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Racial differences in prediabetes prevalence by test type for the US pediatric and adult population: NHANES 1999-2016

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Abstract

Background: Previous studies have shown that US estimates of prediabetes or diabetes differ depending on test type, fasting plasma glucose (FPG) vs hemoglobin A1c (HbA1c). Given age, race, and test differences reported in the literature, we sought to further examine these differences in prediabetes detection using a nationally representative sample.

Methods: Using the National Health and Nutrition Examination Survey (NHANES) 1999-2016, individuals were identified as having prediabetes with an HbA1c of 5.7% to 6.4% or a FPG of 100 to 125 mg/dL. We excluded individuals with measurements in the diabetic range. We ran generalized estimating equation logistic regressions to examine the relationship between age, race, and test type with interactions, controlling for sex and body mass index. We compared the difference in predicted prediabetes prevalence detected by impaired fasting glycemia (IFG) vs HbA1c by race/ethnicity among children and adults separately using adjusted Wald tests.

Results: The absolute difference in predicted prediabetes detected by IFG vs HbA1c was 19.9% for white adolescents, 0% for black adolescents, and 20.1% for Hispanic adolescents; 21.4% for white adults, −1.2% for black adults, and 19.2% for Hispanic adults. Using adjusted Wald tests, we found the absolute differences between black vs white and black vs Hispanic individuals to be significant, but, not between Hispanic and white individuals among children and adults separately.

Conclusions: These observations highlight differences in test performance among racial/ethnic groups. Our findings corroborate the need for further studies to determine appropriate HbA1c cutoff levels for diagnosis of prediabetes by age group and race.

KEYWORDS
adolescents, fasting plasma glucose, HbA1c, prediabetes, race

1 | INTRODUCTION

In 2010, the American Diabetes Association (ADA) modified its guidelines to include hemoglobin A1c (HbA1c) as a diagnostic test for identifying children and adults with prediabetes and type 2 diabetes, based on its convenience as a non-fasting test.[1] HbA1c is not a direct measure of glycemia, but represents the proportion of total hemoglobin with glucose attached to the N-terminal valine of the beta chain and therefore can be affected by factors independent of glycemia.[2]

Previous epidemiologic studies have shown that HbA1c differs by age; even among individuals without diabetes and after adjusting for glucose levels, younger individuals have been shown to have 0.5%

lower HbA1c compared with older individuals.[3] Accordingly, studies in pediatric population demonstrated that HbA1c has lower sensitivity in children compared with adults given that the thresholds used for diagnosing prediabetes (5.7%-6.4%) and diabetes (>6.5%) are the same over the lifespan.[4-6] In addition to age, studies also documented differences in HbA1c by race/ethnicity with HbA1c levels that are 0.3% to 0.4% higher in black individuals compared with white individuals independent of glycemia, but screening thresholds are not race-specific.[7-9]

Previous studies have shown that US estimates of prediabetes or diabetes differ depending on the test type (fasting plasma glucose [FPG] vs HbA1c).[10,11] Given age, race, and test differences reported in the literature, we sought to examine differences in prediabetes detection by test type, race/ethnicity among children and among adults separately using a nationally representative sample.

2 | METHODS

We used the National Health and Nutrition Examination Survey (NHANES) from 1999-2016, which is a cross-sectional, nationally representative examination study of the United States civilian non-institutionalized population.[12] We were focused on prediabetes as an outcome for this analysis due to the small number of individuals with diabetes in the pediatric population.

