Low Hemoglobin A_{1c} in Nondiabetic Adults

An elevated risk state?

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OBJECTIVE—To identify predictors of low hemoglobin A_{1c} (HbA_{1c}) (<5.0%) and to investigate the association of low HbA_{1c} with cause-specific mortality and risk of liver disease hospitalization.

RESEARCH DESIGN AND METHODS—Prospective cohort study of 13,288 participants in the Atherosclerosis Risk in Communities Study. Logistic regression was used to identify cross-sectional correlates of low HbA_{1c}, and Cox proportional hazards models were used to estimate the association of low HbA_{1c} with cause-specific mortality.

RESULTS—Compared with participants with HbA_{1c} in the normal range (5.0 to <5.7%), participants with low HbA_{1c} were younger, less likely to smoke, had lower BMI, lower white cell count and fibrinogen levels, and lower prevalence of hypercholesterolemia and history of coronary heart disease. However, this group was more likely to have anemia and had a higher mean corpuscular volume. In adjusted Cox models with HbA_{1c} of 5.0 to <5.7% as the reference group, HbA_{1c} <5.0% was associated with a significantly increased risk of all-cause mortality (hazard ratio [HR]: 1.32, 95% CI: 1.13–1.55) and of cancer death (1.47, 95% CI: 1.16–1.84). We also noted nonsignificant trends toward increased risk of death from cardiovascular causes (1.27, 95% CI: 0.93–1.75) and respiratory causes (1.42, 95% CI: 0.78–2.56). There was a J-shaped association between HbA_{1c} and risk of liver disease hospitalization.

CONCLUSIONS—No single cause of death appeared to drive the association between low HbA_{1c} and total mortality. These results add to evidence that low HbA_{1c} values may be a generalized marker of mortality risk in the general population.

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Hemoglobin A_{1c} (HbA_{1c}) is the standard measure of glucose control in persons with diagnosed diabetes mellitus and is now recommended for use as a diagnostic test for diabetes (1,2). The 2010 American Diabetes Association recommendations for use of HbA_{1c} as a diagnostic test will likely increase its use in persons without a prior diagnosis of diabetes. A number of studies have demonstrated that HbA_{1c} values, even below the diagnostic threshold of 6.5%, are associated with clinical outcomes including cardiovascular events (3–5), kidney disease (6), and total mortality (3,7–9). Previous studies in nondiabetic populations have also reported a J-shaped association of HbA_{1c} with all-cause mortality (3,7,10,11). The objectives of this study were to examine predictors of low HbA_{1c} (i.e., <5.0%) and investigate the association of low HbA_{1c} with all-cause and cause-specific mortality in a community-based population. Because recent studies have shown a high prevalence of liver disease among persons with low HbA_{1c} (10,12), we also examined the association between low HbA_{1c} and risk of liver disease hospitalization in this cohort.

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RESEARCH DESIGN AND METHODS

Study population

The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing community-based prospective cohort study of 15,792 middle-aged adults from four U.S. communities: Washington County, MD; suburban Minneapolis, MN; Jackson, MS; and Forsyth County, NC. The first study visit occurred between 1987 and 1989 with three follow-up visits that occurred approximately every 3 years (13,14). Visit 2 (1990–1992) was attended by 14,348 participants and is the baseline for the present analysis. Participants were included in our analyses irrespective of the previous occurrence of nonfatal events. We excluded participants who self-identified as other than white or black race ($n = 48$) or who were missing data on HbA_{1c} or other covariates of interest ($n = 970$), leaving a final sample size of 13,288 participants in this analysis. Institutional review boards at each clinical site approved the study protocol, and written informed consent was obtained from all participants.

Measurement of HbA_{1c}

Frozen whole-blood samples collected at ARIC visit 2 were thawed and assayed for the measurement of HbA_{1c} using high-performance liquid chromatography (Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer method in 2003 to 2004 and the Tosoh G7 method in 2007 to 2008; Tosoh Corporation) (15). Both instruments were standardized to the Diabetes Control and Complications Trial assay (16).

