GHb Level and Subsequent Mortality Among Adults in the U.S.

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OBJECTIVE — To examine the association of hyperglycemia, as measured by GHb, with subsequent mortality in a nationally representative sample of adults.

RESEARCH DESIGN AND METHODS — We included adults aged ≥20 years who participated in Third National Health and Nutrition Examination Survey (1988–1994) and had complete information, including baseline diabetes status by self-report and measured GHb (n = 19,025) and follow-up through the end of 2000 for mortality.

RESULTS — In the overall population, higher levels of GHb were associated with increased risk of mortality from all causes, heart disease, and cancer. After adjustment for potential risk factors, the relative hazard (RH) for adults with GHb ≥8% compared with adults with GHb <6% was 2.59 (95% CI 1.88–3.56) for all-cause mortality, 3.38 (1.98–5.77) for heart disease mortality, and 2.64 (1.17–5.97) for cancer mortality. Among adults with diagnosed diabetes, having GHb ≥8% compared with GHb <6% was associated with higher all-cause mortality (RH 1.68, 95% CI 1.03–2.74) and heart disease mortality (2.48, 1.09–5.64), but there was no increased risk of cancer mortality by GHb category. Among adults without diagnosed diabetes, there was no significant association of all-cause, heart disease, or cancer mortality and GHb category.

CONCLUSIONS — These results highlight the importance of GHb levels in mortality risk among a nationally representative sample of adults with and without diagnosed diabetes and indicate that higher levels are associated with increased mortality in adults with diabetes.

Hyperglycemia has been associated with a wide range of adverse outcomes for individuals with glucose values both above and below the threshold for diabetes, including increased cardiovascular disease (CVD) and mortality (1). Studies have consistently found undiagnosed diabetes to be associated with increased risk of mortality (2–4), and many studies have also shown levels of glucose that are elevated, but not enough for a diagnosis of diabetes, such as impaired fasting glucose, to be associated with increased mortality (2–4).

However, most of these studies are based on fasting or postprandial glucose (1–4), and few are based on GHb levels (3,5–8). The GHb level may be a better indicator of hyperglycemia because it provides a measure of an individual's average glucose levels for the previous 3 months. Thus, it may provide a more stable snapshot of glucose levels when used in prospective cohort studies to examine the association of subsequent risk. Currently, GHb is monitored in the treatment of diabetes, and GHb targets for prevention of complications among individuals with diabetes have been established (9). Interest in the use of GHb for the diagnosis of diabetes is increasing (10), and an international effort is underway to standardize the measurement of GHb (11). This focus of GHb in clinical care measures (12) raises important questions about the long-term predictability of GHb.

Examination of the relationship of GHb with mortality reveals several areas of uncertainty, including whether the relationship of GHb with mortality is similar among individuals with and without diabetes from both prospective cohort studies and clinical trials. A few prospective cohort studies have examined the association of GHb with risk of mortality (5–8) and shown an increased risk of mortality with increasing GHb level. Only two studies included individuals with diabetes, but these studies did not examine GHb levels by diabetes status, and none were representative of the general U.S. population.

Recently published findings from three clinical trials among adults with diabetes have added to this uncertainty. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that lower GHb levels increased risk of mortality and did not decrease CVD events (13). Whereas the Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study showed that lowering of GHb levels was associated with a decrease in micro- and macrovascular events and deaths from CVD (14) and the Veterans Administration Diabetes Trial reported that lower GHb levels were not associated with a reduction in cardiovascular events (15). These findings have not led to any changes in glycemic control recommendations (16).

The Third National Health and Nutrition Examination Survey (NHANES III) is the first nationally representative survey to include a measure of GHb and has mortality status available through linkage to the National Death Index. The objective of this study was to examine the association of GHb with subsequent mortality in a nationally representative sample of U.S. adults.

RESEARCH DESIGN AND METHODS — We analyzed data among 20,024 adults aged ≥20 years who were sampled as part of NHANES III. NHANES III was conducted between 1988 and 1994 by the National Center for Health Statistics. A stratified multistage

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sample design was used to produce a nationally representative sample of the non-institutionalized U.S. civilian population (17). The survey included a physical examination, laboratory tests, and questionnaires on health- and nutrition-related topics. The overall response rate for adults aged ≥20 years who completed the interview and examination was 77% (18).

