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Should the Hemoglobin A_{1c} Diagnostic Cutoff Differ Between Blacks and Whites?:

A Cross-sectional Study

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Abstract

Background—Hemoglobin A_{1c} (HbA_{1c}) levels are known to be consistently higher in black persons than in white persons at any given glycemic level. Whether the optimal diagnostic threshold of HbA_{1c} should differ between blacks and whites is unclear.

Objective—To compare the relationships between HbA_{1c} level and the prevalence of retinopathy in black and white U.S. adults.

Design—Cross-sectional study.

Setting—A nationally representative sample of the National Health and Nutrition Examination Survey from 2005 through 2008.

Patients—2804 white persons and 1008 black persons aged 40 years or older in the United States.

Measurements—Prevalence of retinopathy. Logistic regression models and restricted cubic spline models were constructed separately for white and black populations to test the HbA_{1c} levels at which risk for retinopathy begins to increase.

Results—After adjustment for age, sex, hypertension, body mass index, family history of diabetes, oral antidiabetic medication use, and insulin use, the lowest HbA_{1c} category for which the prevalence of retinopathy was significantly higher than the reference category (<5.5%) was 6.0% to 6.4% for white persons (risk difference, 4.8% [95% CI, 0.5% to 9.1%]) and 5.5% to 5.9%

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for black persons (risk difference, 5.3% [CI, 1.0% to 9.5%]). The restricted cubic spline models indicated that the risk for retinopathy increased at lower HbA_{1c} levels in black persons than in white persons.

Limitation—The cross-sectional design of the study precluded examining the effect of the duration at each HbA_{1c} level.

Conclusion—The prevalence of retinopathy begins to increase at a lower HbA_{1c} level in black Americans than in white Americans. The findings of this study do not support increasing the diagnostic threshold of HbA_{1c} in black persons.

Diabetes is an important public health concern. An estimated 25.8 million (8.3%) U.S. children and adults have diabetes (1). In 2010, the International Expert Committee proposed use of a hemoglobin A_{1c} (HbA_{1c}) level of 6.5% or higher as a new threshold for diagnosing diabetes (2, 3); this threshold was subsequently adopted by the American Diabetes Association and the World Health Organization. The expert committee selected 6.5% on the basis of the prevalence of diabetic retinopathy associated with this level. Retinopathy has been accepted as the best criterion for comparing glycemic measures because it is a specific, objective, and relatively early clinical complication of diabetes (4, 5). However, this recommendation did not address the ongoing debate about the interpretation of HbA_{1c} values among black persons and the possible need for race-based HbA_{1c} cutoff points (6–13). A growing body of evidence from epidemiologic and clinical studies shows that HbA_{1c} levels are consistently higher among black persons than among white persons (14–16), and several studies indicate that the correlation between HbA_{1c} level and blood glucose level differs between these 2 racial groups (17–19). The mechanism underlying this racial difference in HbA_{1c} level has not been established, and no consensus has been reached on whether different diagnostic cutoffs of HbA_{1c} should be used for different racial populations (20). In this context, we analyzed data from the National Health and Nutrition Examination Survey (NHANES) from 2005 through 2008 to examine the association between HbA_{1c} level and the prevalence of retinopathy in blacks and whites, and we tested whether the thresholds at which the risk for prevalent retinopathy begins to increase differ between blacks and whites in the United States.

Methods

Study Population

We analyzed data from NHANES, a nationally representative study conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention. We identified participants by using a stratified multistage probability design with oversampling of certain age and racial or ethnic groups (21). Sample weights were provided so that analyses could be adjusted to reflect the noninstitutionalized U.S. civilian population. Participants were interviewed for demographic, socioeconomic, dietary, and health-related information and had medical, dental, and physiologic examinations as well as laboratory testing (21). Only participants aged 40 years or older who had none of the exclusion criteria (for example, blindness, eye infections, or eye patches on both eyes) had retinal imaging examinations (21).

