Distribution of HbA_{1c} Levels For Children and Young Adults in the U.S.

Third National Health and Nutrition Examination Survey

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OBJECTIVE — To describe the distribution of HbA_{1c} levels among children and young adults in the U.S. and to evaluate the effects of age, sex, race/ethnicity, socioeconomic status, parental history of diabetes, overweight, and serum glucose on HbA_{1c} levels.

RESEARCH DESIGN AND METHODS — We analyzed HbA_{1c} data from the Third National Health and Nutrition Examination Survey, 1988–1994, for 7,968 participants aged 5–24 years who had not been treated for diabetes. After adjusting for the complex sample design, we compared the distributions of HbA_{1c} in subgroups and developed multiple linear regression models to examine factors associated with HbA_{1c}.

RESULTS — Mean HbA_{1c} level was 4.99% (SD 0.50%) and varied from 4.93% (95% CI ±0.04) in non-Hispanic whites to 5.05% (±0.02) in Mexican-Americans to 5.17% (±0.02) in non-Hispanic blacks. There were very small differences among subgroups. Within each age-group, among men and women, among overweight and nonoverweight subjects, and at any level of education, mean HbA_{1c} levels were higher in non-Hispanic blacks than in non-Hispanic whites. After adjusting for confounders, HbA_{1c} levels for non-Hispanic blacks (5.15%, 95% CI ±0.04) and Mexican-Americans (5.01%, ±0.04) were higher than those for non-Hispanic whites (4.93%, ±0.04).

CONCLUSIONS — These data provide national reference levels for HbA_{1c} distributions among Americans aged 5–24 years and show statistically significant racial/ethnic differences in HbA_{1c} levels that are not completely explained by demographic and health-related variables.

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Concentration of HbA_{1c} is an indicator of average blood glucose concentration over the preceding 2–3 months. HbA_{1c} is currently considered the best index of metabolic control for diabetic patients in clinical settings (1,2) and participants in epidemiological studies as well as a measure of risk for the development of micro- and macrovascular complications (3,4). HbA_{1c} concentration is also related to prevalent coronary disease or carotid intimal thickening in nondiabetic individuals (5,6). It has been suggested as a diagnostic and screening tool for diabetes in the general population (7–9). The use of this test and the distribution of HbA_{1c} levels are also being used increasingly by quality assurance programs to assess the quality of diabetes care (10).

Although the normative distribution for HbA_{1c} levels has been described and standardized for adults (11), normal ranges for children have not been established. Diabetes in children and adolescents is on the rise, perhaps due to the increase in type 2 diabetes (12) and possibly type 1 diabetes (13). With the increase in diabetes in children and the accompanying increased use of HbA_{1c} concentration as a glycemic indicator, it is important to develop reference levels and standards for HbA_{1c} for this population.

Here, we describe the distribution of HbA_{1c} levels in a nationally representative sample of U.S. children, adolescents, and young adults aged 5–24 years. We also evaluate the effects of age, sex, ethnicity, socioeconomic status (SES), parental history of diabetes, overweight, and blood glucose on the distribution of HbA_{1c}.

RESEARCH DESIGN AND METHODS

— The Third National Health and Nutrition Examination Survey (NHANES III) was conducted from 1988 to 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of the U.S. population (14). The NHANES III included a nationally representative probability sample of the U.S. civilian noninstitutionalized population, identified through a complex multistage cluster sampling design, with oversampling of young people, non-Hispanic blacks, and Mexican-Americans. During a household interview, participants or a proxy respondent for children provided information on participants' sociodemographics, health status, and family medical history. Physicians and health care technicians conducted a standard examination on sampled subjects in a mobile examination center within 4 weeks of the household interview.

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Abbreviations: CDC, Centers for Disease Control and Prevention; HPLC, high-performance liquid chromatography; NHANES III, Third National Health and Nutrition Examination Survey; SES, socioeconomic status.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The NHANES III collected several indicators of SES: the educational attainment of the head of household (defined as the family member ≥17 years of age who owned or rented the dwelling), income, and occupation. We used education as a proxy for SES because unlike income data, education data in NHANES III were relatively complete. We also used the poverty income ratio so that we could analyze across the 6 years of the survey in a comparable manner (14).

For this analysis, we defined race/ethnicity as non-Hispanic white, non-Hispanic black, Mexican-American, and other race (including other Hispanics, Asians, and Native Americans). For the total U.S. estimates, all racial/ethnic groups were combined. BMI was calculated as weight in kilograms divided by height in meters squared. BMI percentiles were calculated on the basis of the CDC growth charts (15). We defined overweight as the age- and sex-specific BMI exceeding the 95th percentile.

