



Age and the Burden of Death Attributable to Diabetes in the United States

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Received for publication October 11, 2001; accepted for publication June 19, 2002.

Diabetes is a well-established cause of cardiovascular disease (CVD) and all-cause mortality. The burden of death attributable to diabetes in the United States is not well quantified, particularly with regard to age. The authors analyzed data from the Second National Health and Nutrition Examination Survey (NHANES II) (1976–1980) and the NHANES II Mortality Study, in which a nationally representative cohort of 9,250 adults aged 30–75 years was followed for 12–16 years, to determine all-cause and cause-specific mortality. Overall, between 1976 and 1980, the prevalence of diagnosed diabetes was 4.3%. By 1992, the relative hazard of all-cause mortality was 1.9 (95% confidence interval: 1.5, 2.3), and the population attributable risk (PAR) was 3.6%. The relative hazard of CVD mortality was 2.3 (95% confidence interval: 1.8, 2.8), and the PAR was 5.2%. Including participants with undiagnosed diabetes in the estimates increased the PAR for all-cause mortality to 5.1% and that for CVD mortality to 6.8%. Women had a higher prevalence of diagnosed diabetes than men and a greater relative hazard of death than nondiabetic women, leading to a higher PAR for women (3.8% for all causes and 7.3% for CVD) versus men (3.3% for all causes and 3.8% for CVD). These data suggest that diabetes accounts for at least 3.6% of all deaths and 5.2% of CVD deaths in US adults. Improvements in diabetes prevention and treatment should produce noticeable effects on US life expectancy.

diabetes mellitus; mortality

Abbreviations: CI, confidence interval; NHANES II, Second National Health and Nutrition Examination Survey; PAR, population attributable risk.

It is estimated that 5.9 percent of US adults over age 20 years have been diagnosed with diabetes mellitus (1, 2). By the year 2025, the prevalence of diagnosed diabetes in US adults may reach 8.9 percent (3). Diabetes is a well-established risk factor for lower extremity amputation, retinopathy, nephropathy, neuropathy, and cardiovascular disease (4). Thus, it is not surprising that diabetes contributed to more than 190,000 deaths in the United States in 1997 (5) and that it was listed as the underlying cause of death for approximately 62,000 people (6), making it the seventh-leading cause of death. However, such attributions are subject to two major sources of bias. First, most studies estimating the burden of diabetes are based on death certificate coding, where underreporting of diabetes may lead to 50

percent of all deaths attributable to diabetes being missed (7). Second, there is an assumption that all deaths among people with diabetes are solely related to diabetes (i.e., that the etiologic fraction is 100 percent), leading to an overestimate of the number of deaths (8, 9).

A more sound approach is calculation of the population attributable risk (PAR), which is independent of death certificate coding and makes no a priori assumption about the etiologic fraction. The PAR is a common tool for public health officials and researchers for planning and allocating health care resources and understanding the burden of diabetes. Unfortunately, to our knowledge, there are no previously published studies with data on the PAR of diabetes-related death in the United States (10, 11), nor have

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any studies attempted to determine the number of excess deaths after accounting for known risk factors for all-cause or cardiovascular disease mortality.

Therefore, we sought to quantify the burden of death attributable to diabetes in the United States, independent of causes of death ascribed on death certificates, using a nationally representative sample of adults. In the calculation of PARs, we paid special attention to the effect of age, since there is some controversy over the benefits of aggressive diabetes care among older persons (12), and gender, since there is evidence of an increased risk of cardiovascular disease among women with diabetes (13).

MATERIALS AND METHODS

Methods

Data sources. Data were obtained from the Second National Health and Nutrition Survey (NHANES II) Mortality Study, a prospective cohort study that passively followed participants over 30 years of age who underwent a detailed examination ($n = 9,250$). NHANES II was conducted between 1976 and 1980 by the US National Center for Health Statistics (14). The response rate for adults aged 20–74 years who were selected and completed the examination was 68 percent (15).

Participants. Participants were classified as having previously diagnosed diabetes if they answered “yes” to the questions “Do you have sugar diabetes?” and “Did a doctor tell you that you had it?” ($n = 542$, 6.5 percent).

Baseline assessments. Data on participants’ age at interview, sex, race, years of education (less than high school, high school or greater), and personal health characteristics were obtained by interview (16, 17). The physical examination included measurements of height, weight, and blood pressure (18). Body mass index was calculated as weight (kg) divided by height (m) squared for each participant. Laboratory measures included standard blood assays for serum total cholesterol level (19).