To examine the difference in retinopathy prevalence between white and black participants, we included non-Hispanic white and black adults aged 40 years or older in this study ($n = 5202$). We excluded those with missing information on HbA_{1c} level ($n = 459$), incomplete or ungradable retinal imaging examinations ($n = 797$), and missing data on other variables of interest (age, sex, hypertension, body mass index [BMI], and family history of diabetes) ($n = 134$). This left a sample of 3812. We further excluded those who were receiving oral antidiabetic medication ($n = 372$) or insulin ($n = 108$) for the analyses of the population not

treated for diabetes, resulting in a final sample size of 3332. The NHANES protocol was approved by a human subjects review board, and written informed consent was obtained from all participants. Our study was exempted from review by the institutional review board at Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Hemoglobin A_{1c}

Hemoglobin A_{1c} level was measured by using high-performance liquid chromatography. For the 2005 through 2006 NHANES, HbA_{1c} level was measured with an A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, South San Francisco, California); for the 2007 through 2008 NHANES, HbA_{1c} level was measured with an A1c G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, South San Francisco, California). Both instruments were certified by the National Glycohemoglobin Standardization Program, and the final reportable result is traceable to the Diabetes Control and Complications Trial (21). We categorized HbA_{1c} levels as follows for the analyses of the overall study population: less than 5.5%, 5.5% to 5.9%, 6.0% to 6.4%, 6.5% to 6.9%, 7.0% to 7.4%, and 7.5% or higher. For the analyses of the subsample not treated for diabetes, we combined persons with an HbA_{1c} level of 6.5% or higher into a single category to avoid zero cells. Those with an HbA_{1c} level less than 5.5% were used as the reference category.

Diabetic Retinopathy

Two digital images per eye (4 images per participant) were taken through a nonpharmacologically dilated pupil by a technologist using a Canon CR6-45NM ophthalmic digital imaging system and a Canon EOS 10D digital camera (Canon, Tokyo, Japan). The first image was centered on the macula, and the second was centered on the optic nerve. The retinal images were graded at the University of Wisconsin Ocular Epidemiology Reading Center according to the modified Airlie House classification system, as used in the Early Treatment Diabetic Retinopathy Study (22). Diabetic retinopathy was defined as the presence of 1 or more microaneurysms or more severe forms of retinopathy, as determined by using the grading standards of the Early Treatment Diabetic Retinopathy Study (23, 24).

Other Measurements

We identified the variables reported to be risk factors for diabetic retinopathy and potential confounders in previous studies (25–28). We defined hypertension as use of antihypertensive medication or, based on the mean of 3 or 4 readings, systolic blood pressure 140 mm Hg or higher or a diastolic blood pressure 90 mm Hg or higher. Use of oral antidiabetic medication, insulin, and antihypertensive medication was determined on the basis of interviewer-confirmed medication containers matched to a comprehensive prescription drug database (Lexicon Plus) (21). We defined family history of diabetes as self-reported family history of diabetes (yes or no). Body mass index was calculated as kg/m².

Statistical Analysis

We constructed logistic regression models and tested the association between HbA_{1c} level and the prevalence of retinopathy for blacks and whites separately. We developed model 1 to examine the overall study population (including the participants who were receiving treatment for diabetes), adjusted for age, sex, hypertension, BMI, family history of diabetes, and interviewer-confirmed use of oral antidiabetic medication (yes or no) and insulin (yes or no). To minimize the influence of antidiabetic treatments on HbA_{1c} values, we also conducted analyses excluding persons who were receiving either oral antidiabetic medication or insulin (model 2). Because both BMI and family history of diabetes may be strongly correlated with HbA_{1c} level, we conducted a sensitivity analysis excluding these 2

covariates from our models. As effect modification of race on the relationship between HbA_{1c} level and prevalent retinopathy was of interest, we also created regression models that included both white and black participants and tested for interactions between race and HbA_{1c} level by using a likelihood ratio test. We conducted multiple imputation by using the chained equation method (29, 30) in additional sensitivity analyses to test the effect of different missing patterns of HbA_{1c} or retinal data between blacks and whites on our findings. Multiple imputations were done sequentially; we first imputed the data for all of the variables except for missing outcome data and then imputed for those data (31). We conducted several additional analyses to explore for a potential threshold effect in the relationship between HbA_{1c} level and the prevalence of retinopathy. We first fit unadjusted restricted cubic spline models by using HbA_{1c} level as a continuous variable with knots corresponding to the HbA_{1c} cutoff points of interest (5.5%, 6.0%, 6.5%, and 7.0%), and we explored the inflection points suggestive of a threshold for both black and white participants (32). We then examined adjusted sensitivity and specificity of different HbA_{1c} cut points with receiver-operating characteristic curves to identify participants with prevalent retinopathy among the population not treated for diabetes, and we tested whether they suggested different thresholds of HbA_{1c} for white and black persons. The restricted cubic spline model analysis was conducted by using STATA/IC, version 11.0 (StataCorp, College Station, Texas); multiple imputation was performed by using STATA/IC, version 12.0; and all other statistical analyses were conducted by using SAS, version 9.2 (SAS Institute, Cary, North Carolina) and SUDAAN, version 10.1 (Research Triangle Institute, Research Triangle Park, North Carolina), accounting for the complex survey design of the study. Taylor series linearization was used for variance estimation (33).

