese	7	6
Hawaiian	5	5
Other Asian	11	7

Source: Centers for Disease Control

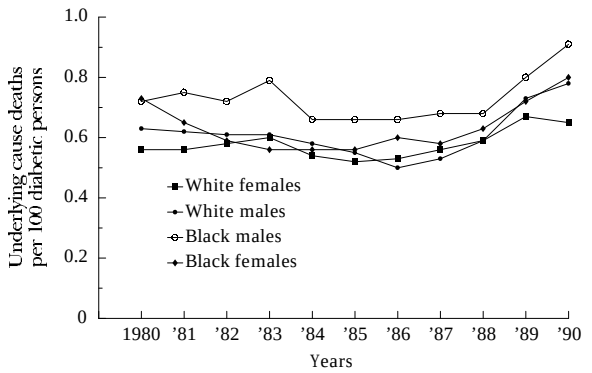
rank for all ages combined is among black women, for whom diabetes is the fourth leading underlying cause of death on death certificates. Diabetes is the third leading underlying cause of death on death certificates of Hispanic women age 45-74 years and American Indian women age 65-74 years. In addition, diabetes is the third leading cause of death in Pima Indians and the second leading cause in Pima Indian women[72].

In the general U.S. population, diabetes listed as the underlying cause of death on death certificates ranks higher in racial and ethnic minority populations than in the white population. Mortality attributed to diabetes on death certificates is higher in blacks than whites[11,70,78], higher in Hispanics than non-Hispanics[78], and higher in Native Americans than in either whites[11,72,79], blacks[11], Hispanics[78], or the general population[72,79]. However, these higher rates are partly due to the higher prevalence of diabetes in minority populations. Black and white diabetes mortality rates based on death certificates and adjusted to the estimated prevalence of diabetes in the U.S. population are more similar to each other than rates computed for the general U.S. population without adjustment for diabetes prevalence[80]. In addition, diabetes is more often recorded as the underlying cause of death for black decedents with diabetes than white decedents (Figure 11.6). Based on the 1986 NMFS, diabetes was selected as the underlying cause for 12.6% of diabetic blacks, compared with 9.2% of diabetic whites (a 25% differential, although the 95% confidence intervals overlapped)[13]. Consequently, the age-adjusted death rates for blacks and whites based on diabetes as the underlying cause of death in Figure 11.11 should be viewed with caution.

There is also a differential between blacks and whites in recording diabetes as any listed cause on death certificates of decedents with diabetes. The 1986 NMFS data found that diabetes was recorded on 36.2% of death certificates for diabetic blacks and 38.6% for diabetic whites (a 7% differential)[13]. Figure 11.12 shows age-adjusted mortality for diabetes as any listed cause on U.S. death certificates.

Most studies of mortality in persons with diabetes have been conducted in white or primarily white populations. Three studies examined the excess risk of mortality in black and white persons with diabetes[25,35,62]. In all three, the risk of mortality due to all causes or cardiovascular disease was higher in blacks with diabetes than in blacks without diabetes, but the excess risk of mortality due to diabetes in blacks was slightly lower than in whites (Table 11.5). Two of the studies[25,35] found that age-adjusted death rates due to cardiovascular disease were similar in magnitude for black and white men with diabetes. This suggests that, while the excess risk conferred by diabetes may be less in black men compared with white men, absolute age-adjusted rates of cardiovascular mortality in diabetic men may not differ between the two races.

Figure 11.11
Age-Adjusted Death Rates Based on Diabetes Listed as the Underlying Cause of Death on Death Certificates, U.S., 1980-90

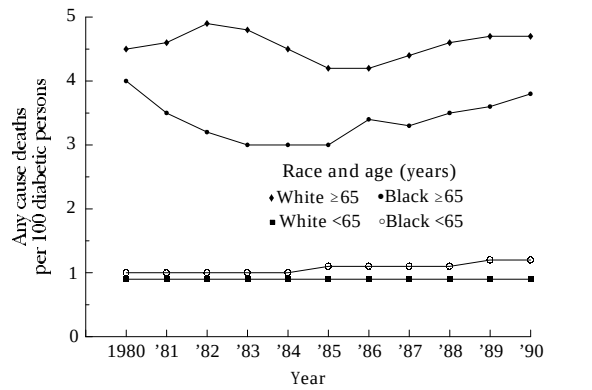


Data are calculated from the number of U.S. death certificates in each year that listed diabetes as the underlying cause of death (estimated in Reference 13 to be 12.6% for black and 9.2% for white diabetic decedents) and the number of people with diabetes in the U.S. as estimated from the U.S. National Health Interview Survey in each year.