Outcomes

ARIC Study investigators conduct continuous surveillance for all hospitalizations and deaths among participants via annual phone calls to participants or proxies, and detailed information on deaths is obtained from family members, coroner reports, or health department death certificates. Methods for the ascertainment of death and its causes in ARIC have been

published previously (13). We classified deaths according to underlying cause, on the basis of coding from the ICD-9 and -10. We divided causes of death into the following major diagnosis categories defined by the ICD codes: *1*) cancers (ICD-10 codes of C00-D48, ICD-9 codes of 140–239); *2*) cardiovascular system (ICD-10 codes of I00–I99, ICD-9 codes of 390–459); *3*) respiratory system (ICD-10 codes of J00–J99, ICD-9 codes of 460–519); *4*) digestive system and liver (ICD-10 codes of K00–K93, ICD-9 codes of 520–579); and *5*) genitourinary system and kidney (ICD-10 codes of N00–N99, ICD-9 codes of 580–629). We also identified incident liver disease hospitalizations from hospital discharge records with an ICD-9 code for liver disease using the following ICD-9 codes (listed anywhere in the hospital discharge record): 570.0–573.9.

Covariates

All covariates were assessed during visit 2 (1990–1992), except education and physical activity, which were assessed during visit 1 (1987–1989). Covariates evaluated as potential confounders included: age (continuous), race/field center (Washington County, MD whites; Minneapolis, MN whites; Forsyth County, NC whites, Forsyth County, NC blacks; and Jackson, MS blacks), sex (male/female), education (less than high school, high school or equivalent, or more than high school), BMI (continuous), waist-to-hip ratio (continuous), cigarette smoking (current, former, or never), alcohol intake (current, former, or never), physical activity [assessed with the use of Baecke index (17)], family history of diabetes, presence of hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication during the previous 2 weeks), total cholesterol (continuous), HDL cholesterol (continuous), prevalent coronary heart disease, prevalent stroke, fasting glucose (continuous), hemoglobin concentration (continuous), red-cell mean corpuscular volume (MCV; continuous), total leukocyte count (continuous), and plasma fibrinogen levels (continuous). Further details about data collection methods in ARIC are described elsewhere (13,18).

Statistical analysis

We divided the baseline study population into groups according to clinical categories of glycated hemoglobin (<5.0, 5.0 to <5.7, 5.7 to <6.5, and ≥6.5% or diagnosed diabetes) (2). With the HbA_{1c} category of 5.0 to <5.7% as reference, we used logistic regression models to identify predictors of low HbA_{1c} (<5.0%) at baseline among persons with HbA_{1c} <5.7% (n = 9,254). To characterize the prospective association of low HbA_{1c} with all-cause and cause-specific mortality and risk of liver disease hospitalization, we used Cox proportional hazards models to estimate the hazard ratios (HRs) and their corresponding 95% CIs across baseline categories of HbA_{1c}. We verified that the proportional hazards assumption was met (19). Two models were used: model 1 was adjusted for age, sex, and race/field center, and model 2 was adjusted for the variables in model 1 plus total and HDL cholesterol, BMI, waist-to-hip ratio, hypertension, family history of diabetes, education level, alcohol use, physical activity, smoking status, hemoglobin, MCV, fibrinogen, and leukocyte count. We performed sensitivity analyses with additional adjustment for serum glucose, pulmonary function tests, white-cell differential, platelet count, and mean corpuscular hemoglobin. We formally tested for interaction by hemoglobin level. We also looked separately at the association among persons with and without anemia (defined as hemoglobin <13.5 g/dL for males and <12.0 g/dL for females) and after restricting the population to persons with ≥3 years of follow-up to address the potential for reverse causality. In all analyses, participants were censored if the participant was lost to follow-up, died of other causes, or reached the end of the follow-up period (31 December 2008). We used a restricted cubic spline model to investigate the continuous association between HbA_{1c} and risk of liver disease hospitalization. All reported P values are two-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed using Stata Statistical software version 11 (StataCorp, College Station, TX).