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The funding source had no role in the design or conduct of the study; collection, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

Results

Study Participants

Table 1 presents the baseline characteristics of the white and black persons in the overall study sample. Compared with whites, blacks were younger, were more likely to be women, had higher HbA_{1c} and fasting plasma glucose levels, were more likely to be diagnosed with diabetes, and were more likely to be receiving oral antidiabetic medication or insulin. Black persons also had higher blood pressure and higher BMIs and were more likely to be receiving antihypertensive medication, have a family history of diabetes, drink less alcohol, smoke, and be less educated. Compared with participants with complete data, those who had missing data were similar in terms of sex, fasting glucose level, BMI, smoking status, and family history of diabetes. However, participants who had missing data had higher 2-hour glucose levels and were older, less educated, more likely to have hypertension, and less likely to drink alcohol. The pattern of missingness was similar between white and black participants, except that the age difference between participants with complete data and those with missing data was greater among white participants than among black participants (data not shown).

Hemoglobin A_{1c} Levels and Prevalence of Retinopathy

The weighted crude prevalence of retinopathy was 6.3% (SE, 0.5%) for white persons and 13.1% (SE, 1.1%) for black persons. Table 2 presents adjusted standardized risks and risk differences with 95% CIs for the prevalence of retinopathy across different HbA_{1c} categories for the overall study population (model 1). In white persons, the adjusted prevalence of retinopathy was significantly higher at HbA_{1c} levels 6.0% to 6.4% or higher,

compared with HbA_{1c} levels less than 5.5% (the reference category). Among black adults, those with HbA_{1c} levels of 5.5% to 5.9% had significantly higher risk for prevalent retinopathy than those with HbA_{1c} levels less than 5.5%; moreover, the adjusted risk difference for black persons with HbA_{1c} levels of 5.5% to 5.9% was similar to white persons with HbA_{1c} levels of 6.0% to 6.4%. This was the case even after we excluded those who were treated for diabetes in model 2 (Table 3). We conducted a sensitivity analysis that excluded BMI and family history of diabetes from our models; the results were consistent with our primary analysis and are not presented. We did not detect a statistically significant interaction between race (white vs. black) and HbA_{1c} levels when we used a likelihood ratio test ($P = 0.81$). The results of the analyses, which included multiple imputations for missing data, did not alter our overall findings (data not shown).

Figure 1 presents the restricted cubic spline models for the prevalence of retinopathy comparing the white and black persons before adjustment. We found that probability of retinopathy began to increase at lower levels of HbA_{1c} in blacks than in whites. There seemed to be a threshold for high retinopathy risk at HbA_{1c} levels near 5.5% among black adults. Among whites, the slope became steeper at higher HbA_{1c} levels. Adjusting for the covariates included in our logistic regression models did not substantially change these results.