To determine the effect of undiagnosed diabetes on estimates of the number of deaths attributable to diabetes, we conducted a subgroup analysis of participants selected for oral glucose tolerance testing at baseline who had fasted for at least 8 hours and had a fasting plasma glucose value ($n = 3,262$). By American Diabetes Association criteria (20), 225 participants (6.9 percent) with a fasting plasma glucose level of ≥ 126 mg/dl were classified as having undiagnosed diabetes.

Outcomes. Mortality status was ascertained for the years 1976–1992 by searching the National Death Index and the Social Security Administration’s Death Master File (21). There was no censoring due to loss to follow-up in this cohort; participants not found to be deceased by December 31, 1992, were assumed to be alive. Deaths were ascribed to cardiovascular disease if any of the following conditions were coded as the underlying cause of death according to the *International Classification of Diseases*, Ninth Revision: hypertensive heart disease (codes 402.0–402.9), ischemic heart disease (codes 410.0–414.9), cardiac arrest (code

427.5), unspecified heart failure (code 428.9), unspecified cardiovascular disease (code 429.2), cerebrovascular disease (codes 430.0–438.9), and diseases of the arteries, arterioles, and capillaries (codes 440.0–444.9).

Analysis

Weighting to the US population. All of the analyses were weighted to the US population at the midpoint of NHANES II (March 1, 1978) using SUDAAN statistical software, version 6.4 (Research Triangle Institute, Research Triangle Park, North Carolina) to account for the complex survey design and to obtain nationally representative estimates (22).

Baseline comparisons. Demographic characteristics and cardiovascular disease risk factors at baseline were compared for participants with diabetes versus those without diabetes using analysis of variance or Pearson’s χ^2 , after stratification by age group. All tests of significance were two-tailed. No corrections were made for multiple comparisons.

Proportional hazards analysis. To determine the independent relative hazard of mortality related to diabetes, we used proportional hazards models to adjust simultaneously for age, sex, race, education, behavioral risk factors (physical activity and smoking), and biologic risk factors (body mass index, systolic blood pressure, and total cholesterol level). There were no significant first-order interactions between diabetes status and any other covariate (all p ’s > 0.05). Graphs of the log-log plot of the relative hazards by time showed that the assumption of proportional hazards was met.

PAR analysis. The following formula was used to calculate the PAR for the entire cohort and then separately for each age group:

$$\text{PAR} = P_e (\text{RH} - 1) / [P_e (\text{RH} - 1) + 1],$$

where P_e is the prevalence of diabetes and RH is the fully adjusted relative hazard (23).

RESULTS

Characteristics and risk factors at baseline

Table 1 summarizes the characteristics of the cohort by age group and diabetes status at baseline. Expected trends were observed across age groups for participants with and without diabetes.

PAR and age

Unlike the relative hazard of death related to diabetes, which decreased with increasing age, the prevalence of diabetes increased from the youngest group to the oldest group (table 2). Thus, the PAR of all-cause mortality due to diabetes increased from the youngest ages to the oldest (table 2). A similar trend was seen for cardiovascular disease mortality (table 2).

TABLE 1. Baseline characteristics of 9,250 adults aged 30–75 years in the Second National Health and Nutrition Examination Survey (1976–1980), by age group and diabetes status†

Characteristic	Age 30–49 years		Age 50–64 years		Age 65–75 years	
	Diabetes (n = 69)	No diabetes (n = 3,264)	Diabetes (n = 220)	No diabetes (n = 3,082)	Diabetes (n = 253)	No diabetes (n = 2,362)
Age (years)	42.2* (0.8)‡	38.7 (0.1)	57.2 (0.4)	56.6 (0.1)	69.4* (0.2)	68.9 (0.8)
Female gender	68.3*	51.4	54.3	52.3	56.2	56.6
Race						
White	76.6*	87.4	85.0*	89.0	85.1*	89.0
Black	20.9	9.9	14.0	8.9	13.6	8.4
Other	2.6	2.7	1.0	2.2	1.2	2.2
Education less than high school	37.4	27.6	47.3	42.6	66.1	57.1
Physical activity level						
Inactive	24.0	22.8	34.3	25.0	31.7	26.7
Low	45.9	43.2	40.9	47.2	48.8	45.2
Moderate	18.4	22.8	15.0	16.9	9.3	16.4
High	11.8	11.1	9.9	10.9	10.2	11.7
Smoking status						
Current smoker	25.7*	42.2	27.3	33.6	12.5*	20.1
Past smoker	21.3	22.1	35.7	28.7	32.2	30.5
Never smoker	53.0	35.7	37.0	37.7	55.3	49.4
Alcohol use (drinks/week)						
0	55.9*	31.3	59.2*	38.3	73.4*	50.7
1–2	41.2	65.7	38.9	58.2	25.5	46.4
≥3	2.9	3.0	1.9	3.5	1.1	2.9
Body mass index§	28.1* (0.8)	25.5 (0.1)	28.2* (0.5)	26.2 (0.1)	27.6* (0.3)	26.0 (0.1)
Total cholesterol level (mg/dl)	219.2 (6.2)	210.5 (1.1)	236.1 (5.3)	237.0 (1.4)	229.5* (2.8)	235.6 (1.5)
Systolic blood pressure (mmHg)	133.6* (3.2)	122.8 (0.7)	144.0* (1.9)	136.3 (0.7)	152.6* (2.1)	145.4 (0.9)
Diastolic blood pressure (mmHg)	84.5* (1.9)	79.2 (0.6)	85.8 (1.1)	83.6 (0.5)	82.1 (0.9)	82.5 (0.5)
Cardiovascular disease¶	11.5*	5.3	18.2*	11.9	29.5*	17.3