HbA_{1c} was measured on whole blood from participants ≥4 years of age with an ion-exchange high-performance liquid chromatography (HPLC) method (Bio-Rad Diamat HPLC; interassay coefficient of variation 2.0). Because the presence of variant hemoglobins (hemoglobins C, D, F, and S) interfere with the HPLC method, NHANES III analysts used the standardized affinity chromatographic method when these hemoglobins were present. Both methods were standardized to the Diabetes Control and Complications Trial reference method. Serum glucose levels of participants ≥12 years of age were measured as part of a standard battery of biochemical assessments (Hitachi Model 737 multichannel analyzer; Boehringer Mannheim, Indianapolis, IN) (16).

Of the 9,401 NHANES III respondents aged 5–24 years who were interviewed and examined, 13% (n = 1,218) did not have their HbA_{1c} levels measured. There were no major differences in HbA_{1c} completion rate by sex, overweight, or education level. The completion rate varied with age (78% in the age group 5–9 years and 95% in the age group 20–24 years; $P < 0.01$) and race/ethnicity (90% among Mexican-Americans, 89% among non-Hispanic whites, and 86% among non-Hispanic blacks; $P < 0.01$). Pregnant women (n = 185) and respondents who reported current treatment for diabetes (n = 20) were excluded from analysis.

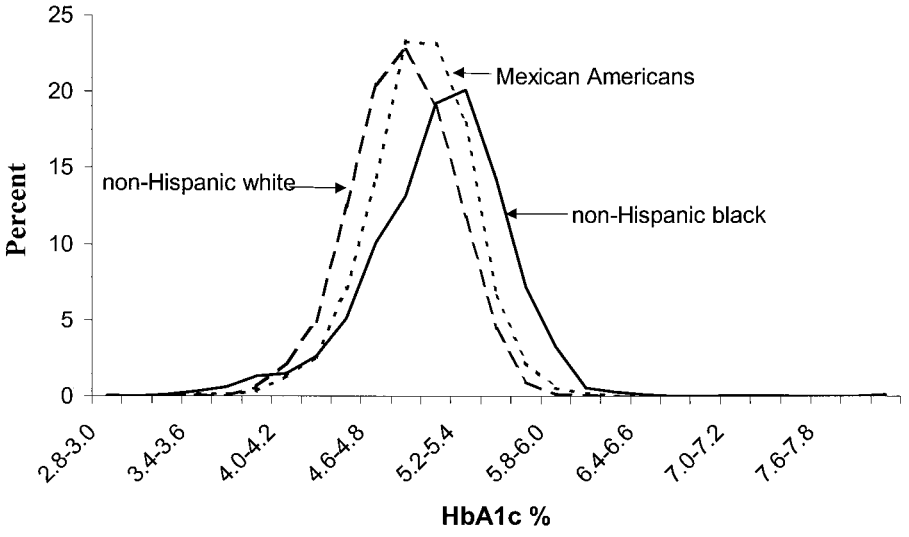

Figure 1—*HbA_{1c} distribution by ethnicity in U.S. children and young adults aged 5–24 years (NHANES III, 1988–1994).*

Statistical analysis

We performed analyses for this study using SAS for data management and SUDAAN to account for unequal probabilities of selection, planned oversampling, differential nonresponse, and the complex sample design (17,18). We used pairwise comparisons to test for the significant mean differences in HbA_{1c} levels among different groups. We used multiple linear regression models to describe the relationship of HbA_{1c} levels with the following independent variables: age, sex, race/ethnicity, education level, and overweight. Separate regression models were run for each age group due to the consistent significant age and sex interaction. Additional models that controlled for fasting glucose levels included the 2,809 children and young adults >12 years of age who had fasting glucose levels measured after fasting for >8 h.

RESULTS — A total of 7,974 children, adolescents, and young adults aged 5–24 years who were not treated for diabetes had their HbA_{1c} levels measured. The mean age was 15 years, 49% were men, and 11% were overweight. Of subjects, ~25% had not completed high school, 34% had completed high school only, and 41% had >12 years of education. White youths were more likely to be from homes having higher levels of education and higher income than youths of other races. More than 40% of non-Hispanic blacks and Mexican-Americans lived below the poverty level compared with only 15% of non-Hispanic whites. The prevalence of overweight was higher among non-Hispanic blacks and Mexican-Americans (15% for both) than among non-Hispanic whites (10%).