The Appendix Table (available at www.annals.org) shows the adjusted sensitivity and specificity for identifying prevalent retinopathy in the white and black populations not treated for diabetes. The receiver-operating characteristics curve shown in Figure 2 represents the diagnostic accuracy of HbA_{1c} level for the prevalence of retinopathy. If the diagnostic threshold of HbA_{1c} were lowered from the currently adopted level of 6.5% to 6.0%, an estimated additional 1.8 (CI, 1.5 to 2.0) million black and 7.6 (CI, 6.6 to 8.6) million white U.S. adults aged 40 years or older would be diagnosed with diabetes, of whom 0.2 (CI, 0.1 to 0.3) million black and 0.8 (CI, 0.4 to 1.1) million white persons would be anticipated to manifest diabetic retinopathy at the time of examination. For both blacks and whites, this translates to diagnosing 9 additional cases of diabetes to detect 1 additional case of prevalent diabetic retinopathy. If we lowered the diagnostic threshold of HbA_{1c} from 6.5% to 5.5%, an additional 5.7 (CI, 5.4 to 6.1) million black and 39.0 (CI, 36.7 to 41.1) million white persons would be diagnosed with diabetes, among which we would identify 0.5 (CI, 0.3 to 0.7) million cases of retinopathy among black persons and 2.2 (CI, 1.8 to 2.7) million cases among white persons. This new diagnostic threshold would result in diagnosing 11 additional cases of diabetes among blacks and 18 additional cases among whites to detect 1 additional case of diabetic retinopathy.

Discussion

In U.S. adults, we found that the risk for prevalent retinopathy begins to increase at lower HbA_{1c} levels in blacks than in whites aged 40 years or older. Although evidence indicates that black persons have higher HbA_{1c} values than white persons at any given underlying glycemic level (16–19, 34), the results of our study suggest that the risk for diabetic retinopathy is higher for blacks at any given HbA_{1c} level between 5.0% and 7.0% and that the risk of retinopathy at an HbA_{1c} level of 5.5% to 5.9% for blacks was similar to the risk at an HbA_{1c} level of 6.0% to 6.4% among whites. Therefore, our findings argue against increasing the HbA_{1c} diagnostic threshold for blacks.

Several epidemiologic and clinical studies indicate that HbA_{1c} levels are 0.2% to 0.4% higher in blacks than in whites at any given glycemic level (10, 17–20). Ziemer and colleagues (18) studied participants in 2 cross-sectional studies (SIGT [Screening for Impaired Glucose Tolerance] and NHANES III [Third National Health and Nutrition

Examination Survey]) and found that black participants had higher HbA_{1c} levels than white participants across the full spectrum of glycemia. Selvin and colleagues (19) analyzed cross-sectional data from the ARIC [Atherosclerosis Risk in Communities] study and reported that HbA_{1c} values were higher in black participants than in white participants, even in analyses stratified by diabetes status and adjusted for known confounding factors. The disparity in HbA_{1c} level did not extend to other measures of glycemia, such as glycated albumin. Although growing evidence shows that the relationship between HbA_{1c} level and glycemic level may differ between black and white persons, the pathophysiologic mechanism underlying this difference remains unknown. The possibilities include racial differences in preprandial or postprandial glycemia (35, 36), differences in erythrocyte turnover, rates of glucose attachment to or release from hemoglobin, and erythrocyte life span (37).

In response to the recent International Expert Committee recommendation to dichotomize HbA_{1c} levels for the diagnosis of diabetes (<6.5% for a nondiabetic diagnosis vs. ≥6.5% for a diabetic diagnosis), there has been active debate over whether a higher cutoff should be used in black adults than in white adults (7, 11, 20). The new diagnostic cutoff of HbA_{1c} adopted by the American Diabetes Association and the World Health Organization was determined on the basis of cross-sectional data linking HbA_{1c} level and the prevalence of retinopathy (3, 38, 39); therefore, we conducted race-specific stratified analyses of NHANES data and examined, separately for blacks and whites, the threshold at which the risk for prevalent retinopathy begins to increase. Our results suggest that the HbA_{1c} levels at which the risk for prevalent retinopathy begins to increase are lower in black adults than in white adults, arguing against a higher HbA_{1c} diagnostic cutoff for blacks.

Our study has several limitations. First, the cross-sectional design of the study precluded us from examining the effect of the duration at each HbA_{1c} level. The development of retinopathy depends on both the level of hyperglycemia and the duration at that level; therefore, longitudinal studies with repeated HbA_{1c} measurements would lend greater validity to our findings. Second, although the relationship between higher HbA_{1c} levels and increased prevalence of retinopathy was stronger in black persons than in white persons, our study was not able to detect a significant interaction between HbA_{1c} level and race. Finally, although we detected differences between white and black persons in the association between HbA_{1c} level and the prevalence of diabetic retinopathy, what underlies these differences is unclear. Race is a complex and multifaceted concept, and recognition that it is as much a social construct as a biological one, if not more so, is increasing (40). Therefore, whether the differences we detected are mostly due to biological differences or to other sociobehavioral differences, including disparities in access to health and preventive care, is unclear.