RESULTS—Of the 13,288 participants included in the study, 3,078 (23.2%) died by the end of follow-up period (maximum follow-up was 18 years). The demographic, clinical, and lifestyle characteristics of the study population are shown stratified by HbA_{1c} categories in Table 1. Overall, the mean age was 57 years, 55% were women, and 24% were black. Persons with higher HbA_{1c} were more likely to be older and current or former smokers.

The odds ratios and 95% CIs for predictors of low HbA_{1c} are shown in Table 2. Compared with those with HbA_{1c} values 5.0 to <5.7%, participants with HbA_{1c} values <5.0% were younger, had a lower BMI, were less likely to smoke, had lower total cholesterol levels, and were much less likely to have hypertension, a family history of diabetes, or a history of cardiovascular disease. Participants with HbA_{1c} <5.0% were more likely to have either low (<12.9 g/dL) or high hemoglobin (>14.7 g/dL).

Of the total 13,288 participants included in this study, 1,113 (8.4%) participants died of cancer, 1,085 (8.2%) died of cardiovascular disease, 235 (1.8%) died of respiratory system disease, 82 (0.6%) died of digestive system or liver disease, and 61 (0.5%) died of genitourinary system or kidney disease.

The HRs for all-cause and cause-specific mortality by baseline HbA_{1c} category are shown in Table 3. Comparing models 1 and 2, we observed that multiple adjustments strengthen the association of low HbA_{1c} with cause-specific and all-cause mortality, which is consistent with negative confounding. Using the group with HbA_{1c} of 5.0 to <5.7% as the reference group, HbA_{1c} values <5.0% were associated with a significantly increased risk of all-cause mortality (HR: 1.32, 95% CI: 1.13–1.55) and of cancer death (1.47, 95% CI: 1.16–1.84) in model 2. Low HbA_{1c} was also associated with an increased risk of cardiovascular system deaths (1.27, 95% CI: 0.93–1.75) and respiratory system deaths (1.42, 95% CI: 0.78–2.56), but these associations were not statistically significant, possibly owing to the smaller number of deaths due to these causes. Low HbA_{1c} was not significantly associated with risk of deaths related to the digestive system or liver disease (0.96, 95% CI: 0.34–2.71) or deaths due to conditions of the genitourinary system and kidney disease deaths (1.01, 95% CI: 0.23–4.42). Similar results were observed after adjustment for fasting serum glucose, pulmonary function tests, white-cell differential, platelet count, and mean corpuscular hemoglobin and when the analysis was restricted to persons with ≥3 years of follow-up (data not shown). Tests for interaction by hemoglobin level were not significant (all P values for interaction >0.1). However, in sensitivity analyses among persons with anemia (10.2% of the study population), we observed stronger associations of low HbA_{1c} with all-cause mortality (1.60, 95% CI: 1.07–2.39), cancer

Table 1—*Baseline characteristics of the study population by HbA_{1c} category at baseline (ARIC visit 2)*

