Diabetes and the Risk of Infection-Related Mortality in the U.S.

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OBJECTIVE — To determine whether diabetes predicts infection-related mortality and to clarify the extent to which this relationship is mediated by comorbid conditions that may themselves increase risk of infection.

RESEARCH DESIGN AND METHODS — We performed a retrospective cohort study using the Second National Health and Nutrition Examination Survey Mortality Study of 9,208 adults aged 30–74 years in 1976–1980. We defined demographic variables, diabetes, cardiovascular disease (CVD), and smoking by self-report; BMI, blood pressure, and serum cholesterol from baseline examination; and cause-specific mortality from death certificates.

RESULTS — Over 12–16 years of follow-up, 36 infection-related deaths occurred among 533 adults with diabetes vs. 265 deaths in 8,675 adults without diabetes (4.7 vs. 1.5 per 1,000 person-years, $P < 0.001$). Diabetes (RR 2.0, 95% CI 1.2–3.2) and congestive heart failure (2.8, 1.6–5.1) were independent predictors of infection-related mortality after simultaneous adjustment for age, sex, race, poverty status, smoking, BMI, and hypertension. After subdividing infection-related deaths into those with ($n = 145$) and without ($n = 156$) concurrent cardiovascular diagnoses at the time of death, diabetic adults were at risk for infection-related death with CVD (3.0, 1.8–5.0) but not without CVD (1.0, 0.5–2.2).

CONCLUSIONS — These nationally representative data suggest that diabetic adults are at greater risk for infection-related mortality, and the excess risk may be mediated by CVD.

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A lthough diabetes is widely believed to predispose serious infection and the experimental literature supports an association between diabetes and infection, reviews of this topic have concluded that strong epidemiological evidence linking diabetes to serious infection is lacking (1–3). Individuals with diabetes might be at higher risk for moderate or severe infection-related morbidity caused by altered defense mechanisms, including the effects of hyperglycemia (4), obesity (5), and/or the effects of neuropathy and impaired tissue perfusion on injury and wound healing (6). Alternatively, individuals with diabetes may have a similar incidence of infection but a higher case-fatality rate from serious infections caused by altered host defenses and/or the increased presence of underlying disorders that predispose mortality. For example, cardiac disease is known to predispose patients to mortality from pneumonia (7) and septic shock (8). It may also be plausible that individuals with diabetes have poorer outcomes from infection or increased nosocomial infection caused by differential treatment. Only limited evidence exists that diabetes increases the risk of mortality from infection in general (9,10), and these studies failed to investigate potential mediators or confounders. Better information regarding the risk of serious infection related to diabetes would help define the public health burden of diabetes and possibly enhance our understanding of the mechanisms involved. Therefore, we sought to determine whether diabetes predicts infection-related mortality and to clarify the extent to which this relationship was mediated by cardiovascular disease (CVD) or adiposity.

RESEARCH DESIGN AND METHODS — The Second National Health and Nutrition Examination Survey (NHANES II) was a national probability survey of the U.S. civilian noninstitutionalized population from 1976 to 1980; the NHANES II Mortality Study includes a subsample of 9,252 adults aged 30–74 years who were followed passively for mortality through 1992 (11,12). All participants in the mortality study underwent complete history, physical, and laboratory testing at the time of the initial survey. The participants were traced through national death and/or social security indexes; if a participant was determined to be deceased, the death certificate was retrieved. Participants not determined to be deceased by 31 December 1992 were presumed to be alive. Two participants were excluded because identifying information wasn't available, and 42 participants who were known to be deceased were excluded because a death certificate wasn't available. This resulted in a study population of 9,208 individuals.

Exposure data were measured only at baseline. Participants underwent an interview that included recording of medical history and body measurements, physical examination, and blood testing (12). Participants who answered "yes" to the questions "Do you have diabetes or sugar

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diabetes?" and/or "Has a doctor told you that you have diabetes?" were classified as having diabetes. Duration of diabetes was determined by the response to the question "About how old were you when the doctor first told you that you had diabetes?" Assessment of baseline congestive heart failure (CHF) was based on the question "Has a doctor ever told you that you had heart failure?" Similarly, individuals who responded "yes" to the question "Has a doctor ever told you that you had a heart attack?" were classified as having had a previous heart attack. The respondents were classified as "smokers" if they answered "yes" when asked if they had smoked 100 cigarettes throughout their lifetime. The average of two seated blood pressure readings was recorded. Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or use of antihypertensive mediations. Standing height and weight were measured to calculate BMI. We divided participants into quintiles of BMI, with the 5th quintile defining obesity (BMI $\geq$30 kg/m^2). Fasting blood samples were analyzed for serum cholesterol using standard techniques. Household size and income data were used to identify those at or below the federal poverty level (12).