In summary, although there is evidence that HbA_{1c} levels are consistently higher in black persons than in white persons for any given glycemic level, we found that the HbA_{1c} level at which the prevalence of retinopathy begins to increase is paradoxically lower in black than in white U.S. adults. The results of our study argue against recommending a higher HbA_{1c} threshold for diagnosing diabetes in black persons. Longitudinal studies with larger samples are warranted to determine whether a lower threshold of HbA_{1c} should be considered for the diagnosis of diabetes in this population.

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Figure 1.

Results of restricted cubic spline models showing the association between HbA_{1c} value and the probability of retinopathy in U.S. adults aged 40 years or older not treated for diabetes. The lines represent the probability determined from restricted cubic spline models, with knots specified at HbA_{1c} levels of 5.5%, 6.0%, 6.5%, and 7.0%.

Figure 2.

Receiver-operating characteristics curve of HbA_{1c} for detecting the prevalence of retinopathy at each possible threshold in U.S. adults aged 40 years or older not treated for diabetes. Adjusted for age, sex, hypertension, BMI, and family history of diabetes.

Table 1

Participant Baseline Characteristics, by Race*

Characteristic	White Persons	Black Persons	P Value
Age at examination, y	57.1 ± 0.4	54.4 ± 0.4	<0.001
Women, %	52.4 ± 0.9	55.9 ± 1.6	0.035
HbA _{1c} level, %	5.6 ± 0.03	6.1 ± 0.04	<0.001
Fasting plasma glucose level mmol/L	6.0 ± 0.1	6.5 ± 0.1	<0.001
mg/dL	108.3 ± 1.0	116.2 ± 2.5	
2-hour glucose level (OGTT) mmol/L	6.9 ± 0.1	6.7 ± 0.2	0.29
mg/dL	124.5 ± 2.7	120.5 ± 3.0	
Diagnosed with diabetes, %	8.9 ± 0.9	19.7 ± 1.3	<0.001
Receiving oral antidiabetic medication, %	7.5 ± 0.7	15.0 ± 1.1	<0.001
Receiving insulin, %	1.9 ± 0.3	4.2 ± 0.6	0.001
Family history of diabetes, %	38.2 ± 1.1	53.5 ± 2.2	<0.001
Systolic blood pressure, mm Hg	125.9 ± 0.5	129.7 ± 0.9	<0.001
Diastolic blood pressure, mm Hg	72.5 ± 0.3	74.2 ± 0.5	<0.001
Receiving antihypertensive medication, %	39.2 ± 1.3	45.0 ± 1.9	0.028
Body mass index, kg/m ²	28.9 ± 0.2	30.9 ± 0.3	<0.001
Alcohol consumption, %			
<1 drink/wk	60.2 ± 1.7	71.5 ± 2.0	0.004
1 to <7 drinks/wk	23.9 ± 1.2	17.7 ± 1.5	

Characteristic	White Persons	Black Persons	P Value
7 drinks/wk	15.9 ± 1.2	10.8 ± 1.1	
Smoking status, %			
Never	47.7 ± 1.4	50.6 ± 1.9	<0.001
Former	33.1 ± 1.1	22.8 ± 1.7	
Current	19.3 ± 1.5	26.7 ± 1.6	
Education level, %			
Less than high school	13.2 ± 1.7	27.4 ± 1.9	<0.001
High school or equivalent	27.5 ± 1.2	21.3 ± 1.3	
College or more	59.3 ± 2.5	51.3 ± 1.6	

HbA_{1c} = hemoglobin A_{1c}; OGTT = oral glucose tolerance test.

* Data are based on all participants aged 40 y or older and are means (±SEs) or proportions (±SEs) weighted to reflect the U.S. population. Sample size varies for certain characteristics.