	HbA_{1c} <5.0% (n = 1,005)	HbA_{1c} 5.0 to <5.7% (n = 7,957)	HbA_{1c} 5.7 to <6.5% (n = 2,067)	HbA_{1c} ≥6.5% or diagnosed diabetes (n = 2,259)
Demographics				
Age (years), mean (SD)	55.4 (5.5)	56.6 (5.7)	58.1 (5.7)	58.1 (5.7)
Female sex (%)	53.5	56.6	52.5	54.1
Center and race (%)				
Washington County, MD whites	27.7	26.8	21.0	24.6
Minneapolis, MN whites	31.9	31.0	19.6	18.6
Forsyth County, NC whites	25.3	27.0	18.7	16.7
Forsyth County, NC blacks	1.8	1.8	4.4	4.1
Jackson, MS blacks	13.3	13.4	36.3	36.0
BMI (kg/m^2), mean (SD)	26.5 (4.7)	27.0 (4.8)	29.0 (5.8)	31.0 (6.0)
Waist-to-hip ratio, mean (SD)	0.90 (0.09)	0.91 (0.08)	0.94 (0.07)	0.97 (0.07)
Education status (%)				
Less than high school	13.3	16.6	30.7	32.9
High school or equivalent	40.6	43.7	38.0	39.1
More than high school	46.1	39.7	31.3	28.1
Alcohol use (%)				
Current	64.1	62.4	49.0	41.8
Former	17.0	17.2	26.0	30.5
Never	18.7	20.4	25.1	27.7
Baecke physical activity index score, mean (SD)	2.49 (0.81)	2.51 (0.81)	2.36 (0.75)	2.32 (0.75)
Smoking status (%)				
Current	13.0	21.6	31.1	20.6
Former	42.9	38.2	35.2	39.0
Never	44.1	40.3	33.8	40.4
Clinical characteristics				
Hypertension (%)	27.1	28.6	42.6	58.0
Family history of diabetes (%)	19.4	21.2	24.2	37.6
History of stroke (%)	1.3	1.2	2.1	4.5
History of coronary heart disease (%)	2.6	4.6	6.9	10.6
HbA_{1c}, mean (SD)	4.8 (0.20)	5.4 (0.21)	6.0 (0.17)	7.5 (2.0)
Serum glucose (mg/dL), mean (SD)	97.9 (8.4)	100.5 (8.9)	106.5 (10.0)	175.3 (77.4)
Total cholesterol (mg/dL), mean (SD)	199.1 (36.7)	209.0 (37.8)	214.0 (39.7)	214.3 (44.3)
HDL cholesterol (mg/dL), mean (SD)	52.9 (18.6)	51.4 (17.0)	47.4 (15.0)	43.5 (14.4)
Hemoglobin (g/dL), mean (SD)	13.7 (1.5)	13.7 (1.3)	13.6 (1.3)	13.8 (1.4)
Anemia (%)	12.0	9.1	11.7	11.5
White blood cell count (per fL), mean (SD)	5.5 (1.6)	5.9 (2.0)	6.2 (1.9)	6.5 (2.0)
Mean red-cell volume (nL), mean (SD)	91.2 (5.3)	90.2 (4.6)	88.4 (5.5)	88.1 (5.4)
Fibrinogen (mg/dL), mean (SD)	276.8 (55.7)	294.3 (59.4)	317.0 (67.4)	322.2 (70.9)

mortality (1.94, 95% CI: 1.03–3.65), and cardiovascular death (1.51, 95% CI: 0.74–3.09). Among participants without anemia, the results were somewhat attenuated but remained significant for all-cause mortality (1.22, 95% CI: 1.03–1.46) and cancer death (1.35, 95% CI: 1.05–1.74).

Compared with persons with HbA_{1c} 5.0 to <5.7%, those persons with high HbA_{1c} (≥6.5%) also had an increased risk of all-cause mortality and deaths from cancer, cardiovascular disease, diseases of the respiratory system, digestive system and liver disease, diseases of the genitourinary system, and kidney disease (Table 3). Similar results were observed among persons with and without anemia, after adjustment for fasting serum glucose, pulmonary function tests, white-cell differential, platelet count, mean corpuscular hemoglobin, and when the analysis was restricted to persons with ≥3 years of follow-up (data not shown).

There were 353 hospitalizations for liver disease during follow-up. Fig. 1 presents the adjusted HRs and 95% CIs from the restricted cubic spline model for the association of baseline HbA_{1c} with risk of hospitalization for liver disease. We observed a pronounced J-shaped association; both very low and high HbA_{1c} values were associated with an increased risk of liver hospitalization in this population.