* $p < 0.05$ for the age-specific contrast between persons with and without diabetes.

† Results are reported as mean values (with standard errors) or percentages and are weighted to the US population as of March 1, 1978.

‡ Numbers in parentheses, standard error.

§ Weight (kg)/height (m)².

¶ Cardiovascular disease at baseline, defined by self-reported history of heart attack, stroke, or angina.

PAR and gender

Overall, women had a slightly higher prevalence of diagnosed diabetes than men (4.7 percent vs. 3.8 percent, $p =$

0.05) (table 3). The relative hazard of mortality among women with diagnosed diabetes compared with those without diabetes was 1.83 (95 percent confidence interval (CI): 1.32, 2.55) for all-cause mortality and 2.67 (95 percent

TABLE 2. Prevalence of diabetes and percentage of deaths attributable to diabetes (population attributable risk) in the Second National Health and Nutrition Examination Survey (1976–1980), by age group at baseline

Age group (years) at baseline	Diabetes prevalence	All-cause mortality			Cardiovascular disease mortality		
		Adjusted relative hazard*	95% CI†	PAR‡	Adjusted relative hazard*	95% CI	PAR
30–49	1.9	2.7	1.2, 6.1	3.1	5.1	1.1, 24.0	7.2
50–64	5.7	1.9	1.4, 2.5	4.9	2.2	1.5, 3.1	6.4
65–74	9.2	1.8	1.5, 2.3	6.9	2.3	1.8, 3.0	10.7

* Adjusted for age, sex, race, education, smoking, physical activity, total cholesterol level, body mass index, and systolic blood pressure.

† CI, confidence interval; PAR, population attributable risk.

TABLE 3. Prevalence of diabetes, relative hazard of mortality, and population attributable risk of death related to diabetes among participants in the NHANES II* Mortality Study (1976–1992) aged 30–74 years at baseline, by method used to identify diabetes

Method used to identify diabetes	Diabetes prevalence	All-cause mortality			Cardiovascular disease mortality		
		Adjusted relative hazard†	95% CI*	Population attributable risk	Adjusted relative hazard†	95% CI	Population attributable risk
Self-report only‡							
Both sexes	4.3	1.9	1.5, 2.3	3.6	2.3	1.8, 2.8	5.2
Women	4.7	1.83	1.32, 2.55	3.8	2.67	1.83, 3.88	7.3
Men	3.8	1.90	1.49, 2.42	3.3	2.04	1.43, 2.91	3.8
Self-report or fasting glucose level§							
Both sexes	8.9	1.6	1.3, 2.0	5.1	1.8	1.3, 2.5	6.8
Women	9.6	1.85	1.29, 2.66	7.5	2.37	1.34, 4.22	11.6
Men	8.0	1.59	1.15, 2.21	4.5	1.65	0.99, 2.75	4.9

* NHANES II, Second National Health and Nutrition Examination Survey; CI, confidence interval.

† Adjusted for age, sex, race, education, smoking, physical activity, total cholesterol level, body mass index, and systolic blood pressure.

‡ Based on all 9,250 participants in the NHANES II Mortality Study. Diabetes was defined by self-report.

§ Based only on 3,262 participants in NHANES II who were selected for oral glucose tolerance testing. Diabetes was defined by a fasting glucose level of ≥ 126 mg/dl or self-reported diabetes.

CI: 1.83, 3.88) for cardiovascular disease mortality. The relative hazard of death for men with diagnosed diabetes compared with those without diabetes was also increased: 1.90 (95 percent CI: 1.49, 2.42) for all-cause mortality and 2.04 (95 percent CI: 1.43, 2.91) for cardiovascular disease mortality. The increased risk of all-cause and cardiovascular disease mortality for women with diagnosed diabetes translated to a higher PAR for women (3.8 percent for all causes and 7.3 percent for cardiovascular disease) compared with men (3.3 percent for all causes and 3.8 percent for cardiovascular disease) (table 3).

