All-Cause Mortality Risk Among a National Sample of Individuals With Diabetes

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OBJECTIVE — Little is known about the relative contributions of modifiable risk factors to overall diabetes mortality. The purpose of the current study is to *1*) assess the association between modifiable risk factors and all-cause mortality among a nationally representative sample of individuals with diabetes and 2) determine the population-attributable risk percent (PAR%) for these factors.

RESEARCH DESIGN AND METHODS — We analyzed data from a nationally representative sample of 1,507 adults over the age of 17 years with a self-reported diagnosis of diabetes from the Third National Health and Nutrition Examination Survey (NHANES III) mortality study. Our main outcome measures were all-cause mortality and PAR%. We used the Cox proportional hazard analysis to determine hazard ratios (HRs) for known diabetes risks and calculated PAR%.

RESULTS — Among adults with diabetes, the HRs for all-cause mortality were significant for individuals who had an A1C ≥8% (HR 1.65, 95% CI 1.11–2.45) or reported no regular physical activity (1.58, 1.24–2.02) or current tobacco use (1.77, 1.15–2.73). The population-attributable risk was 15.3% for A1C value ≥8%, 16.4% for no regular physical activity, and 7.5% for current tobacco use.

CONCLUSIONS — Health systems may consider prioritizing care to include smoking cessation, increasing physical activity, and moderate glycemic control among patients with diabetes. This study suggests that focusing on these areas may result in significant reductions in mortality in individuals with diabetes.

Diabetes Care 33:2360–2364, 2010

Optimal disease management for individuals with diabetes often involves significant lifestyle modifications (including diet, physical activity, and smoking cessation) in addition to complex medication regimens to control blood glucose, blood pressure, and serum lipid levels. These treatments have the potential to improve risk factors for morbidity and mortality among individuals with type 2 diabetes (1). Given the complexity of care for individuals with diabetes and the time limitations of health care providers (2), the relative association of each of these factors will be useful to inform policy and planning for appropriate diabetes care.

The purpose of the current study was to determine the association of modifiable risk factors for all-cause mortality among a nationally representative sample of individuals with diabetes and to assess the population-attributable risk percent (PAR%) for death for risk factors including blood pressure, lipid and glycemic control, smoking, and physical activity. Previous studies using data from the National Health and Nutrition Examination Survey (NHANES) have not examined the relative contribution of lifestyle factors such as physical activity (3) or have relied on older data that did not include information on glycemic control (4). In addition, previous studies have presented relative risk estimates for these factors, which do not necessarily give an indication of the public health implications of the exposure of interest or its effect on the population (3,5). In contrast, PAR% calculations are suitable in addressing public health policy questions regarding appropriate interventions, population-based treatment strategies, and quality improvement efforts (6).

RESEARCH DESIGN AND METHODS

— We used data from the Third National Health and Nutrition Examination Survey (NHANES III) mortality follow-up file (7). For this database, the National Center for Health Statistics linked NHANES III participants aged ≥17 years by probabilistic matching to the National Death Index to determine mortality status through the year 2000. For a selected sample of NHANES III records, the death certificates were reviewed to verify correct matches (7). Overall, 20,042 adult NHANES III participants were eligible for matching, of whom 3,384 were identified as deceased (7). The mean observation time between the NHANES III survey and ascertainment of mortality status was 7.58 years (95% CI 7.17–7.99). The underlying cause of death was based on ICD-9 codes from 1986 to 1998 and on ICD-10 codes from 1999 to 2000. Death was classified from heart disease for ICD-9 codes 390–398, 402, and 404–429 and ICD-10 codes I00–I09, I11, I13, and I20–I51. Cancer deaths were based on ICD-9 codes 140–208 and ICD-10 codes C00–C097. NHANES III was conducted between 1988 and 1994 and used a stratified multistage sampling design with oversampling of Mexican Americans, African Americans, and individuals over age 60 years. The survey consisted of multiple components including a household interview, a physical examination, and laboratory tests. Information on medical history

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Received 12 May 2010 and accepted 16 August 2010. Published ahead of print at http://care.diabetesjournals.org on 25 August 2010. DOI: 10.2337/dc10-0846.
The views expressed in this article are those of the author and do not necessarily represent the views of the Department of Veterans Affairs.

was obtained during the household interview, and a total of 1,507 adults reported a diagnosis of diabetes. Women who reported only gestational diabetes were excluded from our analysis. This study was approved by the Institutional Review Board at the VA Puget Sound Medical Center.