CONCLUSIONS—Compared with persons with HbA_{1c} in the normal range, we found that low HbA_{1c} values (<5.0%) were associated with an increased risk of all-cause mortality and death from various causes, including cancer. This finding is consistent with previous studies that have documented a J- or U-shaped association between HbA_{1c} and all-cause mortality (3,7,8,10,11). Our results are contrary

Table 2—*Adjusted* associations of low HbA_{1c} (<5.0% vs. 5.0 to <5.7%) among persons without diabetes* (N = 9,254)

Variable	OR (95% CI)
Age <50 years	1.19 (0.98–1.45)
Age 50–59 years	1.00 (reference)
Age ≥60 years	**0.67 (0.57–0.79)**
Female (vs. male)	0.84 (0.69–1.02)
Field center and race	
Washington County, MD whites	1.00 (reference)
Minneapolis County, MN whites	0.86 (0.72–1.04)
Forsyth County, NC whites	1.06 (0.87–1.28)
Forsyth County, NC blacks	1.18 (0.70–2.03)
Jackson County, MS blacks	1.04 (0.82–1.33)
Hypercholesterolemia	**0.66 (0.55–0.80)**
BMI categories (kg/m^2)	
<25	1.00 (reference)
25–30	**0.85 (0.73–0.98)**
>30	**0.73 (0.60–0.89)**
Hypertension	1.13 (0.96–1.32)
Family history of diabetes	0.89 (0.76–1.06)
Education status	
Less than high school	1.00 (reference)
High school or equivalent	1.04 (0.84–1.29)
College or above	1.20 (0.96–1.49)
Alcohol use	
Current	1.00 (reference)
Former	1.08 (0.89–1.30)
Never	0.93 (0.77–1.13)
Baecke physical activity index score	
Quartile 1 (<1.75)	1.00 (reference)
Quartile 2 (1.75–2.25)	1.09 (0.87–1.35)
Quartile 3 (2.25–3.0)	0.89 (0.72–1.10)
Quartile 4 (>3.0)	0.83 (0.67–1.03)
Smoking status	
Current	1.00 (reference)
Former	**1.89 (1.51–2.36)**
Never	**1.86 (1.47–2.34)**
History of stroke	1.43 (0.80–2.56)
History of coronary heart disease	**0.65 (0.43–0.98)**
Hemoglobin (g/dL)	
Quartile 1 (<12.9)	**1.35 (1.08–1.68)**
Quartile 2 (12.9–13.7)	1.00 (reference)
Quartile 3 (13.8–14.7)	1.17 (0.95–1.44)
Quartile 4 (>14.7)	**1.27 (1.04–1.55)**
WBC count (per fL)	
Quartile 1 (<4.8)	1.00 (reference)
Quartile 2 (4.8–5.7)	0.86 (0.72–1.02)
Quartile 3 (5.7–6.9)	**0.75 (0.62–0.90)**
Quartile 4 (>6.9)	**0.64 (0.51–0.79)**
Mean red-cell volume (nL)	
Quartile 1 (<87)	1.00 (reference)
Quartile 2 (87–90)	1.25 (0.98–1.59)
Quartile 3 (90–93)	**1.50 (1.19–1.89)**
Quartile 4 (>93)	**2.25 (1.79–2.84)**
Plasma fibrinogen level (mg/dL)	
Quartile 1 (<260)	1.00 (reference)
Quartile 2 (260–295)	0.88 (0.74–1.03)
Quartile 3 (295–337)	**0.60 (0.50–0.74)**
Quartile 4 (>337)	**0.68 (0.55–0.84)**

OR, odds ratio; WBC, white blood cell. *Model was adjusted for all listed variables. Boldface estimates indicate a P value of < 0.05.

to a recent analysis of the European Prospective Investigation of Cancer-Norfolk Study that reported no increase in risk of mortality at low normal HbA_{1c} values in a relatively homogenous population of Caucasians (20). The debate regarding the HbA_{1c}–mortality association also extends to the mortality curves for fasting and 2-h glucose, which are reported to be J-shaped in some studies (21–24). No single cause of death appeared to drive the association between low HbA_{1c} and risk of death in our study. Prior studies have suggested that liver disease may be an important contributor to low HbA_{1c} values (10,12). Consistent with this hypothesis, we observed that low HbA_{1c} values were associated with an increased risk of hospitalization due to liver disease in the ARIC Study population.

