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Elevated Hemoglobin A_{1c} (HbA_{1c}) in Adults without a History of Diabetes in the U.S.

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Objective: to examine the prevalence and correlates of elevated HbA_{1c} in a large, nationally representative sample of adults without diabetes in the United States.

Research Design and Methods: we analyzed data from 15,934 participants without diagnosed diabetes aged 20 and older who had HbA1c measurements in the 1999-2006 National Health and Nutrition Examination Survey (NHANES), a cross-sectional and nationally representative sample of the U.S. population.

Results: The overall prevalence of HbA1c >6% was 3.8% corresponding to 7.1 million adults in the U.S. population. Approximately 90% of these individuals had fasting glucose ≥ 100 mg/dl. Older age, male gender, non-Hispanic black race/ethnicity, hypercholesterolemia, higher body mass index, and lower attained education were significantly associated with having a higher HbA1c level even among individuals with normal fasting glucose (<100 mg/dl) and after multivariable adjustment.

Conclusions: A single elevated HbA1c level (HbA1c >6%) is common in the general population of adults without a history of diabetes and is highly reliable for the detection of elevated fasting glucose. Non-diabetic adults with elevated HbA1c are likely to have impaired fasting glucose and an array of other risk factors for type 2 diabetes and cardiovascular disease.

Hemoglobin A_{1c} (HbA_{1c}) is an integrated measure of circulating glucose levels and tracks well in individuals over time. Epidemiologic studies have shown that HbA_{1c} values in non-diabetic adults predict incident diabetes (1-5), cardiovascular disease morbidity and mortality (6-10) and total mortality (7). In these studies, HbA_{1c} values well within in the "normal" range (i.e., HbA_{1c} <6%) were independently associated with clinical outcomes. There is presently renewed interest in utilizing HbA1c for the diagnosis and/or screening for diabetes mellitus (11), however there have been few epidemiologic investigations of HbA1c in non-diabetic adults. The objective of the present study was to examine the prevalence and correlates of elevated HbA_{1c} in a large, nationally representative sample of U.S. adults without diagnosed diabetes who participated in the National Health and Nutrition Examination Survey (NHANES 1999-2006). We hypothesized that (a) elevated HbA1c levels (e.g. HbA1c >6%) are common in the general population of non-diabetic adults in the U.S. and; (b) HbA1c levels would be associated with risk factors for type 2 diabetes and its complications even in the absence of elevated glucose levels.

RESEARCH DESIGN AND METHODS

Study Population: The NHANES is an ongoing cross-sectional, multistage, stratified, clustered probability sample of the U.S. civilian non-institutionalized population conducted by the National Center for Health Statistics (NCHS), a branch of the Centers for Disease Control (12). Detailed in-person interviews, physical examinations, and blood samples were obtained from 18,986 participants aged 20 or older in the 1999-2006 surveys who participated in the mobile examination visit. For the present study, we excluded those individuals who reported that a doctor or health-care profession had every told them they had diabetes (N=1900), were missing information on diabetes status (N=288), or who were missing HbA1c data (N=986).

The protocols of conduct for the NHANES were approved by the NCHS institutional review board and informed consent was obtained from all participants.

Fasting Plasma Glucose Subsample: Approximately one half of NHANES participants were sampled to attend the morning session. These participants were instructed to fast at least nine hours prior to the appointment time. Fasting plasma glucose values are available for those adults 20 and older who attended the morning examination and were fasting 8 or more hours (N=9232). Our analyses of fasting glucose were limited to the fasting subpopulation of adults without diabetes who were non-missing HbA1c data (N=7772). In the plasma glucose fasting subsample, we conducted analyses comparing HbA1c levels among individuals with normal fasting glucose (<100 mg/dl), impaired fasting glucose (IFG) (100- <126 mg/dl), and undiagnosed diabetes (fasting glucose ≥126 mg/dl) (13). Beginning in the 2005 survey, an oral glucose tolerance test (OGTT) was added to the laboratory protocol. Thus, OGTT data were available for participants in the morning fasting subsample in the 2005-2006 survey only.