Causes of death were coded according to the International Classification of Diseases, 9th revision (ICD9). Underlying and contributing causes of death were recorded. Based on previous studies (9,13), we categorized a death as infection-related if an infection-related code was listed as an underlying or contributing cause of death. These included ICD9 codes 001–139, 320, 321, 326, 421, 460–466, 480–487, 510, 513, 567, 590, 599, 680–686, 711, and 730. To investigate the contribution of CVD outcomes to infectious mortality, we also identified death certificates that included ischemic heart disease (ICD9 codes 410–414), nonischemic nonvalvular heart disease (including CHF) (ICD9 codes 415–429), or cerebrovascular disease (ICD9 codes 430–438) as an underlying or contributing cause of death. With these data, we subdivided infection-related deaths into two groups: infection-related death with CVD (death certificate recorded both categories) and infection-related death without CVD (death certificate recorded infection but no cardiovascular diagnoses).

NHANES II used a complex sample design to ensure a representative national probability sample of the U.S. population (12). To adjust adequately for the sample weights, strata, and primary sample unit clusters, Stata 6.0 (Stata Corporation, College Station, TX) survey estimation commands were used. Totals, means, and proportions obtained using the appropriate design variables are point estimates for the entire population surveyed. Mortality rates were computed using the mortality density function (i.e., weighted number of deaths divided by the weighted person-years at risk in each stratum of interest). Follow-up time accrued from the date of baseline examination to the date of mortality from any cause or from 31 December 1992 for each individual. Cumulative mortality was calculated using a life-table approach based on weighted data (14). Log-rank tests were used to compare mortality in those with and without diabetes. Poisson regression (incorporating the strata, primary sample units, and sample weights) was used to calculate unadjusted and adjusted mortality rate ratios related to diabetes and selected comorbid conditions (15). All significance tests were two-tailed. Regression models were screened for pairwise interactions involving age or diabetes status. When significant interactions were found, stratified models were constructed.

RESULTS — A total of 8,675 adults without diabetes and 533 adults with diabetes were studied. We considered most individuals to have type 2 diabetes because only 28 reported onset before 30 years of age. Insulin use was reported by 134 participants, and use of oral diabetes drugs was reported by 215 participants. As expected, compared with their nondiabetic counterparts, adults with diabetes were older, more likely to have hypertension, more likely to be obese (BMI $\geq$30 kg/m^2), and more likely to have had a prior diagnosis of CHF or heart attack (Table 1).

During 12–16 years of follow-up, 2,103 deaths occurred, 301 of which were related to infection (Table 2). Most of the infection-related deaths were ascribed to pneumonia ($n = 174$, 58%) or sepsis ($n = 76$, 25%). Compared with their nondiabetic counterparts, diabetic women were at higher risk for all-cause and infection-related mortality (age-adjusted RR 1.9 [95% CI 1.5–2.3] and 2.4

[1.2–4.7], respectively), as were diabetic men (1.7 [1.4–2.1] and 1.7 [0.8–4.7], respectively). Using a life-table approach, the cumulative incidence of infection-related mortality by 75 years of age was significantly greater in those with diabetes than in those without (11.3 vs. 6.8%, $P <$ 0.001; Fig. 1).

A history of heart disease at baseline was also a significant predictor of infection-related mortality. Our analysis suggested that CHF was a stronger predictor of infection-related mortality than was heart attack. The age-adjusted RR of infection-related mortality for those with a history of CHF was 3.2 (95% CI 1.7–5.9, $P <$ 0.001), compared with age-adjusted RR of 1.5 (0.99–2.3, $P = 0.06$) for past heart attack.

In contrast, there was no relationship between adiposity and the risk of infection-related mortality. In fact, it seemed that obese adults (BMI $\geq$30 kg/m^2) were at marginally lower risk than their leanest counterparts (BMI $\leq$22 kg/m^2; age-adjusted RR 0.69; 95% CI 0.4–1.2, $P =$ 0.17). Likewise, there was no relationship between infection-related mortality and either hypertension, blood pressure, or total cholesterol (data not shown).