The exact mechanisms underlying the association of low HbA_{1c} values with increased risk of death are not known. We found that low HbA_{1c} values were significantly associated with higher mean red-cell volume and low hemoglobin. Other studies have demonstrated associations of red-cell indices with long-term mortality in the general population (25,26). The etiology of these relationships is largely unclear but may reflect that some disease processes affect red-cell turnover and thus HbA_{1c}. Whereas high HbA_{1c} values are almost entirely determined by circulating glucose levels (27), it is probable that nonglycemic factors such as red-cell turnover may be of disproportionate importance in the low range of HbA_{1c}. Our observations suggest low HbA_{1c} values may be a general marker of ill health, analogous to the well-documented U-shaped association between cholesterol and mortality (28–30). There is strong evidence that some disease processes reduce circulation of cholesterol-bearing lipoproteins (28). Low HbA_{1c} values may characterize a mix of healthy people and a group in which low HbA_{1c} is a marker or signal of underlying health issues, such as liver disease or early stages of cancer (3,10). This hypothesis is consistent with the negative confounding observed in our study; once traditional risk factors for death were added to our models, the association of low HbA_{1c} with all-cause mortality and cause-specific mortality became stronger.

Certain limitations should be considered in interpreting the results of this study. We were limited to information available from the death certificate for the classification of the underlying cause of death, which may have resulted in misclassification,

Table 3—*Adjusted HRs (95% CI) for cause-specific mortality by HbA_{1c} category*

	HbA_{1c} <5.0%	HbA_{1c} 5.0 to <5.7%	HbA_{1c} 5.7 to <6.4%	HbA_{1c} ≥6.5% or self-reported diabetes
All-cause mortality (n = 3,078)				
Model 1*	1.14 (0.98–1.34)	1.00 (reference)	**1.56 (1.42–1.72)**	**2.32 (2.13–2.53)**
Model 2**	**1.32 (1.13–1.55)**	1.00 (reference)	**1.31 (1.18–1.45)**	**1.82 (1.66–2.01)**
Deaths from cancer (n = 1,113)				
Model 1*	**1.28 (1.02–1.61)**	1.00 (reference)	**1.34 (1.14–1.61)**	**1.42 (1.21–1.67)**
Model 2**	**1.47 (1.16–1.84)**	1.00 (reference)	1.16 (0.98–1.36)	**1.24 (1.05–1.47)**
Deaths from cardiovascular disease (n = 1,085)				
Model 1*	1.04 (0.76–1.42)	1.00 (reference)	**1.95 (1.65–2.31)**	**3.64 (3.15–4.20)**
Model 2**	1.27 (0.93–1.75)	1.00 (reference)	**1.51 (1.27–1.79)**	**2.40 (2.05–2.82)**
Deaths from respiratory system disease (n = 235)				
Model 1*	1.31 (0.76–2.25)	1.00 (reference)	**2.18 (1.58–3.02)**	**1.95 (1.39–2.74)**
Model 2**	1.42 (0.78–2.56)	1.00 (reference)	**2.02 (1.43–2.87)**	**1.97 (1.35–2.89)**
Deaths from digestive system and liver disease (n = 82)				
Model 1*	0.88 (0.31–2.46)	1.00 (reference)	1.22 (0.67–2.22)	**1.75 (1.02–3.00)**
Model 2**	0.96 (0.34–2.71)	1.00 (reference)	1.00 (0.54–1.83)	1.26 (0.70–2.26)
Deaths from genitourinary system and kidney disease (n = 61)				
Model 1*	0.94 (0.22–4.02)	1.00 (reference)	1.57 (0.71–3.44)	**4.95 (2.72–9.00)**
Model 2**	1.01 (0.23–4.42)	1.00 (reference)	1.29 (0.58–2.87)	**3.17 (1.63–6.15)**