Source: Reference 21

Research is needed on the impact of diabetes on mortality among racial and ethnic minority groups. Most of what is known about diabetes mortality in these groups has been derived from U.S. vital statistics data,

Figure 11.12
Death Rates Based on Diabetes as Any Listed Cause on Death Certificates, U.S., 1980-90



Data are calculated from the number of U.S. death certificates in each year that listed diabetes (~38% of deaths of diabetic decedents) and the number of people with diabetes in the U.S. as estimated from the National Health Interview Survey in each year.

Source: Centers for Disease Control, calculated from U.S. cause-of-death data

which have serious limitations and inaccuracies. These data do not allow valid examination of the risk of mortality in diabetic persons compared with nondiabetic persons, nor do they allow examination of most risk factors for mortality.

RISK FACTORS AND RISK MARKERS FOR MORTALITY AND EXCESS MORTALITY

Studies of risk factors for mortality from all causes and from heart disease/ischemic heart disease in people with diabetes are plagued by a number of analysis problems, including sample sizes insufficient to detect associations and differences in design and methodology. It is not surprising that not all studies find the same risk factors associated with mortality and that the strength of these associations varies among studies.

In the following discussion of risk factors for mortality in persons with diabetes, an arbitrary distinction is made between risk factors and risk markers. Risk factors are presumed to influence the occurrence of mortality, whereas a risk marker (e.g., measures of renal function such as microalbuminuria) usually occurs later in the causal pathway toward mortality and may not be a causal factor.

RISK FACTORS

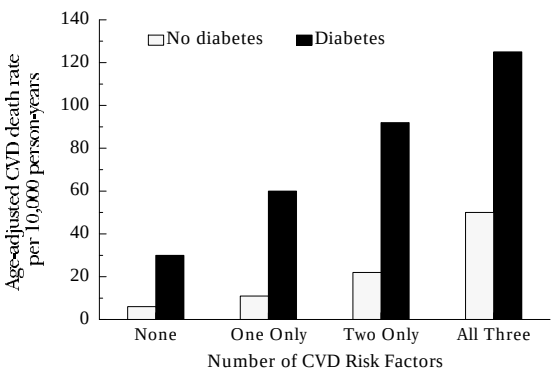
Although mortality of persons with diabetes (and also those without diabetes) increases with age, most studies examining the effects of age in persons with diabetes find that excess mortality risk declines with increasing age and age at onset of diabetes (Tables 11.1 and 11.5; see also the previous section on life expectancy). Most studies of excess mortality due to all causes (Table 11.1) or to that caused by cardiovascular disease or ischemic heart disease (Table 11.5) also find a greater excess risk associated with diabetes in women than men. Although the relative risk is greater for women, death rates from ischemic heart disease are higher for diabetic men than diabetic women[22].

Studies examining modifiable risk factors for all-cause mortality and heart disease mortality have found that the major risk factors are generally the same for persons with and without diabetes[26,37,53,61,65]. However, risk factors are often more prevalent in persons with diabetes[25,28,29,35,58,65] and may be more prevalent in women with diabetes than men with diabetes[37,66,67,81]. It has been suggested that cardiovascular risk factors cluster within individuals (i.e., an individual with a high level of one risk factor is also likely to have high levels of other risk factors) and that this clustering of risk factors is more common among persons with diabetes, particularly women[81].

The two risk factors for mortality most consistently found in persons with diabetes are hypertension or high blood pressure, particularly elevated systolic blood pressure[24-26,33,34,52,55,60-62,68,82,83] and smoking[26,30,34,43,52,55,61,62,84,85]. Although less consistently identified as a risk factor, perhaps because the association is not always linear, elevated cholesterol and triglyceride levels have also been associated with mortality in persons with diabetes[25,26,34,37,43,56,85]. Physical inactivity is a risk factor for premature mortality in the general population, and two studies found that non-leisure-time physical inactivity[26] and lack of cardiovascular fitness[86] are associated with mortality in persons with diabetes. Central or abdominal obesity was a more important risk factor for mortality than general obesity for persons with diabetes in one study[53]. Higher 2-hour post-challenge glucose concentrations[53] and higher glycosylated hemoglobin[55,39] were associated with mortality in some studies, but glycemic control was not a risk factor for mortality in other studies[55].