The distribution of HbA_{1c} levels by race/ethnicity is shown in Fig. 1. The distribution of HbA_{1c} levels was slightly higher among non-Hispanic blacks than among Mexican-Americans and non-Hispanic whites.

Overall sex-related differences in HbA_{1c} means levels (5.02% in men vs. 4.95% in women) were significant ($P < 0.01$) but very small. Participants 10–14 years of age, non-Hispanic blacks, overweight participants, those of low SES, and those with a positive parent history of diabetes had a statistically higher mean HbA_{1c} level than their counterparts ($P < 0.01$ for each) (Table 1). Among the 2,809 youths whose fasting serum glucose levels were measured, those with fasting serum glucose ≥126 mg/dl had a higher mean HbA_{1c} level than those with fasting glucose 110–125 mg/dl or those with fasting glucose <110 mg/dl (6.9, 5.1, and 4.9%, respectively). However, the magnitude of these mean differences was generally small (range 0.05–0.23%).

Mean HbA_{1c} levels were highest among non-Hispanic blacks for both sexes and in every age group ($P < 0.01$).

Table 1—*Mean, SE, and percentiles for HbA_{1c} by age, sex, ethnicity, education, and overweight among U.S. children and youths (NHANES III, 1988–1994)*

	Mean	SE	10%	20%	30%	40%	50%	60%	70%	80%	90%	95%
Total	4.99	0.01	4.47	4.63	4.74	4.85	4.94	5.03	5.13	5.24	5.39	5.52
Age (years)												
5–9	4.98	0.02	4.46	4.64	4.75	4.84	4.93	5.01	5.11	5.23	5.37	5.47
10–14	5.03	0.02	4.53	4.69	4.81	4.90	4.99	5.08	5.17	5.28	5.43	5.57
15–19	4.97	0.02	4.45	4.62	4.73	4.83	4.93	5.02	5.11	5.22	5.37	5.51
20–24	4.97	0.02	4.43	4.60	4.70	4.81	4.92	5.02	5.13	5.24	5.39	5.53
Sex												
Male	5.02	0.02	4.50	4.68	4.80	4.90	4.98	5.07	5.17	5.27	5.42	5.55
Female	4.95	0.01	4.44	4.60	4.70	4.79	4.90	4.99	5.08	5.20	5.37	5.49
Ethnicity												
Non-Hispanic white	4.93	0.02	4.44	4.60	4.70	4.79	4.89	4.97	5.06	5.17	5.31	5.42
Non-Hispanic black	5.16	0.01	4.54	4.77	4.93	5.05	5.15	5.26	5.36	5.47	5.64	5.78
Mexican-American	5.05	0.01	4.55	4.73	4.83	4.92	5.01	5.09	5.18	5.27	5.40	5.51
Education												
<High school	5.04	0.02	4.48	4.67	4.80	4.91	5.00	5.10	5.20	5.30	5.46	5.57
High school	5.01	0.02	4.50	4.66	4.77	4.87	4.95	5.05	5.14	5.25	5.40	5.55
>High school	4.94	0.02	4.44	4.59	4.70	4.79	4.90	4.98	5.07	5.19	5.34	5.46
Poverty												
Low	5.02	0.02	4.47	4.66	4.77	4.88	4.98	5.08	5.17	5.28	5.44	5.58
Medium	4.98	0.02	4.47	4.64	4.74	4.84	4.93	5.02	5.11	5.23	5.37	5.48
High	4.90	0.02	4.43	4.56	4.67	4.76	4.86	4.94	5.02	5.13	5.30	5.44
Parent history of diabetes												
Yes	5.09	0.04	4.47	4.71	4.82	4.93	5.03	5.12	5.21	5.3	5.48	5.59
No	4.98	0.01	4.47	4.63	4.74	4.84	4.94	5.03	5.12	5.24	5.39	5.51
Overweight												
Yes	5.10	0.03	4.49	4.72	4.86	4.96	5.04	5.13	5.24	5.35	5.51	5.66
No	4.97	0.01	4.47	4.63	4.73	4.83	4.93	5.02	5.12	5.23	5.38	5.50
Fasting glucose (n = 2,809)												
≥126 mg/dl*	6.91		—	—	5.0	5.37	5.75	5.9	5.97	7.27	—	—
110–125 mg/dl	5.1		4.37	4.72	4.77	4.9	5.14	5.2	5.25	5.29	5.5	5.75
<110 mg/dl	4.98		4.48	4.63	4.73	4.84	4.94	5.03	5.12	5.22	5.37	5.5

*Some cells are empty due to the small number of participants with fasting glucose ≥126 mg/dl.