To determine the relationship of diabetes and CVD to infection-related mortality independent of potential confounders, we conducted a series of multivariate analyses (Table 3). We found that previous heart attack alone no longer predicted infection-related mortality after adjusting for age and sex, although CHF at baseline did. Therefore, we retained only CHF in the final model. After adjustment for age, sex, race, BMI, hypertension, smoking, poverty status, and CHF, diabetes remained a strong predictor of infection-related mortality (RR 2.0, 95% CI 1.2–3.2, $P = 0.009$). CHF was also a strong predictor of infection-related mortality (2.8, 1.6–5.1, $P = 0.001$). When our outcome definition was restricted to infection as the underlying cause, we found a similar result for diabetes (Table 3). No statistically significant relationship existed between adiposity and infection-related mortality.

We performed several subsidiary analyses. To assess the contribution of concurrent CVD to infection-related mortality, we repeated the multivariate analyses after subdividing infection-related deaths into those with ($n = 145$) and without ($n = 156$) CVD at the time of

Table 1—*Selected baseline characteristics of 9,208 adults by sex and baseline diabetes status*

	Women		Men	
Characteristic	With diabetes	Without diabetes	With diabetes	Without diabetes
n	303	4574	230	4101
Age (years)	56.5 ± 0.8	49.1 ± 0.3	58.8 ± 1.0*	48.9 ± 0.3
White	82.5	88.1	84.3	88.3
Smoker	39.2*	49.2	73.3	75.5
At or below poverty level	17.6*	11.6	13.9∗	7.7
Cholesterol (mmol/l)	6.0 ± 0.1	5.8 ± 0.03	5.8 ± 0.1	5.7 ± 0.03
Systolic blood pressure (mmHg)	144.0 ± 2.0*	128.9 ± 0.7	144.5 ± 1.6*	132.0 ± 0.6
Diastolic blood pressure (mmHg)	83.4 ± 1.0*	79.5 ± 0.4	85.5 ± 1.1*	82.95 ± 0.5
Hypertension	69.6*	37.2	64.5*	40.7
CHF	2.9*	0.77	3.9*	1.4
Heart attack	7.7*	2.5	15.5*	5.3
BMI (kg/m^2)	28.9 ± 0.51*	25.7 ± 0.12	26.8 ± 0.38*	25.9 ± 0.06
Quintiles of BMI (kg/m^2)				
≤22	16.4*	27.3	14.0	14.5
23–24.3	10.3*	21.3	20.8	21.1
24.4–26.5	11.7*	16.6	20.3	25.8
26.6–29.9	20.0*	16.4	24.1	24.8
≥30.0	41.5*	18.4	20.7	13.7

Data are % and mean ± SE and are weighted to account for the complex sampling design. *$P < 0.05$ for sex-specific comparison between adults with versus without diabetes.

death (Table 3). In these analyses, diabetes remained a strong predictor of infection-related death with CVD but was unrelated to infection-related death without CVD. The same pattern emerged for CHF.

To explore the potential impact of misclassification of diabetes status on the risk associated with diabetes, we reclassified 65 individuals whose death certificates listed diabetes as the cause of death as diabetic, with similar results for infection-related mortality (adjusted RR 2.4, 95% CI 1.6–3.6). Using an alternate definition of diabetes (use of insulin or oral medications and/or a fasting glucose level ≥7 mmol/l [126 mg/dl] and/or a 2-h glucose 211.1 mmol/l [200 mg/dl], 579 patients) did not substantially alter the risk of infection-related mortality (1.8, 1.2–2.7). Compared with nondiabetic participants, those who reported a duration of diabetes <2.5 years had a similar risk of infection-related mortality (2.4, 0.9–6.5) as those who reported a duration >12.5 years (1.9, 0.7–5.7). Finally, analyses restricted to those with presumed type 2 diabetes (age at onset ≥30 years) were not significantly different (1.7, 1.05–2.8).

There was modest evidence of an interaction between diabetes and age ($P = 0.066$ for diabetes × age). There was a strong relationship between diabetes and infection-related mortality in individuals <70 years of age at baseline (RR 2.5, 95% CI 1.4–4.4), whereas individuals with diabetes who were ≥70 years of age at baseline were not at increased risk (0.8, 0.3–2.4).