In NHANES, participants visit a mobile examination center where medical, dental, and physiological measurements and laboratory tests are performed by trained medical personnel.[10] All individuals had an HbA1c level drawn and a subset (morning session) was invited to provide a FPG sample after verification of fasting status.[13] Individuals who use medications for diabetes are excluded from the FPG measurement. HbA1c assays were performed on whole blood using the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8.[13]

NHANES uses a stratified multistage probability sampling design, oversampling adolescents aged 12 to 19 years, non-Hispanic blacks, and Mexican Americans to provide reliable statistical estimates for these subpopulations. We used the sample weights for the FPG, which accounts for the additional probability of selection into the subsample component and provides nationally representative estimates for the population studied.[14]

Based on ADA criteria, individuals were identified as having prediabetes with HbA1c of 5.7% to 6.4% or FPG of 100 to 125 mg/dL.[1] We therefore excluded individuals who had measurements in the diabetic range. Normal weight was defined as body mass index (BMI) <85th percentile (children) or BMI <25 kg/m^2 (adults), overweight as BMI ≥85th and < 95th percentile (children) or BMI ≥25 and < 30 kg/m^2 (adults), and obese as BMI ≥95th percentile (children) or BMI≥30 kg/m^2 (adults).

We generated a long dataset in which each individual's test result (HbA1c and FPG) were represented as separate observations. We ran generalized estimating equation logistic regressions to examine the relationship between age, race, and test type with interactions, controlling for sex and BMI. We conducted chi-square tests to examine the association between race/ethnicity and demographic characteristics (sex and weight status) for each age group. Because we found a significant three-way interaction, we calculated predicted prediabetes proportions for all combinations of test type, race, and age group. We then compared the difference in predicted prediabetes detected by impaired fasting glucose (IFG) vs HbA1c by race/ethnicity among children and adults separately, using adjusted Wald tests. We used a Bonferroni correction of $P < .008$ to determine statistical significance. We note that differences in test type by sex and weight status were not the focus of this study. As a result, sex and weight status were included as covariates in the analyses, but were not key variables of interest. Because "other" race represents a variety of races, we included these individuals in the dataset but did not perform statistical comparisons for that race group. Statistical analyses were performed with the Stata software version 15.

3 | RESULTS

Figure 1 shows inclusion and exclusion criteria. Table 1 shows the demographic characteristics and the overall breakdown of prediabetes status for the population. Figure 2 shows the predicted prediabetes proportion according to age group, race, and test type. For example, the prevalence of prediabetes in white adolescents 12 to 17 years detected by FPG was 22.4% vs 2.4% for HbA1c; whereas the prevalence of prediabetes in black adults detected by FPG was 26.3% vs 27.5% for HbA1c. We observed larger differences in predicted prediabetes by test type (IFG vs HbA1c) among Hispanics and non-Hispanic whites while there was little difference in prediabetes identified by FPG as compared to HbA1c among non-Hispanic blacks. (Figure 2).

4 | DISCUSSION

The lack of a significant difference in rates of predicted prediabetes detected by IFG vs HbA1c (IFG-HbA1c) among US black children and adults indicates that there are comparable rates of prediabetes detection with either test type. This is in contrast to what we found for white and Hispanic adolescents and adults, for whom there were significant differences in the rates of prediabetes detected by IFG vs HbA1c (IFG-HbA1c), with much lower estimates using HbA1c vs FPG. Our findings are consistent with previous studies that have evaluated the prevalence of prediabetes by race.[8.]

Menke et al described the prevalence of prediabetes for individuals in NHANES who had FPG, HbA1c, and 2 hour oral glucose tolerance tests performed.[10] They reported estimates of 29.8% by FPG vs 19.3% by HbA1c among US white adults and 20.7% by FPG and 26.4% by HbA1c among US black adults. Andes performed a similar study but focused on children (12-18 years) and young adults (19-34 years).[11] They reported estimates of 12.4% by FPG vs 2.3% by HbA1c among US white young adults, and 9.7% by FPG vs 1.7% by HbA1c among US white adolescents; 10.7% by FPG vs 18.2% by HbA1c among US black young adults, and 7.8% by FPG vs 16.7% by