There are numerous reports on the impact of risk factors on death rates in persons with NIDDM[24,26,33,34,39,40,46,47,53,55,61-63,65,85-87]. Several studies suggest that mortality may be decreased by reducing modifiable risk factors[25,26,29,53,86]. Among men screened for MRFIT, cardiovascular deaths increased with an increasing number of CVD risk factors[25] (Figure 11.13). It was estimated that 68% of cardiovascular deaths in MRFIT men taking medication for diabetes

Figure 11.13
Age-Adjusted CVD Death Rates for Men Screened for MRFIT



CVD, cardiovascular disease; MRFIT, Multiple Intervention Risk Factor Trial.

Source: Reference 25

could be prevented by eliminating smoking and decreasing serum cholesterol levels and systolic blood pressure. Although this study and others suggest that mortality may be decreased by reducing modifiable risk factors, long-term clinical trials of the effect of risk-factor reduction on the mortality of populations with NIDDM have not been conducted.

RISK MARKERS

Two major groups of risk markers for mortality in persons with NIDDM are 1) clinical measures of renal function including proteinuria, albuminuria, and microalbuminuria[24,33,39,41,55,85,88,89], and 2) eye disorders including poor visual acuity, cataract, and retinopathy[31,39,41,55,56,90]. It is unclear whether the former group comprise determinants of mortality or, like the latter group of risk markers, comprise indicators of more advanced or severe disease. However, these risk markers identify persons with increased risk of mortality who should be targeted for intensive intervention.

In summary, risk factors for mortality in persons with NIDDM include age, age at onset of diabetes, sex, insulin use, duration of diabetes, metabolic control, and typical cardiovascular risk factors (e.g., smoking, hypertension or elevated blood pressure, elevated cholesterol level, physical inactivity). In addition, persons with NIDDM having clinical risk markers and complications (e.g., microalbuminuria, retinopathy) are at increased risk for mortality.

Although there have been no long-term clinical trials of the effect of risk factor reduction on the mortality of populations with NIDDM, it is possible that a substantial proportion of NIDDM mortality could be prevented by reducing or preventing cardiovascular risk factors through the promotion of healthy lifestyles, including weight reduction/obesity prevention, increased physical activity, hypertension control, smoking cessation/prevention, and lipid-lowering therapy.

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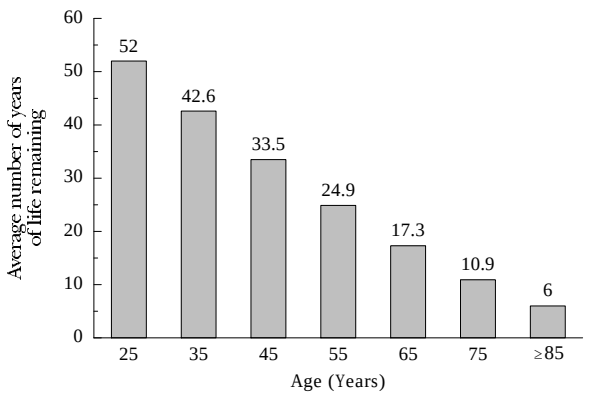
Appendix 11.1

Life Expectancy in the U.S., by Age, 1993



Source: Reference 91

Appendix 11.2

Number of Deaths with Diabetes Listed as the Underlying Cause on Death Certificates and Death Rates per 100,000 U.S. Population, U.S., 1980-90