Exposure variables

Important lifestyle modifications and disease control variables were considered. Physical activity was classified as moderate or vigorous intensity based on MET intensity levels. Physical activity was based on a self-report during the month before the survey. Individuals were classified as inactive if they did not report engaging in any of the following activities during the previous month: walking, jogging, bike riding, swimming, aerobics, dancing, calisthenics, gardening, lifting weights, or other physical activity outside of their occupation. Individuals were considered to fulfill national recommendations for physical activity if they reported five or more episodes per week of moderate-intensity physical activity, or three or more episodes per week of vigorous-intensity physical activity. Individuals reporting some physical activity during the preceding month but not at the recommended levels were classified as obtaining insufficient physical activity (8). Current smokers were defined as people who had smoked >100 cigarettes during their lifetime and were still smoking.

Physical examination included measuring height, weight, blood pressure, and a blood draw. A1C levels were classified as <6%, between 6 and 7%, between 7 and 8%, and ≥8% to correspond to recent American Diabetes Association treatment guidelines (1). Individuals were considered to have hypertension if they had a measured blood pressure of ≥140/90 mmHg or reported being told by their physician that they had high blood pressure and were on an antihypertensive medication. BMI was calculated as the weight in kilograms divided by the squared height in meters (9). The National Heart, Lung and Blood Institute's definition for the cutoff points between normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2) were used (9). All lipid and lipoprotein analyses were conducted on venous blood serum samples. HDL level was available on all adults and was used to measure cholesterol control. Demographic information including age (in years), sex, race/ethnicity (white, African American, Hispanic, or other), education (less than high school, high school, or more than high school), and annual income were obtained at baseline during the interview portion of NHANES III.

Statistical analysis

Each observation was weighted to account for the unequal probability of selection that resulted from the survey cluster design, nonresponse, and oversampling of certain populations. Sampling weights were used to calculate population estimates, and sampling strata and clustering within primary sampling units were accounted for to estimate variances and test for significant differences. All analyses thus took into account the complex survey design and weighted sampling probabilities and were performed using Stata Statistical Software (Release 11; Stata Corporation, College Station, TX). We calculated hazard ratios (HRs) using Cox proportional hazards regression with attained age at the time of censoring as the time scale (10,11). We divided data into three age strata (age 17–50, 51–65, and >65 years). Analyses were stratified by age-group, such that stratified estimates (equal coefficients across strata but with a baseline hazard unique to each stratum) were then obtained. Participants were censored at the end of the follow-up period if they were still alive. Cox proportional hazard models were used to estimate the combined effect of risk factors associated with mortality, controlling for sociodemographic factors (annual income, race/ethnicity, sex, and education).

We calculated the PAR% for mortality among individuals with diabetes of known risk factors, including glycemic control, hypertension, hyperlipidemia, smoking, and physical inactivity. PAR% was calculated as prevalence among decedents $\times$ [(HR $-$ 1)/HR] $\times$ 100%, where prevalence refers to the prevalence of the risk factor among individuals who died, and the hazard ratio (HR) is a multivariable-adjusted hazard ratio for mortality (12). We calculated 95% CIs for PAR% using previously described methods (13). PAR% can be interpreted as the percentage by which mortality rates could be lowered in all individuals with diabetes if the given exposure was abolished, assuming that the observed association is causal.

RESULTS — Overall, 1,507 adults with diabetes were eligible for mortality follow-up. For NHANES III participants with diabetes, 865 were assumed to be alive by virtue of not being identified in the National Death Index, and 642 were deceased during the follow-up period. Overall, 53% of deaths were from cardiovascular disease, 17% were from cancer, and 29% were from other causes of death. The population characteristics of the sample and cumulative mortality by exposure group are displayed on Table 1. Older individuals and individuals with less education were more likely to have died in the follow-up period. Table 2 displays the results of the Cox proportional hazard model for death and the PAR% for each risk factor. Among adults with diabetes, the HRs for all-cause mortality were significant for individuals who had an A1C ≥8% (HR 1.65, 95% CI 1.11–2.45) or reported no regular physical activity (1.58, 1.24–2.02) or current tobacco use (1.77, 1.15–2.73). The population-attributable risk was 15.3% for A1C values ≥8%, 16.4% for no regular physical activity, and 7.5% for current tobacco use.