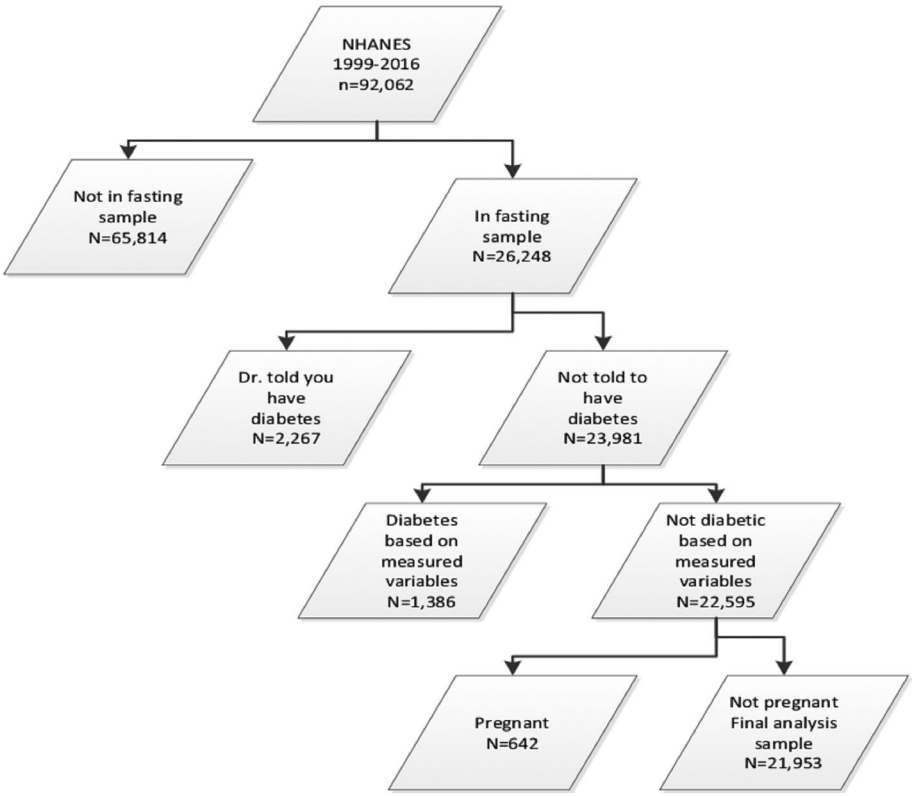

FIGURE 1 Study sample flow diagram

HbA1c among US black adolescents. Our estimates of prediabetes differ from those of Menke and Andes as there were differences in the samples, but there are clear differences in test performance across the race categories.

HbA1c is a recommended diagnostic test for prediabetes and type 2 diabetes for the pediatric population,[2] and longitudinal studies have shown that prediabetes status in childhood is associated with an increased risk of type 2 diabetes later in life. Vijayakumar et al followed a group of American Indian children and adolescents longitudinally over a period of 42 years, and found that children with prediabetes based on ADA criteria, or a 2-hour plasma glucose (PG) (140-199 mg/dL), had a higher incidence of diabetes compared with children who did not have prediabetes.[4] They did however note a lower sensitivity for the HbA1c threshold of 5.7% (8% in boys and 19% in girls) and therefore suggested a lower threshold of 5.4% to identify a greater number of children. Our findings corroborate the need for further studies to help determine appropriate HbA1c cutoff levels for diagnosis of prediabetes by age group and race.

We recognize that the HbA1c test's convenience as a non-fasting test has the potential to improve screening rates in youth at risk of developing type 2 diabetes. However, it is critical that pediatricians using the test understand its opportunities and limitations. Kelsey et al studied children aged 11 to 13 years in the HEALTHY study, a school-based intervention focused on diabetes risk factors in youth at-risk for dysglycemia.[15] They measured HbA1c in the populations of children studied and described a shift in the HbA1c distribution curve to the right in black youth compared with white or Hispanic children; 7.1% of normal weight black children had an HbA1c ≥ 5.7 compared with only 1.3% of Hispanic and 0.1% of white children. They suggested that the "interpretation of prediabetes range HbA1c should be done with caution", particularly given that of the 128 sixth graders in the HEALTHY cohort who had "prediabetes", only one progressed to diabetes and 53 had a normal HbA1c in the eighth grade.[15] We agree with this caution given the race/ethnicity differences in detection by FPG vs HbA1c for black individuals compared with other races. More longitudinal studies are needed to understand whether there are differential long-term risks of prediabetes by age group, race, and test type.