Participants aged 10–14 years had the highest mean HbA_{1c} levels compared with other age groups, except for Mexican-American males, among whom mean HbA_{1c} levels continuously increased with age ($P < 0.01$), and non-Hispanic black males, among whom HbA_{1c} levels were higher in age groups 10–14 and 20–24 years ($P < 0.05$) (Fig. 2). Mean HbA_{1c} levels were higher among overweight than nonoverweight participants in all age and race/ethnic groups ($P < 0.01$). The difference in mean HbA_{1c} levels between overweight and nonoverweight study participants was more pronounced among non-Hispanic blacks (Fig. 3).

In our multiple linear regression analysis, the factors associated with a higher HbA_{1c} level were age 10–14 years ($P < 0.01$), male sex ($P < 0.01$), non-Hispanic black race ($P < 0.001$), Mexican-American ethnicity ($P < 0.01$), positive parent history of diabetes ($P < 0.01$), and overweight ($P < 0.01$). However, even when all previously mentioned factors were included in the model, the HbA_{1c} level was still poorly explained (R^2 = 0.06) by these variables. In a model additionally controlled for fasting glucose (n = 2,809, R^2 = 0.1), non-Hispanic blacks still had a higher HbA_{1c} level than other racial/ethnic groups. Furthermore, HbA_{1c} increased with increasing fasting glucose ($P < 0.01$).

When we fit separate models for each age, male subjects had significantly higher HbA_{1c} levels than female subjects only in the age groups 15–19 ($P < 0.01$) and 20–24 years ($P = 0.03$). Non-Hispanic blacks had higher HbA_{1c} levels than non-Hispanic whites in all age groups ($P < 0.01$), and Mexican-Americans had higher HbA_{1c} levels than non-Hispanic whites in all age groups except 5–9 years ($P < 0.01$). Education less than or equal to high school ($P < 0.01$) was associated with a high HbA_{1c} level among those aged 20–24 years only, whereas overweight was a significant factor among the 10- to 14-year-old subjects only ($P < 0.01$).

CONCLUSIONS — This report provides national reference values for HbA_{1c} distribution among subjects aged 5–24 years in the U.S. who were evaluated by age, sex, race/ethnicity, education, parental history of diabetes, overweight, and glucose status. In general, HbA_{1c} levels were higher in the 10- to 14-year-old age group and higher among overweight participants, those with lower levels of education (among 20- to 24-year-old age group), those with a positive parental his-

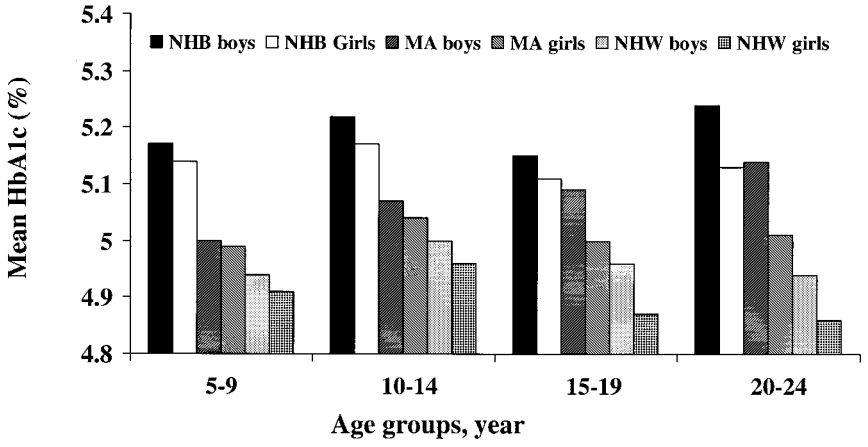

Figure 2— *Mean HbA_{1c} among U.S. children and young adults aged 5–24 years by age group, sex, and ethnicity (NHANES III, 1988–1994). MA, Mexican-American; NHB, non-Hispanic black; NHW, non-Hispanic white.*

tory of diabetes, and those with serum glucose ≥126 mg/dl than in others. We also found consistent differences in HbA_{1c} levels among the different racial/ethnic groups studied, with non-Hispanic blacks having the highest levels, followed by Mexican-Americans and whites, and these differences were not accounted for by other demographic or clinical factors.