Main exposure

GHb was measured during the examination for all adults aged ≥20 years. GHb measurements were standardized to the Diabetes Control and Complications Trial (17). We analyzed GHb levels as categorical and continuous. For the categorical analysis, GHb levels were classified as <6%, between 6 and 7%, between 7 and 8%, and ≥8%. These levels were selected to correspond to the American Diabetes Association treatment guidelines (9).

Other baseline assessments

Participants' age, sex, race/ethnicity, education, and personal health characteristics were obtained by interview. Smoking status was categorized as current, past, or never. Current smoking was defined as self-reported smoking of at least 100 cigarettes during one's lifetime and currently smoking cigarettes. Physical examination included measuring waist circumference, height, weight, and blood pressure and drawing blood (17). BMI was calculated as weight in kilograms divided by the square of height in meters for each participant from the measured height and weight. Systolic and diastolic blood pressure was obtained from the mean of three to five blood pressure measurements. All lipid and lipoprotein analyses were conducted on venous blood serum samples (17). For the present analysis, we chose HDL cholesterol levels as an indicator of cardiovascular risk; HDL is available for all adults.

Previously diagnosed diabetes was determined by self-report. Women who reported diagnosis of diabetes only during pregnancy were not considered to have diagnosed diabetes.

Outcomes

NHANES III participants aged ≥17 years who had data available for matching were matched to the National Death Index (NDI) to determine mortality status. The NDI was searched through 31 December 2000 for follow-up. Linking of NHANES III and the NDI is conducted by probabi-

listic matching. The National Center for Health Statistics (NCHS) conducted the linkage and created scores for potential matches. For a selected sample of NHANES III records, NCHS reviewed the death certificate record to verify correct matches. Overall, there were 20,024 adult NHANES III participants eligible for mortality follow-up by linkage with NDI, of whom 3,384 were assumed to be deceased. A complete description of the methodology used to link NHANES III records to NDI is available (19). This study is based on the restricted-use NHANES III Linked Mortality File (20).

The underlying cause of death is based on ICD-9 codes from 1986 to 1998 and on ICD-10 codes from 1999 to 2000. Heart disease deaths were based on ICD-9 codes 390–398, 402, 404–429, and ICD-10 codes I00–I09, I11, I13, I20–I51. Cancer deaths were based on ICD-9 codes 140–208 and ICD-10 codes C00–C097. Cause of death codes based on ICD-9 and ICD-10 were selected for high comparability between the two coding methods (21).

For NHANES III participants with complete data for all variables included in the analysis ($n = 19,025$), there were 15,967 participants assumed to be alive and 3,058 assumed to be deceased. Among those assumed to be deceased, four participants were missing information on cause of death. Overall, there were 3,058 deaths from all causes, 1,058 deaths from heart disease, and 701 deaths from cancer during 159,879 person-years of follow-up. Person-years of follow-up was calculated for each participant based on the end of follow-up minus the date of examination in NHANES III.

Analysis

All analyses were weighted to the U.S. population using SUDAAN statistical software (version 9.1; RTI International, Research Triangle Park, NC) to account for the complex survey design and the stratified multistage cluster sample and to provide nationally representative estimates (17,18). Demographic characteristics, smoking status, body measurements, blood pressure, HDL cholesterol, diabetes status, and mean years of follow-up were reported for participants at baseline by GHb categories. Mortality per 1,000 person-years was calculated for each GHb category based on the weighted number of deaths and person-years. A log-linear Poisson model was used to calculate 95% CIs.

We constructed proportional hazards models with GHb as both a categorical variable and a continuous variable to determine the relative hazard (RH) of mortality associated with various levels of GHb. We used age as the time scale for analysis with left truncation. For cause-specific analyses (i.e., cancer mortality or cardiovascular mortality), a participant was censored at the age of death he or she died from a cause other than the specific cause of death of interest. We report the results for two proportional hazards models. The first was adjusted for sex and race/ethnicity. The second was adjusted for sex, race/ethnicity, education, smoking status, BMI, systolic blood pressure, and HDL cholesterol. There was a significant first-order interaction with GHb and diagnosed diabetes ($P < 0.05$) for all-cause and heart disease mortality. The results are presented overall and stratified by diagnosed diabetes status. There were no other significant first-order multiplicative interactions between GHb and the other covariates ($P > 0.05$).