CONCLUSIONS — The data gathered during this study support three conclusions. First, diabetes is a strong predictor of mortality related to infection; the relationship between diabetes and infection-related mortality was independent of coexisting heart disease at baseline and other diabetes-related comorbidities. Second, of the several diabetes-related comorbid conditions we investigated, only CHF emerged as a strong independent

Table 2—*All-cause and infection-related mortality in 9,208 adults by sex and baseline diabetes status*

	Women		Men	
	With diabetes	Without diabetes	With diabetes	Without diabetes
Deaths, all causes (*n*)	118	745	131	1,109
All-cause mortality rate (per 1,000 person-years)	23.5	8.3	42.5	13.3
Age-adjusted RR (95% CI)	1.9 (1.5–2.3)	1.0	1.7 (1.4–2.1)	1.0
Infection-related deaths (*n*)	18	88	18	177
Infection-related mortality rate (per 1,000 person-years)	3.5	0.9	6.7	2.2
Age-adjusted RR (95% CI)	2.4 (1.2–4.7)	1.0	1.7 (0.8–4.7)	1.0

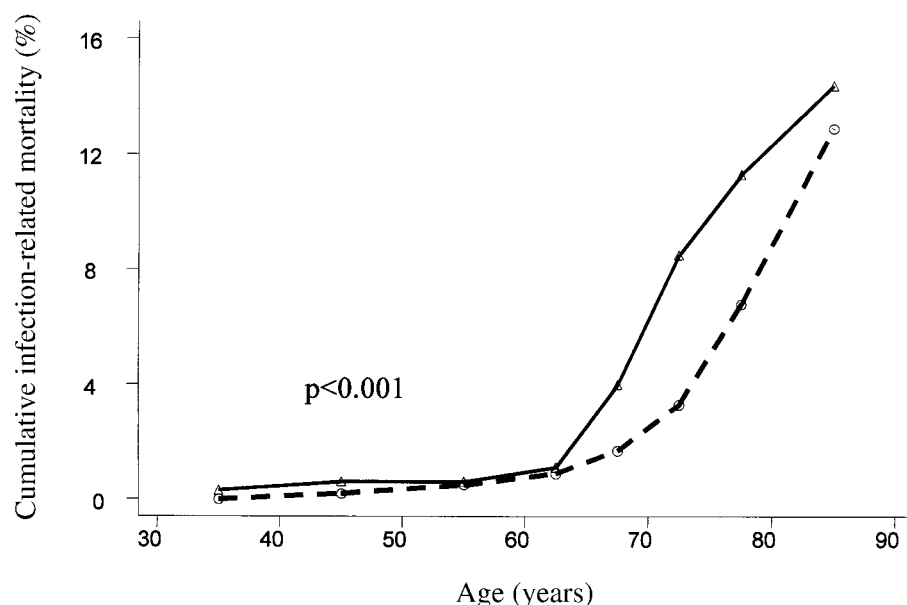Data are weighted to account for complex sample design of NHANES II.

Figure 1—*Cumulative mortality related to infectious diseases in 9,208 adults by age at follow-up and diabetes status at baseline (solid line, individuals with diabetes; dashed line, nondiabetic individuals). Data for life-table calculations were based on weighted estimates to account for the complex sampling design of NHANES II and thus provide nationally representative estimates. A log-rank test was used to compare the mortality curve.*

predictor of infection-related mortality. Third, the association of both diabetes and CHF with infection-related death was confined to individuals whose deaths were ascribed to CVD as well as infection. The strengths of this study include a nationally representative sample, long follow-up, availability of substantial information on exposures, and consideration of all available data on diseases that may have contributed to death.

Several limitations of the study should be noted. We had insufficient power to limit the analysis to the subgroup ($n = 3,172$) of this cohort with a valid oral glucose tolerance test. Therefore, diabetes status was ascertained only once, by self-report at baseline. Self-reported diabetes usually agrees with review of medical records (16) and is believed to be highly specific but only moderately sensitive (17). Harris et al. (18) estimated the prevalence of undiagnosed diabetes in the adult population at the time of NHANES II to be 3.2% and concluded that 86% of self-reported diabetic people actually had diabetes. Furthermore, one would expect diabetes to develop in additional individuals during the follow-up interval. However, misclassification of individuals with diabetes at baseline or those who developed diabetes

subsequent to the baseline evaluation as "nondiabetic" would tend to bias our risk estimates toward the null. Our sensitivity analyses with different definitions of diabetes gave similar results. Loria et al. (11) suggested that the NHANES II passive mortality follow-up design may have underascertainment of mortality, particularly for black participants. However, because differential ascertainment of mortality by diabetes status seems unlikely, such misclassification may affect rates but should not markedly alter relative risks. Death certificates have many limitations, such as low sensitivity for infectious diseases (19), lower likelihood for an infectious disease to be deemed the underlying cause of death when infection

is listed as a cause of death (13), and poor specificity for the major disease category ascribed to the death (20,21). Furthermore, a reporting bias may exist if physicians are more likely to record an infection for a participant known to have diabetes; significant systematic misclassification can produce spurious associations. Despite these limitations, death certificates remain a widely used and accepted tool in population-based research because of their uniform availability.