Such differences in HbA_{1c} levels, which are modest and mostly within a normal range, can be interpreted in several ways. On one hand, such differences may reflect physiological differences in HbA_{1c} metabolism that could be related to genetic or other factors. HbA_{1c} is actually influenced by both the life span of the erythrocyte and its permeability to glucose (19–21). On the other hand, differences in HbA_{1c} may also reflect higher average glycemia over the preceding 2–3 months (which may also be physiological and within normal limits), or the differences may reflect some level of relative insulin resistance. Indeed, an elevated HbA_{1c} level has been associated with excess mortality risk in the general population (22).

In this healthy U.S. population, non-Hispanic black youths consistently had higher HbA_{1c} levels than non-Hispanic white youths, even after data were adjusted for age, sex, education, overweight, and fasting glucose level. Considering the disproportionate rise in type 2 diabetes in minority children (23–27), these differences in HbA_{1c} are noteworthy. We also described significant differences in HbA_{1c} levels associated with age, sex, weight, and education. These differences were significant in some specific subgroups only. The effects of age on HbA_{1c} levels in adults are controversial, as some studies show age-related increases in HbA_{1c} levels and others show little or no increase (28, 29). Differences in results among the studies are likely related to differences in the selection of study subjects. In most ethnic and sex groups, we found mean HbA_{1c} levels highest in the group aged 10–14 years. This may reflect the demonstrated transient increase in insulin resistance experienced at the onset of puberty and the return to near prepubertal insulin sensitivity level by the end of puberty (30). In NHANES III, low level of education was associated with high HbA_{1c} levels in the overall population; however, when we fitted separated models by age-group, the association persisted only among the 20- to 24-year age group. The absence of significant relationship in the younger age groups may be because the level of education was that of the head of the household, most likely a parent, whereas in the oldest group, the education level was that of the youth.

Our study has several strengths and limitations. The NHANES III is a nationally representative sample that oversampled black and Mexican-American children, the two largest racial/ethnic minority groups in the U.S. Some results should, however, be interpreted with caution. The exclusion of youth with diabetes was based on participant response to a question about use of insulin or glucose regulators; however, the validity of data based on responses to such questions is very high. More importantly, the survey did not have compatible physical activity questions for youths aged 8–16 years, and physical activity is a major potential confounder for insulin sensitivity and potentially for glucose and HbA_{1c} levels. These factors may well play a role in the observed ethnic differences as well as other differences in HbA_{1c} levels.

In conclusion, we have provided national reference values for HbA_{1c} distribution among individuals aged 5–24 years in the U.S. The physiopathological meaning of differences in HbA_{1c} levels within a normal range, however, is not established. Although we found small differ-

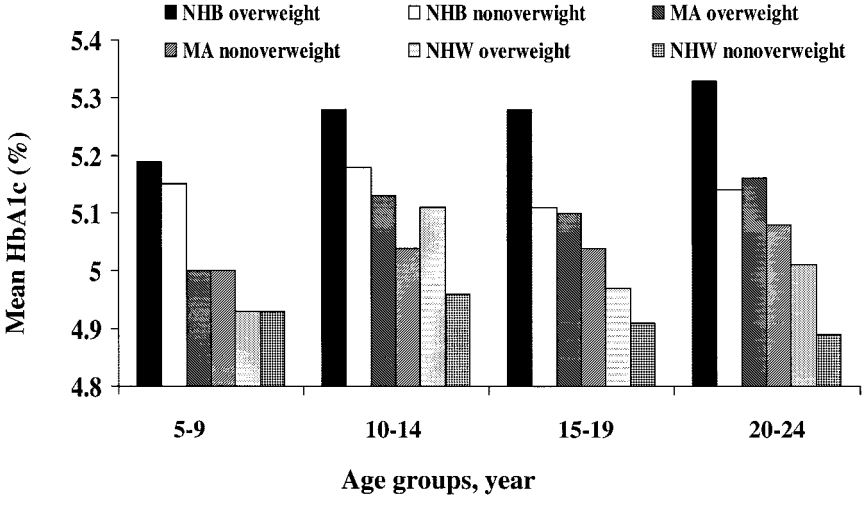

Figure 3— *Mean HbA_{1c} among U.S. children and young adults aged 5–24 years by age group, ethnicity, and overweight (NHANES III, 1988–1994). MA, Mexican-American; NHB, non-Hispanic black; NHW, non-Hispanic white.*

ences in distributions across different groups, we believe that these data may not support the need for separate norms.

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