To examine the association of GHb levels as a continuous variable with mortality, we graphed the relationship of GHb and death using the proportional hazard function to model GHb using a spline regression with three knots (22). Spline regression allows modeling of the relationship between GHb as a continuous variable and mortality to be nonlinear and allows examination of the function relationship.

RESULTS

Baseline comparisons

Overall, adults with GHb levels <6% were younger with a mean age of 45 years compared with ~60 years for adults with GHb levels >6% (Table 1). Race/ethnicity, education, smoking status, history of CVD, and diagnosed diabetes differed by GHb levels. Adults with GHb between 7 and 8% or >8% were also more likely to have risk factors for CVD including higher BMI, waist circumference, and systolic blood pressure and lower HDL cholesterol than adults with GHb <6%.

Overall adult population

Adults with GHb between 7 and <8% and those with GHb >8% had a higher risk of all-cause mortality compared with adults with GHb <6%, even after adjustment for potential confounders (Table 2). Figure 1A presents the relationship of

Table 1—*Baseline characteristics by GHb level among adults aged ≥20 years, NHANES III (1988–1994)*

	GHb <6%	6% ≤ GHb <7%	7% ≤ GHb <8%	GHb ≥8%
Sample size	15,974	1,937	362	752
Age (years)*	45.1 ± 0.5	61.1 ± 1.0	62.6 ± 1.3	59.6 ± 1.5
Male (%)	44.2 ± 0.7	49.7 ± 2.5	53.3 ± 3.7	39.9 ± 5.7
Race/ethnicity (%)*				
Non-Hispanic white	86.6 ± 0.8	72.3 ± 2.3	77.1 ± 3.2	76.6 ± 4.0
Non-Hispanic black	8.7 ± 0.6	22.6 ± 2.1	14.3 ± 2.6	17.1 ± 3.4
Mexican American	4.7 ± 0.4	5.2 ± 0.8	8.6 ± 1.5	6.3 ± 1.0
Education (%)*				
Less than high school	19.5 ± 1.0	37.2 ± 2.5	48.2 ± 4.2	32.7 ± 4.6
High school graduate	33.3 ± 0.9	33.7 ± 2.6	32.7 ± 3.8	35.5 ± 4.3
Some college or higher	47.2 ± 1.4	29.0 ± 3.3	19.1 ± 3.5	32.7 ± 4.6
Smoking status (%)*				
Current smoker	27.0 ± 1.3	28.6 ± 2.3	18.2 ± 3.4	20.7 ± 3.9
Past smoker	28.2 ± 1.0	32.0 ± 2.1	42.4 ± 4.7	46.9 ± 4.8
Never smoker	44.9 ± 1.2	39.4 ± 2.4	39.4 ± 4.4	32.3 ± 4.3
History of CVD (%)*	2.9 ± 0.2	10.4 ± 1.5	18.2 ± 4.6	18.2 ± 5.8
Self-report of angina (%)*	3.5 ± 0.3	9.9 ± 1.3	8.4 ± 2.7	14.6 ± 3.5
History of cancer (%)*	8.6 ± 0.6	16.4 ± 2.1	13.5 ± 3.3	16.2 ± 5.9
Diagnosed diabetes (%)*	1.5 ± 0.2	15.7 ± 1.6	61.9 ± 4.3	82.1 ± 3.3
BMI (kg/m^2)*	26.1 ± 0.1	29.2 ± 0.3	30.0 ± 0.7	31.1 ± 0.4
Waist circumference (cm)*	90.6 ± 0.3	101.7 ± 0.8	103.6 ± 1.5	107.2 ± 1.3
Systolic blood pressure (mmHg)*	121.7 ± 0.5	136.0 ± 1.0	139.6 ± 1.7	135.7 ± 1.6
Diastolic blood pressure (mmHg)	73.9 ± 0.2	76.7 ± 0.6	76.0 ± 0.9	74.8 ± 0.9
HDL cholesterol (mg/dl)*	52.3 ± 0.4	46.7 ± 0.6	43.1 ± 1.0	44.3 ± 1.5

Data are means ± SEM. *$P < 0.05$ based on ANOVA or χ^2.