CONCLUSIONS — In this nationally representative sample of individuals with diabetes, we found three statistically significant risk factors for all-cause mortality. We estimate that mortality rates could be decreased by 15.3, 16.4, and 7.5%, respectively, if the following risk factors were eliminated: having an A1C of ≥8%, physical inactivity, or current smoking. There is evidence from several observational studies that higher levels of physical activity confer protection against premature coronary disease and early mortality. In a study using the NHANES mortality data, Rask et al. (5) also showed a similar effect of smoking and physical inactivity on mortality. This study did not focus specifically on individuals with diabetes or present PAR% (5). In a study of women with diabetes, the age-adjusted relative risk for cardiovascular disease was 0.54 (95% CI 0.39–0.76) for women who performed ≥4 h of moderate or vigorous exercise per week (14). Wei et al. (15) reported that the relative risk of mortality was 1.7 (95% CI 1.2–2.3) in 1,263 men with diabetes with low levels of physical activity followed on average for 12 years. In a national study, U.S. adults with diabetes who walked at least 2 h/week had a 39% lower all-cause mortality (16). Previous studies have shown that cigarette smoking is strongly associated with an increased risk of coronary heart disease among individuals with diabetes,

Table 1—Population characteristics and cumulative mortality of individuals with diabetes in NHANES III

Exposure variable	Total n in group at baseline (population estimate)	Total n (sample) (n = 1,507)	n who died by 2000 (sample)	Cumulative mortality by 2000 (%)	P	Prevalence of exposure among decedents (%)
Age (years)						
17–50	2,270,316	271	30	14	<0.001	11
51–65	3,165,854	467	141	23		22
>65 years	3,666,230	769	471	60		67
Female	4,998,374	847	324	36	0.93	55
Race/ethnicity						
African American	1,351,394	419	170	36	0.08	15
Mexican American	510,073	452	147	24		3.8
White	6,776,564	599	316	37		78
Education						
Less than high school	3,942,673	929	423	44	<0.001	54
High school	2,847,439	324	119	31		27
College	2,225,554	234	88	27		19
Low HDL (<40 for men, <50 for women)	4,096,364	631	244	36	0.05	61
A1C (%)						
<6	1,843,825	264	93	25	0.08	19
6–6.9	1,487,119	273	128	41		24
7–7.9	1,218,314	211	87	37		18
≥8	3,165,530	532	196	30		39
Blood pressure >140/90 or on an antihypertensive drug	4,829,033	884	414	42	<0.001	70
BMI (kg/m^2)						
<25	1,605,000	281	142	43	0.03	26
25–29.9	2,881,650	513	219	36		36
>30	3,546,169	539	171	37		37
Physical activity						
None	2,711,151	565	318	53	<0.001	45
Insufficient	3,478,195	532	177	26		28
Recommended	2,878,555	405	147	31		28
Smoker						
Never	3,747,780	692	276	33	0.23	38
Current	1,670,663	247	97	34		17
Former	3,669,688	566	269	10		45

even more so than individuals without diabetes, and quitting smoking decreases this excess risk substantially (17).

Our results are consistent with other studies that have identified a protective effect of moderate glucose control (3,18). Saydah et al. (3) used NHANES III data to examine A1C level and subsequent mortality among adults in the U.S. These au-

Table 2—Proportional hazards analysis results from all-cause mortality: NHANES III mortality follow-up