Boldface estimates indicate a P value of < 0.05. *Model 1: adjusted for age, sex, race, and field center. **Model 2: adjusted for variables in model 1 plus total and HDL cholesterol, BMI, waist-to-hip ratio, hypertension, family history of diabetes, educational level, alcohol use, physical activity, smoking status, hemoglobin, MCV, fibrinogen, and leukocyte count.

particularly for the noncancer and noncardiovascular outcomes (31–33). We also did not have data available on iron indices, reticulocyte count, or red-cell distribution width. Nonetheless, the ARIC population is a large, diverse cohort with virtually complete follow-up for vital status and comprehensive information on important confounders and major risk factors for mortality. To our knowledge, this study is one of the first comprehensive examinations of the association of low HbA_{1c} with cause-specific mortality in a general population.

In conclusion, our results add to the evidence that low HbA_{1c} values may be a marker of elevated mortality risk in the general population. With new recommendations for the use of HbA_{1c} for diagnosis of diabetes, HbA_{1c} testing will undoubtedly increase. To the extent that HbA_{1c} is adopted for diabetes screening, clinicians will frequently observe HbA_{1c} values in the normal range, including low normal values. Additional work should focus on understanding the nonglycemic determinants of HbA_{1c} and the mechanisms that explain why low HbA_{1c} values in some individuals may reflect an elevated risk state.

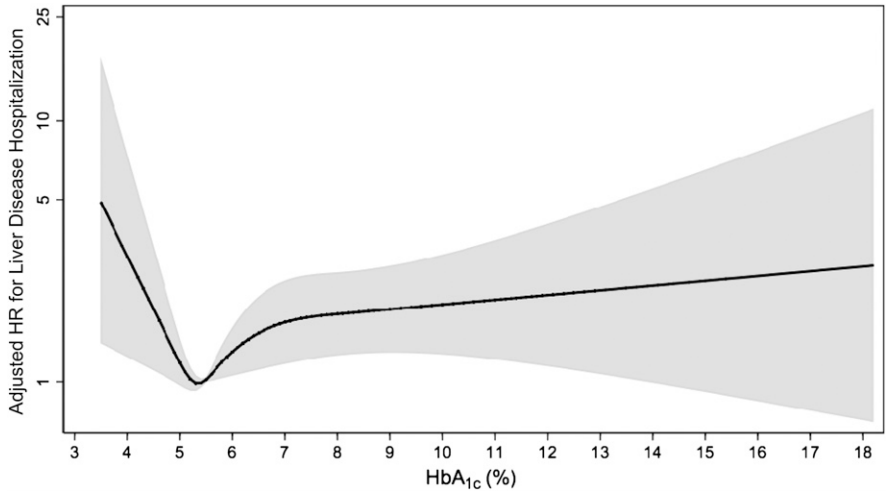

Figure 1—*Adjusted HRs (95% CI) for liver disease hospitalization by baseline HbA_{1c} value. The HR is expressed per absolute increase in one percentage point in the HbA_{1c} value at baseline. The shaded area is the 95% CI from the restricted cubic spline model. The model is centered at the median (5.5%) with knots at the 20th, 40th, 60th, and 80th percentiles. The HRs were adjusted for age, sex, race, field center, total and HDL cholesterol, BMI, waist-to-hip ratio, hypertension, family history of diabetes, education level, alcohol use, physical activity, smoking status, hemoglobin, MCV, fibrinogen, and leukocyte count. The HRs are shown on a natural log scale.*

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V.A. analyzed data, wrote the manuscript, reviewed and edited the manuscript, and contributed to discussion. A.L.C.S. analyzed data, reviewed and edited the manuscript, and contributed to discussion. E.S. reviewed and edited the manuscript and contributed to discussion. V.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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