GHb level and risk of all-cause mortality for all participants aged ≥20 years after adjustment for potential confounders. There seems to be a slight J-shaped relationship; however, there is no significant increased risk of all-cause mortality until GHb levels are >8%.

After adjustment for potential confounders, there was a threefold increased risk for heart disease mortality among all participants with GHb ≥8%, a 77% increased risk among participants with GHb between 7 and 8%, and a 66% increased risk among participants with GHb between 6 and 7% compared with participants with GHb <6%.

After adjustment for potential confounders, there was a greater than twofold risk for cancer mortality among adults with GHb ≥8% and no increased risk among participants with GHb between 7 and 8% or 6 and 7% compared with participants with GHb <6%.

Population with diagnosed diabetes
Among adults with diagnosed diabetes, after adjustment for potential confounders, there was a 68% increased risk of all-cause mortality for those with GHb >8% compared with individuals with GHb <6% (Table 2). There was no significant

increased risk for adults with GHb between 7 and 8% or 6 and 7%. Figure 1*B* presents the relationship of GHb level and risk of all-cause mortality among adults aged ≥20 years with diagnosed diabetes after adjustment for potential confounders. The relationship among adults with diagnosed diabetes appears to be slightly different compared with that for the overall population, with the risk of mortality increasing to GHb ~7% and then leveling off, although the 95% confidence bands include 1.0.

Adults with diagnosed diabetes and GHb ≥8% had a greater than twofold increased risk of heart disease mortality compared with adults with GHb <6%. The risk of heart disease mortality was not significant for GHb categories of 6 to 7% or 7 to 8% compared with GHb <6% after adjustment for potential confounders. There was no significant association of cancer mortality and GHb category among adults with diagnosed diabetes.

Population without diagnosed diabetes
Among adults without diagnosed diabetes, there was no increased risk of all-cause mortality with increased GHb level (Table 2). Adults without diabetes and

with GHb between 6 and 7% or 7 and 8% had higher mortality than those with GHb >8%, probably because of the small number of participants in the highest GHb category. The relationship of GHb level and risk of all-cause mortality for participants without diagnosed diabetes is similar to that for the overall population and appears to be a slight J-shaped relationship (data not shown). There was also no increased risk for heart disease mortality or cancer mortality among adults without diagnosed diabetes associated with increasing GHb category.

CONCLUSIONS — In this nationally representative sample, among adults aged ≥20 years, increasing GHb levels were associated with increased risk of all-cause mortality, heart disease, and cancer mortality. However, this association is mediated by the presence of diagnosed diabetes. Among adults with diagnosed diabetes, GHb ≥8% was associated with a 70% increased risk from all-cause mortality and a 150% increased risk from heart disease mortality. Among adults with diagnosed diabetes and GHb between 6 and 7% and 7 and 8%, there was no significant increased risk of all-cause mortality. However, there was a 90% increased risk

Table 2—RH (95% CI) for GHb and subsequent all-cause, heart disease, and cancer mortality among adults aged ≥20 years in NHANES III