Influence of undiagnosed diabetes

In the foregoing analyses, individuals with undiagnosed diabetes were classified as “nondiabetic.” To determine whether reclassification of these individuals would influence the PAR, we conducted a subsidiary analysis in a subgroup of individuals who underwent oral glucose tolerance testing (table 3). Incorporation of undiagnosed diabetes led to an increase in prevalence (8.9 percent) but a decrease in the relative hazard of death among persons with undiagnosed and diagnosed diabetes compared with nondiabetics for all-cause mortality (relative hazard = 1.60, 95 percent CI: 1.28, 2.00) and cardiovascular disease mortality (relative hazard = 1.82, 95 percent CI: 1.32, 2.51) (table 3). Since the increase in prevalence was proportionally greater than the decrease in the relative hazard, the net effect on the PAR was positive.

DISCUSSION

Beyond confirming an excess risk of mortality among adults with diabetes, these results support two conclusions. First, at least 3.6–5.1 percent of all deaths and 5.2–6.8 percent of cardiovascular disease deaths are attributable to diabetes in the general US population aged 30–75 years.

PARs are even greater for women, whose relative hazard of mortality related to diabetes is greater than that for men. Second, the risk of mortality attributable to diabetes does not diminish with age, even though the relative hazard declines with age. This is due to the increase in the prevalence of diabetes with age, which increases the number of deaths related to diabetes and cancels out the effect of the decreasing relative hazard.

Strengths of this study include its large, nationally representative sample and 12–16 years of follow-up and the ability to evaluate attributable risk estimates for undiagnosed diabetes. Nonetheless, several limitations of this study should be kept in mind. First, there was potential misclassification of vital status, because a person not found to be deceased as of December 31, 1992, was assumed to be alive at the end of follow-up (21, 24, 25). However, since vital status was evaluated independently of diabetes status, misclassification is likely to have been nondifferential and would have produced a conservative bias (10). Second, diabetes status was only assessed at one point in time, at baseline. In populations similar to that of NHANES II, the incidence rate of progression from impaired glucose tolerance to diabetes is approximately 40 per 1,000 person-years (26). Participants with normal glucose tolerance or impaired glucose tolerance who developed diabetes during follow-up were considered to have no diabetes in this study. However, it is to be expected that they would have higher mortality than participants who never developed diabetes, biasing the relative hazard and PAR estimates towards the null (27). For these reasons, the results presented here may be underestimates of the burden of death due to diabetes.

Third, NHANES II did not include individuals living in institutions, including long-term care facilities and nursing homes (14). The National Nursing Home Survey estimated that approximately 60,000 people with diabetes aged 20–74 years were known to be in health care institutions and

nursing homes in 1977 (15). Such persons constitute 1.3 percent of the diagnosed diabetic population estimated from NHANES II (15). It is to be expected that these individuals would have greater mortality than persons who participated in NHANES II. Finally, there was nonresponse in NHANES II at each stage of the survey. In particular, for adults aged 20–74 years, only 68.0 percent of participants selected for the examination completed it and thus were included in the mortality study (14). On the other hand, respondents and nonrespondents did not differ significantly in terms of demographic or health-related characteristics (28).

Methods of estimating deaths attributable to diabetes face multiple biases. The commonly used approach involving national mortality statistics and death certificates suggests that diabetes contributes to 8.4 percent of deaths in the United States (5, 6). However it is suspected that this quantity is an underestimate, because death certificates do not include 37–47 percent of people who have diabetes and die (7–9) and they may underestimate diabetes deaths almost threefold (29). Opposing this underreporting on death certificates is the assumption that the etiologic fraction for deaths among people with diabetes is 100 percent. Similarly, the PAR calculation method used in this paper is likely to underestimate deaths attributable to diabetes, because of the factors described above. While it is difficult to assign an exact estimate to the proportion of deaths due to diabetes in the United States, given the multiple biases, our conservative estimate of 5.1 percent is relatively similar to previously published estimates from mortality statistics (5, 16), and it establishes an empirical lower limit for diabetes-related mortality.

As the prevalence of diabetes continues to increase in the United States, it will become more important to estimate the impact of diabetes on mortality in order to effectively assess progress in treating the disease (30). These results indicate that improvements in the treatment and prevention of diabetes may postpone these deaths and have an impact on life expectancy in the United States, even at older ages. This study suggests a need for research on barriers to and facilitators of treatment for people with diabetes and the development of approaches that promote cooperation by patients with their treatment regimen.

ACKNOWLEDGMENTS

Dr. Sharon H. Saydah was supported by grant T32 HL07024-26 from the National Heart, Lung, and Blood Institute. Dr. Frederick L. Brancati was supported by an Established Investigator Grant from the American Heart Association (Dallas, Texas).

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