Laboratory Measurement of Hemoglobin A1c (HbA1c) and Plasma Glucose: HbA1c measurements for NHANES 1999-2004 were performed by the Diabetes Diagnostic Laboratory at the University of Missouri-Columbia using Primus CLC330 and Primus CLC 385 (Primus Corporation, Kansas City, MO). HbA1c measurements in NHANES 2005-2006 were performed by the Diabetes Laboratory at the University of Minnesota using Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics,

Inc., San Francisco, CA). Both assays use a High Performance Liquid Chromatography (HPLC) system (14). All HbA1c measurements were standardized to the reference method used by the Diabetes Control and Complications Trial (DCCT). Plasma glucose concentration was determined by a hexokinase enzymatic method (15).

Other Variables of Interest: The NHANES examination included measurement of height, weight, and blood pressure. Hypertension was defined as a mean systolic blood pressure of ≥140 mm Hg, a mean diastolic blood pressure of ≥90 mm Hg, or hypertension medication use. Total cholesterol was measured enzymatically. Hypercholesterolemia was defined as a total cholesterol level 240 mg/dl or higher, or lipid medication use. C-reactive protein was measured by latex-enhanced nephelometry, a high-sensitivity assay. Information on age, sex, race/ethnicity, education level, and smoking was based on self-report during the questionnaire portion of the survey. A history of cardiovascular disease was defined on the basis of a self-reported history of coronary heart disease, angina, previous heart attack, or stroke. Smoking status was determined using answers to the questions, "Have you smoked at least 100 cigarettes in your life?" and "Do you now smoke cigarettes?" Alcohol consumption was determined during the computer assisted personal interview using answers to the questions, "In any one year, have you had at least 12 alcoholic drinks of any type of alcoholic beverage?" and "In your entire life, have you had at least 12 drinks of any type of alcoholic beverage?" Detailed information regarding the collection of data in NHANES is available elsewhere (12).

Statistical Analysis: Analyses were performed incorporating the sampling weights (eight year combined weights) to obtain unbiased estimates from the complex NHANES sampling design using StataSE Version 10.0 (StataCorp College Station, TX) and R (Version 2, Free Software Foundation, Inc., Boston, MA). Standard errors for all estimates were obtained using the Taylor series (linearization) method following NCHS recommended procedures (16). Analyses of fasting plasma glucose categories were limited to the morning plasma glucose sample and corresponding eight year fasting subsample weights were used for these analyses. We generated weighted and smoothed histograms (kernel density estimator) to compare the distribution of HbA1c in persons with normal fasting glucose, IFG, and undiagnosed diabetes.

For the purposes of this study, we defined "elevated HbA1c" as HbA1c >6% in this population without a history of diabetes. However, we also assessed the prevalence of elevated HbA1c at cut-points of 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9 and ≥7.0%. Adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were estimated from logistic regression models to assess the association between potential risk factors and elevated HbA1c levels. We conducted multivariable logistic analyses modeling HbA1c >6% as the outcome in the overall population. In the population of adults with normal HbA1c (<6%) and normal fasting glucose (<100 mg/dl) levels, we modeled the association between risk factors of interest and HbA1c level above the weighted median HbA1c level in this population (>5.2%). Model 1 included age, sex, and race/ethnicity. Model 2 included all variables in Model 1 plus hypertension, hypercholesterolemia, body mass index, education, history of cardiovascular disease, alcohol consumption, and C-reactive protein categories. Sensitivity analyses were conducting using the OGTT data only available in NHANES 2005-2006 and employing the appropriate two year fasting weights for this survey.

Estimates from this study are nationally representative of the non-

institutionalized population of adults aged 20 and older in the United States. Prevalence estimates were applied to the 2000 US Census to obtain estimates of the number of non-diabetic individuals with elevated HbA1c in the US in the year 2000.

RESULTS

Mean HbA1c level and proportion of persons with elevated HbA1c (HbA1c >6%) by population characteristics are displayed in Table 1. The mean HbA1c in adults 20 and older without diagnosed diabetes was 5.3% (SE, 0.01). Mean HbA1c level and the proportion of persons with HbA1c >6% increased considerably with age. Non-Hispanic Blacks also had higher HbA1c levels compared to Non-Hispanic whites. In this crude comparison, differences in HbA1c were also observed for hypertension and hypercholesterolemia status, body mass index categories, education level, and C-reactive protein quartiles.