	GHb <6%	6% ≤ GHb <7%	7% ≤ GHb <8%	GHb ≥8%
Overall population (n = 19,025)				
No. deaths/no. participants	2,174/15,974	520/1,937	120/362	244/752
All-cause mortality				
Mortality per 1,000 person-years	9.7 (8.65–26.63)	31.0 (25.7–81.4)	48.8 (33.5–114.5)	45.1 (28.0–99.9)
Model 1	1.0 (reference)	1.3 (1.1–1.5)	1.8 (1.4–2.5)	2.6 (1.9–3.8)
Model 2	1.0 (reference)	1.2 (1.0–1.4)	1.7 (1.3–2.4)	2.6 (1.9–3.6)
Heart disease mortality				
Mortality per 1,000 person-years	2.9 (2.5–7.7)	13.3 (9.7–32.3)	14.7 (7.3–28.0)	18.5 (10.6–39.3)
Model 1	1.0 (reference)	1.8 (1.3–2.5)	1.9 (1.1–3.1)	3.4 (2.0–6.1)
Model 2	1.0 (reference)	1.7 (1.2–2.4)	1.8 (1.1–2.9)	3.4 (2.0–5.8)
Cancer mortality				
Mortality per 1,000 person-years	2.6 (2.2–6.9)	5.9 (3.8–13.3)	8.1 (2.1–12.2)	14.82 (0.001–14.0)
Model 1	1.0 (reference)	0.80 (0.6–1.2)	1.03 (0.4–2.5)	2.90 (1.1–7.9)
Model 2	1.0 (reference)	0.73 (0.5–1.1)	0.93 (0.4–2.2)	2.64 (1.2–6.0)
Diagnosed diabetes (n = 1,455)				
No. deaths/no. participants	109/336	125/317	90/221	221/581
All-cause mortality				
Mortality per 1,000 person-years	35.1 (19.3–72.9)	58.6 (40.2–137.4)	58.8 (37.0–131.4)	55.74 (35.61–125.54)
Model 1	1.0 (reference)	1.1 (0.6–2.0)	1.4 (0.7–2.5)	1.8 (1.1–3.0)
Model 2	1.0 (reference)	1.0 (0.6–1.8)	1.1 (0.6–2.1)	1.7 (1.0–2.7)
Heart disease mortality				
Mortality per 1,000 person-years	11.0 (5.1–21.0)	32.6 (18.9–69.6)	15.9 (5.4–26.6)	23.0 (13.3–125.5)
Model 1	1.0 (reference)	2.3 (1.2–4.4)	1.4 (0.6–5.1)	2.3 (1.0–5.1)
Model 2	1.0 (reference)	1.9 (1.0–3.7)	1.1 (0.4–2.7)	2.5 (1.1–5.6)
Cancer mortality				
Mortality per 1,000 person-years	12.6 (0.001–10.9)	5.0 (1.4–7.7)	8.7 (0.001–8.4)	18.1 (0.001–15.7)
Model 1	1.0 (reference)	0.22 (0.04–1.05)	0.49 (0.09–2.65)	1.38 (0.29–6.67)
Model 2	1.0 (reference)	0.20 (0.05–0.90)	0.43 (0.08–2.28)	1.04 (0.25–4.24)
Nondiabetic population (n = 17,570)				
No. deaths/no. participants	2065/15638	368/1,620	30/141	23/171
All-cause mortality				
Mortality per 1,000 person-years	9.3 (8.3–25.5)	26.3 (20.8–67.0)	34.3 (51.6–64.9)	8.9 (3.7–16.1)
Model 1	1.0 (reference)	1.1 (0.9–1.4)	1.2 (0.7–2.2)	0.6 (0.3–1.1)
Model 2	1.0 (reference)	1.1 (0.9–1.3)	1.2 (0.7–2.2)	0.6 (0.3–1.1)
Heart disease mortality				
Mortality per 1,000 person-years	2.5 (2.0–6.4)	6.0 (3.8–13.6)	7.2 (0.1–7.3)	3.9 (0.1–4.0)
Model 1	1.0 (reference)	0.9 (0.6–1.3)	0.5 (0.1–2.1)	0.8 (0.3–2.4)
Model 2	1.0 (reference)	0.8 (0.6–1.2)	0.6 (0.1–2.3)	0.8 (0.3–2.5)
Cancer mortality				
Mortality per 1,000 person-years	2.5 (2.0–6.4)	6.0 (3.8–13.6)	7.2 (0.1–7.3)	3.9 (0.1–4.0)
Model 1	1.0 (reference)	0.9 (0.6–1.3)	0.5 (0.1–2.1)	0.8 (0.3–2.4)
Model 2	1.0 (reference)	0.8 (0.6–1.2)	0.6 (0.1–2.3)	0.8 (0.3–2.5)

Model 1: with age as the time scale, adjusted for sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other). Model 2: with age as the time scale, adjusted for sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), education (less than high school, high school graduate, or some college or higher), smoking status (current, past, or never), BMI (continuous), systolic blood pressure (continuous), and HDL cholesterol (continuous).

for heart disease mortality for adults with diabetes and GHb between 6 and 7%. There was no significant association of GHb with mortality among adults without diagnosed diabetes.