		Year										
Age		1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990
0-14	Number	53	46	63	51	36	44	36	41	40	53	35
	Rate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
15-24	Number	128	149	134	129	119	121	140	119	119	136	115
	Rate	0.3	0.4	0.3	0.3	0.3	0.3	0.4	0.3	0.3	0.4	0.3
25-34	Number	572	554	533	584	578	537	634	618	656	687	674
	Rate	1.5	1.4	1.4	1.5	1.4	1.3	1.5	1.4	1.5	1.6	1.6
35-44	Number	900	916	922	1,064	1,072	1,165	1,174	1,203	1,395	1,432	1,510
	Rate	3.5	3.5	3.3	3.6	3.5	3.7	3.6	3.5	4.0	3.9	4.0
45-54	Number	2,188	2,167	2,060	2,078	2,005	1,991	2,158	2,258	2,502	2,784	2,834
	Rate	9.6	9.6	9.2	9.3	9.0	8.9	9.5	9.8	10.5	11.3	11.3
55-64	Number	5,789	5,620	5,643	5,900	5,495	5,819	5,780	5,914	6,109	6,942	6,969
	Rate	26.6	25.7	25.6	26.7	24.8	26.3	26.3	27.2	28.4	32.7	33.0
65-74	Number	10,111	9,841	9,711	10,185	9,934	10,159	10,269	10,789	11,092	13,168	13,280
	Rate	64.6	62.0	60.2	62.1	59.8	60.3	60.0	61.9	62.9	73.7	73.6
75-84	Number	10,134	10,221	10,339	10,923	10,857	11,308	11,048	11,470	11,907	14,160	14,537
	Rate	130.3	128.1	126.1	129.7	125.6	127.4	121.3	122.6	124.1	143.9	145.2
≥85	Number	4,971	5,120	5,170	5,328	5,690	5,817	5,939	6,118	6,548	7,470	7,706
	Rate	219.0	218.5	212.6	212.2	219.9	218.6	217.1	217.4	227.5	252.6	255.0
Total	Number	34,851	34,642	34,583	36,246	35,787	36,969	37,184	38,532	40,368	46,833	47,664
	Rate	15.3	15.1	14.9	15.5	15.2	15.5	15.5	15.9	16.5	19.0	19.2
Age-adjusted rate		15.3	15.0	14.6	15.1	14.6	14.8	14.7	14.7	15.4	17.6	17.7

Source: Reference 21

Appendix 11.3

Number of Deaths with Diabetes as Any Listed Cause on Death Certificates and Death Rates per 100,000 U.S. Population, U.S., 1980-90

		Year										
Age		1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990
0-14	Number	69	75	93	82	61	59	57	53	60	74	48
	Rate	0.1	0.1	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1
15-24	Number	209	231	180	208	201	206	217	209	195	196	185
	Rate	0.5	0.5	0.4	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
25-34	Number	918	910	968	953	991	960	1,094	1,117	1,135	1,106	1,122
	Rate	2.5	2.3	2.5	2.4	2.4	2.3	2.6	2.6	2.6	2.6	2.6
35-44	Number	2,038	2,046	2,042	2,282	2,426	2,525	2,652	2,738	2,903	2,973	3,045
	Rate	7.9	7.8	7.3	7.8	8.0	8.0	8.0	8.0	8.3	8.2	8.1
45-54	Number	6,956	6,979	6,729	6,809	6,648	6,736	6,890	7,231	7,516	7,716	7,720
	Rate	30.6	30.9	30.0	30.5	29.7	30.0	30.4	31.4	31.4	31.4	30.8
55-64	Number	21,873	21,926	21,759	22,513	22,383	22,803	22,809	22,647	22,646	22,798	22,412
	Rate	100.5	100.1	98.8	101.8	101.0	103.0	103.7	104.1	105.2	107.3	106.2
65-74	Number	41,000	40,875	40,898	42,370	43,036	44,058	44,218	45,735	46,195	47,306	47,643
	Rate	262.0	257.5	253.6	258.5	259.2	261.7	258.2	262.5	262.1	264.9	264.0
75-84	Number	42,938	42,661	43,340	45,539	46,462	4,7607	48,220	48,830	50,549	51,925	53,066
	Rate	551.9	534.6	528.6	540.7	537.3	536.4	529.4	521.9	526.9	527.8	530.0
≥85	Number	19,919	20,223	20,724	21,787	22,332	23,309	23,945	24,700	26,057	26,747	27,310
	Rate	877.7	863.0	852.4	867.7	863.0	876.0	875.3	877.8	905.4	904.4	903.9
Total	Number	135,931	135,939	136,764	142,570	144,548	148,284	150,120	153,271	157,265	160,848	162,567
	Rate	59.8	59.2	59.0	61.0	61.3	62.3	62.5	63.3	64.3	65.2	65.4
Age-adjusted rate		59.8	58.7	57.9	59.2	58.9	59.4	59.1	59.3	59.8	60.2	60.1

Source: Reference 21