Figure 1 displays the count of persons (in millions) with elevated HbA1c at cut-points between 6.0 and 7.0%. The prevalence of HbA1c >6.0% in persons without a history of diabetes was 3.8% (95%CI 3.5, 4.2) (see Table 1), corresponding to 7.1 million adults (95%CI 6.5, 7.8) in the U.S (Figure 1). The prevalence estimates for HbA1c cut-points of >6.1%, ≥6.5%, and ≥7.0% were 2.9 (2.6, 3.2), 1.6 (1.4, 1.8) and 0.8 (0.6, 0.9). These correspond to 5.4 million (4.8, 6.0), 3.0 million (2.6, 3.3), and 1.5 million (1.1, 1.7) individuals in the U.S. population, respectively. These prevalence estimates suggest the yield of individuals in the U.S. with elevated HbA1c at different cut points if HbA1c alone was used to screen for diabetes.

Figure 2 displays the distributions of HbA1c in persons with normal fasting glucose (fasting glucose <100 mg/dl), IFG (fasting glucose 100 -<126 mg/dl), and undiagnosed diabetes (fasting glucose ≥126 mg/dl), revealing substantially overlapping distributions in persons with normal glucose and IFG but a right-skewed distribution in persons with undiagnosed diabetes with a much higher mode. The mean HbA1c levels in persons with normal fasting glucose, impaired fasting glucose, and undiagnosed diabetes were 5.2% (SE, 0.01), 5.5% (SE, 0.01), and 6.9% (SE, 0.16), respectively (not shown). Similarly, the distribution of persons in the fasting glucose categories (<100 mg/dl, 100-125 mg/dl, and ≥126 mg/dl) varied substantially depending on the HbA1c cut-point. For instance, among persons with HbA1c >6.0%, 45.6% had undiagnosed diabetes, 45.3% had IFG, and 9.1% had normal fasting glucose. By contrast, among persons with an HbA1c ≥7.0%, 91.7% had undiagnosed diabetes, 6.6% had IFG, and only 1.7% had normal glucose levels. Comparing the distribution of fasting glucose categories among persons with HbA1c>6.1% and HbA1c ≥6.5% yielded intermediate results. Among persons with HbA1c >6%, 53.3% have undiagnosed diabetes, 38.6% have IFG, and 8.1% have normal fasting glucose. Among persons with HbA1c ≥6.5%, 76.7% had undiagnosed diabetes, 19.6% had IFG, and 1.7% had normal fasting glucose (see Figure A available in the online appendix at http://care.diabetesjournals.org).

Multivariable logistic regression analysis demonstrated that older age, male gender, non-Hispanic black and Mexican American race/ethnicity, hypertension, higher body mass index, a less than high school education, and higher C-reactive protein levels were all associated with the prevalence of elevated HbA1c (HbA1c >6%) even after multivariable adjustment in this population of adults without diagnosed diabetes (see Table A in the online--). Current alcohol consumption was associated lower HbA1c. We next examined the same variables but limited the population to persons with normal HbA1c (HbA1c <6%) and with a fasting glucose <100 mg/dl and assessed the

association with having an HbA1c level above the median in this population (HbA1c >5.2%) (see Table 2). Similar associations were observed as in the model of HbA1c >6% in the full population. In Table 2, higher age, male gender, non-Hispanic black and Mexican American race/ethnicity, hypercholesterolemia, higher body mass index, and lower attained education were significantly associated with having a higher HbA1c level, even after adjustment. Current smoking was associated with higher HbA1c and current alcohol consumption with lower HbA1c in this population with normal glucose levels. Additional adjustment for fasting glucose did not alter these results (data not shown). Our results were also unchanged in sensitivity analyses of NHANES 2005-2006—the only years for which OGTT data were available—where we further excluded persons with impaired glucose tolerance (2-hour glucose ≥140 mg/dl) from our multivariable models (data not shown).

CONCLUSIONS

This analysis suggests that elevated HbA1c (>6%) is common in the general population of non-diabetic adults. The overall prevalence of HbA1c >6% was 3.8% corresponding to 7.1 million individuals in the U.S. population. Approximately, 45% percent of these individuals have IFG and 45% have fasting glucose ≥126 mg/dl. Elevated HbA1c levels were particularly common among older adults, non-Hispanic blacks, and obese individuals. We found that demographic characteristics and risk factors for type 2 diabetes and its complications including older age, male gender, non-white race/ethnicity, lower attained education level, adiposity, and hypercholesterolemia were associated with elevated HbA1c even in the presence of normal fasting glucose.