Previous studies that have examined the association of hyperglycemia and mortality using fasting glucose or post-challenge glucose levels have also shown an increased risk of mortality with increasing glucose levels (2–4). Hypergly-

cemia is also associated with an increased risk of incident CVD. A recent meta-analysis of >38 reports of hyperglycemia as a risk factor for CVD found an increased risk of CVD for all measures of hyperglycemia: fasting glucose, causal glucose, postchallenge glucose, and GHb level (1). Few of the studies included in the meta-analysis were nationally representative, and some studies did not take diabetes status into account. GHb levels

themselves have also been associated with an increased risk of incident disease including CVD among individuals with diabetes (23) and colorectal cancer among individuals with and without diabetes (24).

However, there is limited evidence on the association of GHb with mortality either among the diabetic population (25) or the general population (3,5–8). Among the diabetic population, one
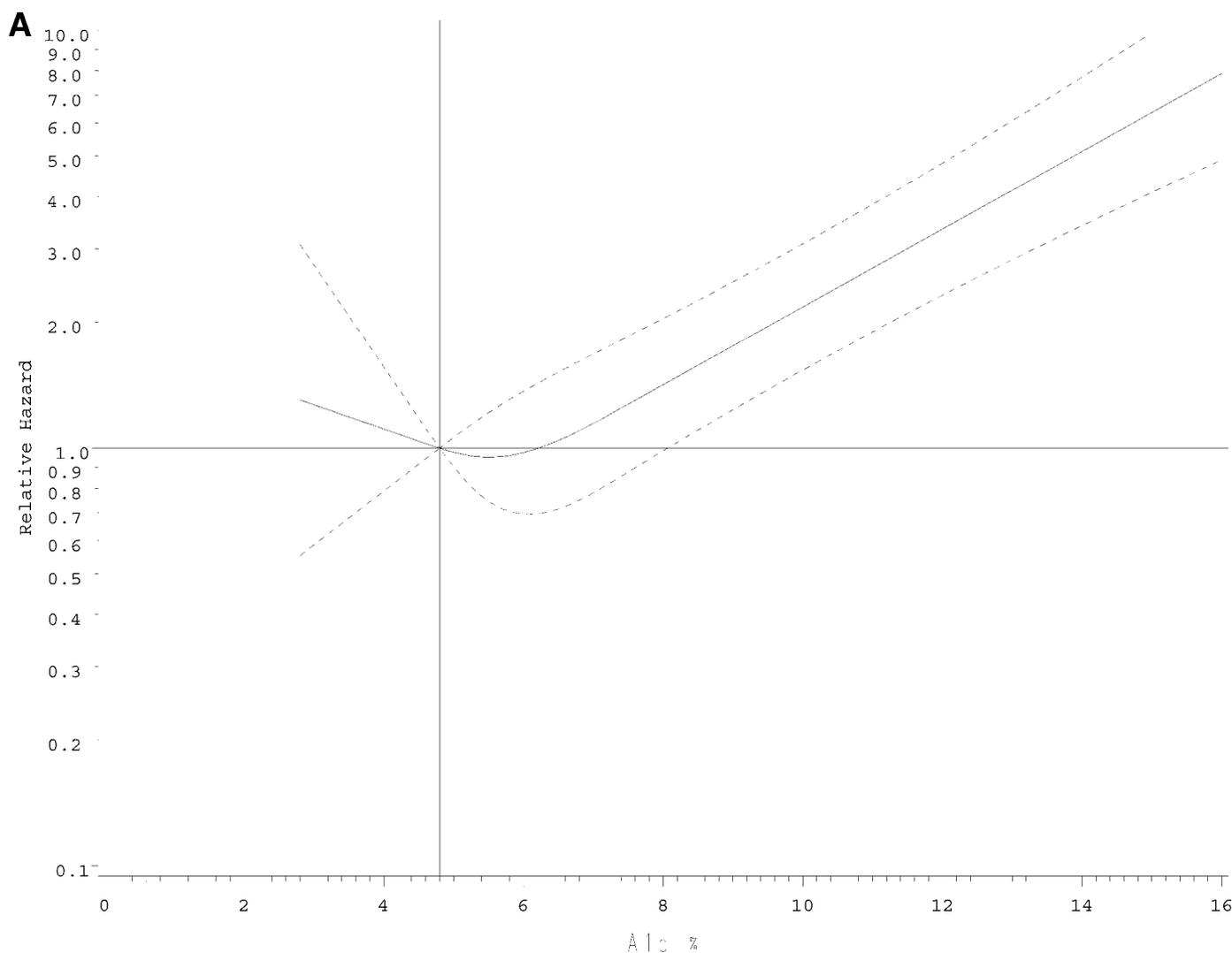
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y-axis: Relative Hazard (10.0, 9.0, 8.0, 7.0, 6.0, 5.0, 4.0, 3.0, 2.0, 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1)