Table 2
Adjusted Standardized Risk for the Prevalence of Retinopathy in U.S. Adults Aged 40 Years or Older (Model 1) *

Variable	HbA _{1c} Category					
	<5.5%	5.5%–5.9%	6.0%–6.4%	6.5%–6.9%	7.0%–7.4%	7.5%
White persons (<i>n</i> = 2804)						
Sample size	1242	1034	276	98	52	102
Risk (95% CI), %	3.9 (2.6 to 5.1)	5.1 (4.0 to 6.3)	8.7 (4.8 to 12.6)	11.7 (5.7 to 17.6)	16.2 (8.9 to 23.6)	23.6 (12.4 to 34.8)
Risk difference (95% CI), %	0	1.3 (–0.3 to 2.8)	4.8 (0.5 to 9.1) [†]	7.8 (2.1 to 13.5) [†]	12.4 (4.7 to 20.1) [†]	19.7 (8.3 to 31.2) [†]
Black persons (<i>n</i> = 1008)						
Sample size	255	352	184	70	41	106
Risk (95% CI), %	4.5 (1.6 to 7.4)	9.7 (6.1 to 13.3)	10.9 (5.4 to 16.3)	14.8 (7.0 to 22.5)	22.4 (6.9 to 37.9)	42.1 (29.2 to 55.0)
Risk difference (95% CI), %	0	5.3 (1.0 to 9.5) [†]	6.4 (–0.4 to 13.2)	10.3 (3.7 to 16.9) [†]	17.9 (2.0 to 33.8) [†]	37.6 (24.6 to 50.7) [†]

HbA_{1c} = hemoglobin A_{1c}.

* Adjusted for age, sex, hypertension, body mass index, family history of diabetes, oral antidiabetic medication use, and insulin use.

[†] Statistically significant result ($P < 0.05$).

Adjusted Standardized Risk for the Prevalence of Retinopathy in U.S. Adults Aged 40 Years or Older Not Treated for Diabetes (Model 2)^{*}

Table 3

Variable	HbA _{1c} Category			
	<5.5%	5.5%–5.9%	6.0%–6.4%	6.5%
White persons (<i>n</i> = 2527)				
Sample size	1232	995	208	92
Risk (95% CI), %	3.2 (2.1 to 4.3)	4.4 (3.3 to 5.6)	7.5 (3.2 to 11.8)	12.3 (4.5 to 20.1)
Risk difference (95% CI), %	0	1.2 (−0.4 to 2.8)	4.3 (−0.1 to 8.6)	9.1 (1.6 to 16.6) [†]
Black persons (<i>n</i> = 805)				
Sample size	245	335	153	72
Risk (95% CI), %	3.6 (1.1 to 6.1)	8.1 (4.8 to 11.4)	8.5 (4.5 to 12.5)	17.1 (6.9 to 27.2)
Risk difference (95% CI), %	0	4.5 (0.7 to 8.3) [†]	4.9 (0.03 to 9.8) [†]	13.5 (4.2 to 22.7) [†]

HbA_{1c} = hemoglobin A_{1c}.

^{*} Adjusted for age, sex, hypertension, body mass index, and family history of diabetes.

[†] Statistically significant result (*P* < 0.05).

Sensitivity and Specificity for Detecting the Prevalence of Diabetic Retinopathy in U.S. Adults Aged 40 Years or Older Not Treated for Diabetes*

Appendix Table

HbA _{1c}	White Persons		Black Persons	
	Threshold, %	Sensitivity (95% CI), %	Specificity (95% CI), %	Sensitivity (95% CI), % Specificity (95% CI), %
5.5	61.0 (51.0 to 70.9)	66.0 (63.4 to 68.6)	86.1 (76.4 to 95.8)	45.6 (42.4 to 48.7)
6.0	22.3 (12.5 to 32.2)	93.6 (92.4 to 94.8)	38.2 (26.8 to 49.6)	83.9 (81.8 to 86.0)
6.5	9.3 (3.6 to 15.0)	98.2 (97.6 to 98.8)	18.5 (9.8 to 27.3)	95.0 (93.7 to 96.3)
7.0	7.4 (2.7 to 12.1)	99.3 (98.9 to 99.7)	13.4 (6.5 to 20.3)	98.0 (97.2 to 98.8)

HbA_{1c} = hemoglobin A_{1c}.

* Adjusted for age, sex, hypertension, body mass index, and family history of diabetes.