Significant advantages of adopting HbA1c for the screening and diagnosis of diabetes are the high repeatability of the measurement (17,18) and the high specificity of elevated values for detecting undiagnosed diabetes (19-21). Recent recommendations have stated that diagnosis based on HbA1c should be confirmed using a glucose-dependent test (FPG or OGTT) or by a second HbA1c (11). However, glucose dependent tests and are less reliable (repeatable) compared to HbA1c (17). Requiring confirmation of a highly reliable test by one that is less reliable, poses problems for the interpretation of any discrepancy between the two values. In a previous study, we analyzed repeated measurements taken approximately two weeks apart on an unselected sample of individuals without diabetes and found 100% of persons with HbA1c ≥7% had a second HbA1c measurement of ≥7% ~2 weeks later and 80% of persons with HbA1c ≥6.5 had an HbA1c level ≥6.5% two weeks later (Pearson's r=0.95) (17). There is little marginal gain to repeating the HbA1c test within a short (several week) time period. Furthermore, we show in the present study that 92% of persons with HbA1c ≥7.0% also had a fasting plasma glucose ≥126 mg/dl and 77% of persons with HbA1c ≥6.5% had a FPG ≥126 mg/dl. At the population level, elevated HbA1c is rare in the absence of elevated fasting glucose.

Additional advantages to using HbA1c for screening and/or diagnosis of diabetes include national standardization of the assay (22,23), the low analytic variability (high methodological quality of the assay, even when compared to glucose) (24), the widespread availability of the HbA1c test and its current use in the management and treatment of diabetes, and that the patient does not need to be fasting.

It is unclear why non-diabetic Non-Hispanic blacks have consistently higher HbA1c even in the setting of normal fasting glucose levels and after adjustment for demographic and clinical characteristics. Further research should determine whether

this disparity stems from racial differences in post-prandial glycemia or from racial differences in the tendency of hemoglobin to undergo glycosylation.

This study has several strengths including the large, nationally representative sample of healthy, non-diabetic individuals. We benefited from the rigorous measurement of risk factors using standardized protocols and strict quality control data collection and laboratory procedures in NHANES. Important limitations include the cross-sectional design which limits our conclusions regarding the temporality of the observed associations. Additionally, we had only a single measurement of fasting glucose. The American Diabetes Association recommends repeating an elevated fasting glucose measurement to confirm the diagnosis of diabetes (13). The use of a single measurement of fasting glucose rather than two will overestimate the prevalence of undiagnosed diabetes (17). Nonetheless, interpretation of single measurements of fasting glucose and HbA1c as analyzed in this study reflects a common clinical decision-making setting. While we cannot rule out the possibility of laboratory differences over time, all HbA1c measurements were standardized to the DCCT reference method and analyses by the NHANES laboratory and our research group show no evidence of differences in calibration of the HbA1c assay across survey periods. The lack of OGTT data in the fasting glucose subsample for all survey years is an important limitation of this study. Nonetheless, similar results were obtained in multivariable models utilizing the OGTT measurements in the subgroup from the 2005-2006 NHANES.

To date, the diagnostic utility of HbA1c has largely been assessed by its accuracy (as measured by its sensitivity and specificity) to detect glucose-defined diabetes cases (25). The concordance of HbA1c with fasting glucose is important and, as confirmed by our data, an HbA1c ≥6.5% is specific for the detection of undiagnosed diabetes defined by a single fasting glucose level. Thus, it seems reasonable to adopt a single elevated HbA1c as diagnostic for diabetes. However, the real test of utility for HbA1c as a screening or diagnostic test of diabetes is its association with long-term clinical outcomes in an initially non-diabetic population specifically in comparison to fasting glucose levels. To address this question we need large, observational studies of HbA1c in populations of persons without diabetes.