x-axis: A1c % (0, 2, 4, 6, 8, 10, 12, 14, 16)

Figure 1—*RH of all-cause mortality for GHb levels compared with the referent of 4.8% (the 12.5th percentile, as indicated by the vertical line) among adults aged ≥20 years and older overall (A) and with diagnosed diabetes (B) in the U.S. NHANES III Linked Mortality File (19). Age was the time scale, adjusted for sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), education (less than high school, high school graduate, or some college or higher), smoking status (current, past, or never), BMI (continuous), systolic blood pressure (continuous), and HDL cholesterol (continuous). ——, Fitted three-knot spline relationship; – – –, pointwise upper and lower 95% CI limits.*

study showed that a 1% increase in GHb level corresponded to an increased risk of all-cause mortality, ischemic heart disease mortality, and diabetes mortality after adjustment for other risk factors (25). Among the nondiabetic population, the results have been mixed (5–8), with one study showing an increased risk among women but not in men after adjustment for potential confounders (8).

Most previous studies have either analyzed GHb categorically or continuously, but few have examined the shape of the relationship of GHb with mortality (5–8,25). Results presented from both the spline regression and the categorical analyses indicate that the association of GHb levels with mortality among the overall population and adults with diag-

nosed diabetes seems to differ. There seems to be a slight J-shaped relationship among the overall population, whereas there is a possible threshold effect in the diabetic population. This possible J-shape relationship was also observed in a study based in New Zealand (5). These authors found that GHb levels >7 and <4% were associated with increased mortality compared with GHb levels of 4–5%, among adults without a diagnosis of diabetes (5).

The American Diabetes Association recommends GHb of <7% for most individuals with diabetes (9). These recommendations are also promoted by the National Diabetes Education Program (26) and are based on evidence from randomized clinical trials showing that lowering GHb levels reduces diabetes mi-