	Reference category	HR	95% CI	P	PAR%	95% CI
A1C (%)						
≥8	A1C <6%	1.65	1.11–2.45	0.01	15.3	1.6 to 27.8%
7–7.9		1.45	0.93–2.26	0.09	5.7	−1.8 to 13.4%
6–6.9		1.31	0.80–2.14	0.26	5.9	−5.6 to 18.0%
Low HDL*	HDL ≥40 for men, ≥50 for women	1.31	0.96–1.80	0.09	14.4	−5.3 to 31.9%
Hypertension†	No history of hypertension or blood pressure <140/90 mmHg	1.26	0.96–1.66	0.08	14.4	−4.7 to 32.0%
BMI ≥30 kg/m^2	BMI <30 kg/m^2	1.05	0.71–1.53	0.80	1.8	−15.1 to 17.1%
No physical activity	Insufficient or recommended levels	1.58	1.24–2.02	<0.001	16.4	6.0 to 26.8%
Current smoker	Nonsmoker	1.77	1.15–2.73	0.01	7.5	0.9 to 15.1%

PAR% = prevalence among decedents × [(HR − 1)/HR]. *<40 for men, <50 for women. †Blood pressure >140/90 mmHg or under treatment. Models control for age, sex, race/ethnicity, and education.

thors reported that among individuals with diabetes, having an A1C of ≥8% was associated with higher all-cause mortality risk (HR 1.68, 95% CI 1.03–2.74), compared with adults with an A1C of <6%, which is similar to our findings. However, this study did not examine the effect of physical activity or present population-attributable risks (3).

Despite clinical trial data to support blood pressure and lipid control among individuals with diabetes (19,20), these factors were not significant in our study, although the hazard ratios were in the expected direction. These nonstatistically significant findings may be a result of insufficient power in the current study. In addition, since NHANES III data were collected, the complexity of care for individuals with diabetes has increased, including the use of antihypertensive and antilipemic agents (21). Our results are consistent with older HNANES data from 1982 to 1984 on risk factors for mortality from all causes and from coronary heart disease among individuals with diabetes (4). This study reported that age, male sex, severe overweight (defined as a BMI ≥31.1 kg/m^2 for men and ≥32.3 kg/m^2 for women), and nonleisure time physical inactivity were associated with coronary heart disease mortality among persons with diabetes. Neither cholesterol nor hypertension were found to be associated with coronary heart disease mortality in this population of individuals with diabetes (4).

Limitations of our study include the potential biases introduced by the self-report of health conditions and level of physical activity. Because we do not know the actual duration of physical activity and do not have information on nonleisure physical activity, total activity levels may be underestimated. In addition, estimates of PAR% from observational data make an implicit assumption of causality: that abolishing exposure would, in fact, reduce risk to the level observed among unexposed individuals. We could also over- or underestimate PAR% because of the assumption that the prevalence of other risk factors would remain the same if one of them were changed (22). In practice, a particular intervention aimed at one risk factor could alter population levels of other risk factors, either favorably or unfavorably. PAR% also assumes that the other risk factors not included in our regression model are uncorrelated with the target exposure; in fact, risk factors may cluster within people. These limitations are balanced by the strengths of our study. Unlike measures of association such as relative risk, PAR% depends on both the strength of the association between the exposure and disease and the prevalence of the exposure in the population (6). In contrast, the relative risk offers a measure of the strength of association between the risk (e.g., degree of hyperglycemia) and mortality for the average individual. PAR% can assess the potential benefit to be gained for a population rather than for individual-level interventions.

In conclusion, we found significant associations between physical inactivity, smoking and poor glycemic control, and all-cause mortality among individuals with diabetes. Previous reports have demonstrated poor adherence to physical activity recommendations by individuals with diabetes (23) and low rates of physical activity and smoking cessation counseling by physicians (21). Clinicians and health systems may consider prioritizing their care to include avoidance of tobacco and increasing physical activity levels among all patients with diabetes (24). Population-based programs (e.g., quality improvement efforts) for individuals with diabetes may consider prioritizing these areas, especially given limited improvements in mortality rates among individuals with diabetes over the past 2 decades (25).

Acknowledgments— This study was supported by the Epidemiologic Research and Information Center, VA Puget Sound Health Care System, Seattle, Washington.

No potential conflicts of interest relevant to this article were reported.

K.M.N. conceived this study, acquired the data for analysis, and performed the statistical analysis. K.M.N., E.J.B., and T.K. developed the analysis plan, contributed to the discussion, and reviewed and wrote the manuscript.

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