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Table 1. Mean hemoglobin A1c (HbA1c) and proportions of elevated levels (HbA1c >6%) by population characteristics in adults 20 and older without diagnosed diabetes, U.S. 1999-2006

	Unweighted N	HbA1c, Mean (SE)	HbA1c >6.0%, Percentage (SE)
Overall	15934	5.3 (0.01)	3.8 (0.17)
Age group			
20-39	6318	5.1 (0.10)	1.0 (0.13)
40-59	4789	5.4 (0.01)	4.4 (0.33)
60-69	2070	5.5 (0.03)	9.1 (0.73)
70+	2757	5.5 (0.02)	8.3 (0.59)
Sex			
Male	7524	5.3 (0.01)	4.3 (0.26)
Female	8410	5.3 (0.01)	3.4 (0.22)
Race/ethnicity			
Non-Hispanic White	8310	5.3 (0.01)	3.2 (0.20)
Non-Hispanic Black	3038	5.4 (0.01)	6.6 (0.45)
Mexican American	3436	5.4 (0.01)	3.9 (0.36)
Other	998	5.4 (0.03)	6.0 (0.83)
Hypertension			
No	10144	5.2 (0.97)	2.2 (0.16)
Yes	5780	5.5 (0.01)	7.3 (0.41)
Hypercholesterolemia			
No	10347	5.2 (0.95)	2.9 (0.18)
Yes	5494	5.4 (0.01)	5.7 (0.35)
Smoking			
Never Smoker	8300	5.3 (0.01)	3.5 (0.23)
Former Smoker	4029	5.4 (0.02)	5.1 (0.39)
Current Smoker	3583	5.3 (0.01)	3.2 (0.32)
Body mass index, kg/m^2			
< 25	5199	5.2 (0.01)	1.1 (0.14)
25- <30	5578	5.3 (0.01)	3.2 (0.26)
≥ 30	4789	5.5 (0.01)	7.8 (0.46)
Education			
Post High School	7403	5.3 (0.01)	2.8 (0.21)
High School	3799	5.3 (0.01)	4.0 (0.35)
Less than HS	4701	5.4 (0.01)	6.7 (0.45)
History of cardiovascular disease	1168	5.5 (0.02)	8.7 (0.91)
Alcohol consumption			
Never	4553	5.4 (0.01)	5.8 (0.41)
Former	1490	5.4 (0.02)	6.2 (0.73)
Current	8794	5.3 (0.01)	2.7 (0.18)
C-reactive protein quartiles, mg/dl			
0.01-<0.08	3472	5.2 (0.01)	1.1 (0.17)
0.08-<0.19	3376	5.3 (0.01)	2.7 (0.29)
0.19-<0.44	4065	5.4 (0.01)	4.4 (0.38)
0.44-29.6	4527	5.5 (0.02)	7.5 (0.47)

Table 2. Adjusted odds ratios (95%CIs) of HbA1c above the median (HbA1C>5.2%) in adults 20 and older without diagnosed diabetes and with normal fasting glucose and normal HbA1c levels, U.S. 1999-2006

Variable	Model 1, Odds Ratio (95% CI), N=4622	Model 2, Odds ratio (95% CI), N=4256
Age group		
20-39	1.0 (ref)	1.0 (ref)
40-59	2.8 (2.4,3.4)*	2.7 (2.2,3.3)*
60-69	4.6 (3.6,5.8)*	3.3 (2.4,4.6)*
70+	6.9 (5.1,9.3)*	6.0 (3.9,9.1)*
Sex		
Female	1.0 (ref)	1.0 (ref)
Male	1.4 (1.2,1.7)*	1.5 (1.2,1.9)*
Race/ethnicity		
Non-Hispanic White	1.0 (ref)	1.0 (ref)
Non-Hispanic Black	2.9 (2.4,3.7)*	2.4 (1.8,3.1)*
Mexican American	1.7 (1.3,2.2)*	1.4 (1.0,1.8)*
Other	1.8 (1.3,2.5)*	1.9 (1.4,2.6)*
Hypertension (yes vs no)	---	1.2 (0.9,1.5)
Hypercholesterolemia (yes vs no)	---	1.4 (1.2,1.7)*
Smoking		
Never	---	1.0 (ref)
Former	---	1.0 (0.8,1.2)
Current	---	1.5 (1.2,1.9)*
Body mass index, kg/m^2		
< 25	---	1.0 (ref)
25- <30	---	1.2 (0.9,1.5)
≥ 30	---	1.9 (1.4,2.7)*
Education		
Post high school	---	1.0 (ref)
High school or equivalent	---	1.3 (1.0,1.7)*
Less than high school	---	1.5 (1.2,1.9)*
History of cardiovascular disease	---	0.9 (0.7,1.3)
Alcohol consumption		
Never	---	1.0 (ref)
Former	---	0.8 (0.5, 1.1)
Current	---	0.6 (0.5, 0.8)*
C-reactive protein quartiles, mg/dl		
0.01-<0.08	---	1.0 (ref)
0.08-<0.19	---	1.0 (0.8,1.4)
0.19-<0.44	---	1.1 (0.8,1.4)
0.44-29.6	---	1.1 (0.8,1.6)