crovascular complications (16) including CVD (16). The benefit of glucose control in preventing CVD in individuals with type 2 diabetes is still uncertain. Recently, three randomized clinical trials have addressed the question of whether lowering glucose levels in individuals with type 2 diabetes, measured by GHb, to the levels of adults without diabetes would reduce morbidity and mortality from CVD. The findings from these trials have, however, added uncertainty to this question (13,14), with two studies finding an increased risk of mortality and one study finding no increased risk (13,14). Our findings suggest that after taking into account other well-established CVD risk factors, lowering GHb <8% does not result in improvement in heart disease mor-
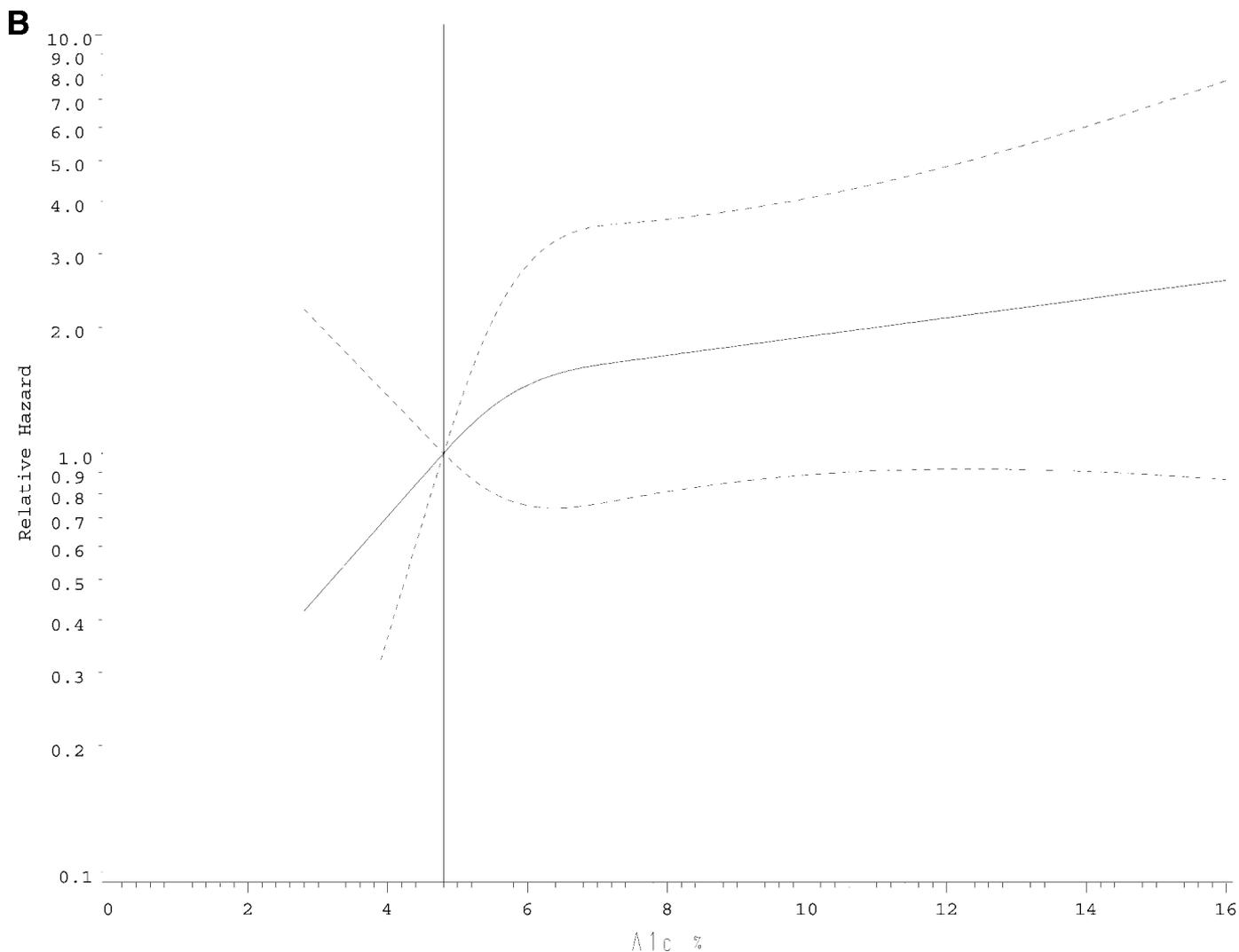
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Figure 1—*Continued.*

tality. In fact, among adults with diabetes, there was an increased risk of heart disease mortality associated with GHb between 6 and 7%. Further studies are needed to determine treatment strategies for the prevention of CVD in individuals with diabetes.

There are two main limitations of our analysis. The first is that we had relatively few deaths from certain causes and were, therefore, unable to look at specific types of cancer or other causes. Based on the smaller sample size for the population with diagnosed diabetes and the smaller number of deaths from cancer, the study may have been underpowered to detect a significant increase in risk. The second limitation is that GHb was only measured at baseline, and we have no information on how changes in GHb may or may not have influenced a participant's risk of mortality.

Nonetheless, this study also has a number of strengths. First, NHANES III is the first nationally representative survey to measure GHb levels among adults and the first study to provide nationally representative estimates of the risk of mortality associated with GHb levels, and second, there was relatively little loss to follow-up for mortality.

In summary, we found that GHb of ≥8% was associated with a greater than twofold increased risk of all-cause mortality in the overall population and >60% increased risk for all-cause mortality among adults with diabetes. There was also a significant increased risk of heart disease overall and for adults with diabetes.

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