Four cohort studies have investigated infection-related mortality in diabetic participants. Of these, two studies (which did not have nondiabetic comparison groups) reported percentages of deaths caused by infection ranging from 4 to 8.7% (22,23). This compares with 14.5% in our study, which used a broader definition of infection-related mortality. Two cohort studies compared infection-related mortality in diabetic and nondiabetic individuals. Moss et al. (10) reported an age-standardized mortality ratio of 1.7 for older-onset diabetic individuals for pneumonia and influenza in a Wisconsin cohort of patients with diabetes. Gu et al. (9) analyzed NHANES I follow-up data and reported an age-adjusted diabetic mortality rate ratio for infection deaths of 2.3 for men and 1.8 for women. However, neither of these studies focused specifically on infection-related mortality, precluding more detailed comparison with our study. Liebovici et al. (24) found an increased prevalence of diabetes in individuals hospitalized for infections but similar mortality for diabetic versus nondiabetic patients. Studies have reached different conclusions regarding diabetes and the risk of pneumonia (25–28) and sepsis (29–31), which were the leading causes of death in our study. One reason for the divergent results may be reliance on a cohort of hospitalized patients,

Table 3—Adjusted RRs of infection-related death associated with diabetes and CHF

Outcome	Deaths (n)	Diabetes		CHF	
		RR	95% CI	RR	95% CI
Infection-related mortality	301	2.0*	(1.2–3.2)	2.8*	(1.6–5.1)
Infection as underlying cause	111	1.9	(0.9–4.0)	0.9	(0.3–3.5)
Infection-related death with CVD†	145	3.0*	(1.8–5.0)	5.2*	(2.6–10.6)
Infection-related death without CVD†	156	1.0	(0.5–2.2)	0.5	(0.2–1.7)

Data are adjusted for age, sex, race, diabetes, CHF, adiposity, smoking, poverty status, and hypertension. Weighted Poisson regression was used to account for the complex sample design of NHANES II. *Significant at $P < 0.01$; †CVD at death.

which may introduce unpredictable selection biases.

Our finding that CHF is a strong predictor of fatal infection is consistent with previous reports. CHF has been noted to predispose pneumonia (26,28). This may be caused by the effects of pulmonary edema on airway clearance, mucociliary function, and lymphatic drainage, which lead to decreased bacterial clearance (32). In contrast, although some laboratory evidence suggests an altered immune response in obesity (5), we found no evidence that degree of adiposity predicts infection-related mortality or influences the risk associated with diabetes.

With inadequate data on glycemic control, neuropathy, or lower extremity disease, we were unable to determine whether altered host-defense mechanisms are responsible for the increased risk of infection, and our data allow conclusion only about mortality rather than incidence of infection. However, our data suggest that CVD may mediate the increased susceptibility to infection-related mortality. Although the diabetes-specific risk of infection-related mortality was independent of heart failure or previous heart attack at baseline, much of the increased risk of infection could be explained by the finding that diabetes strongly predisposed infection-related death when ischemic heart disease, stroke, or heart failure at death was also present. In fact, when these deaths were excluded, participants with diabetes were at the same risk for infection-related mortality as those without diabetes. This suggests that when CVD develops in adults with diabetes, the two conditions increase the susceptibility to infection or increase the severity of infection, leading to higher risk of death. The premature CVD associated with diabetes may explain the increased risk before 70 years of age but not after.

Our results have three possible implications. First, they support the application of aggressive measures to prevent infection in adults with diabetes, including vaccination against pneumonia and influenza. Second, they suggest that prevention of diabetes-related CVD might significantly reduce the risk of fatal infection. Third, they highlight the need for further studies to ascertain the mechanisms underlying the relationship between diabetes and infection. One helpful step would be to include careful surveillance for infections as outcomes in future prospective studies of diabetes complications.

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