*p-value < 0.05

Model 1: age, sex, and race/ethnicity.

Model 2: all variables in Model 1 plus hypertension, hypercholesterolemia, body mass index, education, history of cardiovascular disease, alcohol consumption, and C-reactive protein categories.

Definitions: Absence of diabetes=no history of diabetes and fasting plasma glucose <100mg/dl; Normal HbA1c level: HbA1c<6%

Figure 1. Count in millions (95%CI) of persons at different HbA1c cut-points in the U. S. 2000 Census population aged 20+ and without diabetes

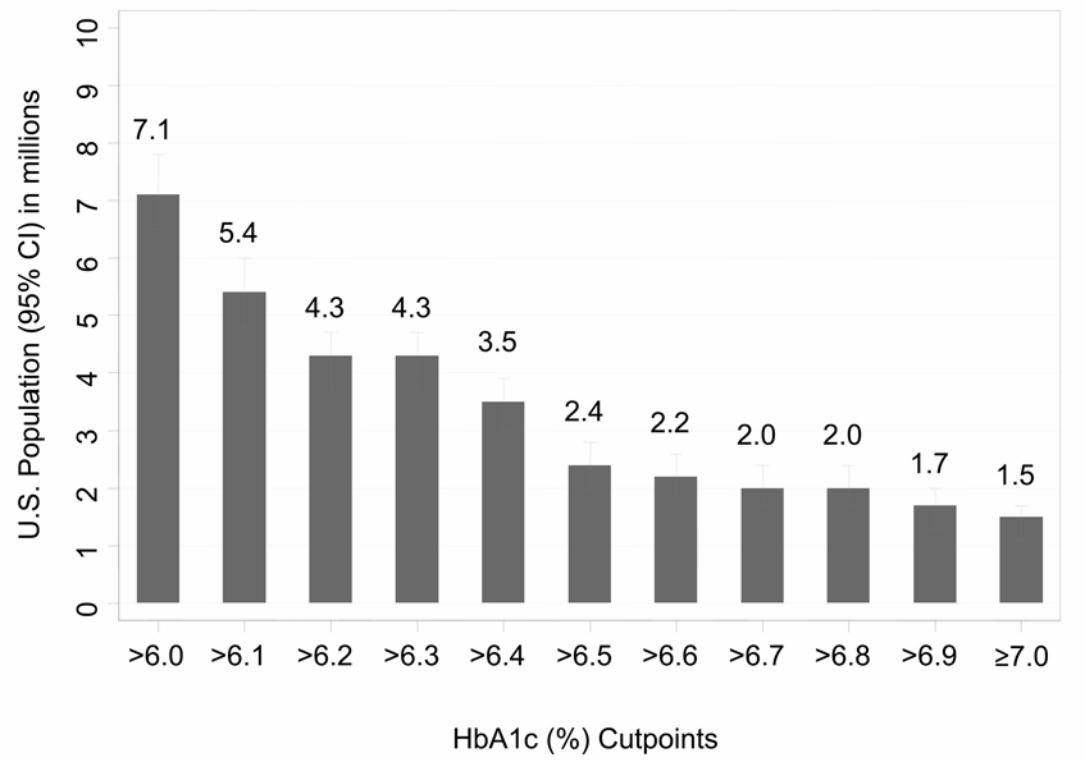

Figure 2. Weighted smoothed histogram comparing distributions of hemoglobin A1c (HbA1c) by fasting glucose category, adults 20+ without diagnosed diabetes, U.S. 1992-2006