We acknowledge limitations of our study including the cross-sectional study design, the use of FPG as a gold standard (2 hour oral glucose tolerance test might be considered the gold standard, which was not performed here), the classification based on one blood draw, and the definitions of prediabetes are based originally on adult data. We elected to use the age categories of 12 to 17 years vs ≥18 years to allow for comparison across the literature. We recognize that the mechanism of T2D in young adults may be more similar to children compared with older adults, but the diagnostic criteria do not differ across the adult population. We acknowledge that FPG has higher sensitivity and lower reproducibility compared with HbA1c.[16] It is also possible that youth are less likely to follow the fasting protocol than adults, although participants were asked about their food intake before the fasting samples were drawn. NHANES does not have data on non-glycemic factors that alter HbA1c measurements, such as disorders that affect blood cell turnover, hemoglobinopathies, and medications. Furthermore, NHANES does not provide information about pubertal staging, which is a known period of insulin resistance. We

TABLE 1 Characteristics of study sample by age and race/ethnicity category, NHANES 1999-2016

	Children, 12-17 y (n = 4651)[a] weighted % (n)						Adults, ≥18 y (n = 17 302)[a] weighted % (n)					
Race/ethnicity	Overall (n = 4651)	NH White (n = 1253)	NH Black (n = 1322)	Hispanic (n = 1729)	Other (n = 347)	*P*-value	Overall (n = 17 302)	NH White (n = 7935)	NH Black (n = 3378)	Hispanic (n = 4582)	Other (n = 1407)	*P*-value
Sex												
Male	50.0% (2392)	48.8% (634)	50.8% (722)	51.2% (859)	55.1% (177)	.2563	48.6% (8527)	48.4% (3942)	45.9% (1634)	51.7% (2243)	48.7% (708)	.0008
Female	50.0% (2259)	51.2% (619)	49.2% (600)	48.8% (870)	44.9% (170)		51.4% (8775)	51.6% (3993)	54.1% (1744)	48.3% (2339)	51.3% (699)	
Weight status[b]												
Normal weight	71.9% (3249)	74.7% (938)	66.0% (893)	65.5% (1149)	77.6% (269)	.0001	36.0% (6110)	36.9% (2922)	30.0% (1059)	27.7% (1308)	54.3% (821)	.0001
Overweight	15.6% (762)	14.4% (170)	17.8% (216)	19.0% (333)	13.1% (43)		33.4% (5741)	33.6% (2647)	29.2% (975)	39.0% (1769)	26.5% (350)	
Obese	12.5% (602)	11.0% (135)	16.3% (199)	15.5% (239)	9.3% (29)		30.6% (5227)	29.5% (2249)	40.7% (1290)	33.3% (1468)	19.2% (220)	
Glucose status												
Impaired fasting glucose (100-125 mg/dL)	17.8% (760)						36.4% (6481)					
HbA1c (5.7-6.4%)	4.1% (233)						17.6% (3751)					
Prediabetes (either IFG or HbA1c)	20.5% (914)						42.6% (7894)					

[a]Number of subjects within each age group may not sum to equal the total due to missing data.

[b]Weight status was defined by body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. The US Centers and Disease Control and Prevention (CDC) growth chart was used for children 12 to 17 years: normal/underweight was defined as less than 85th percentile; overweight, from 85th to less than 95th percentile; and obese, 95th percentile and higher. Standard BMI cutoffs were used for adults: normal weight, <25 kg/m^2; overweight, 25 to 29.9 kg/m^2; obese, ≥30 kg/m^2.

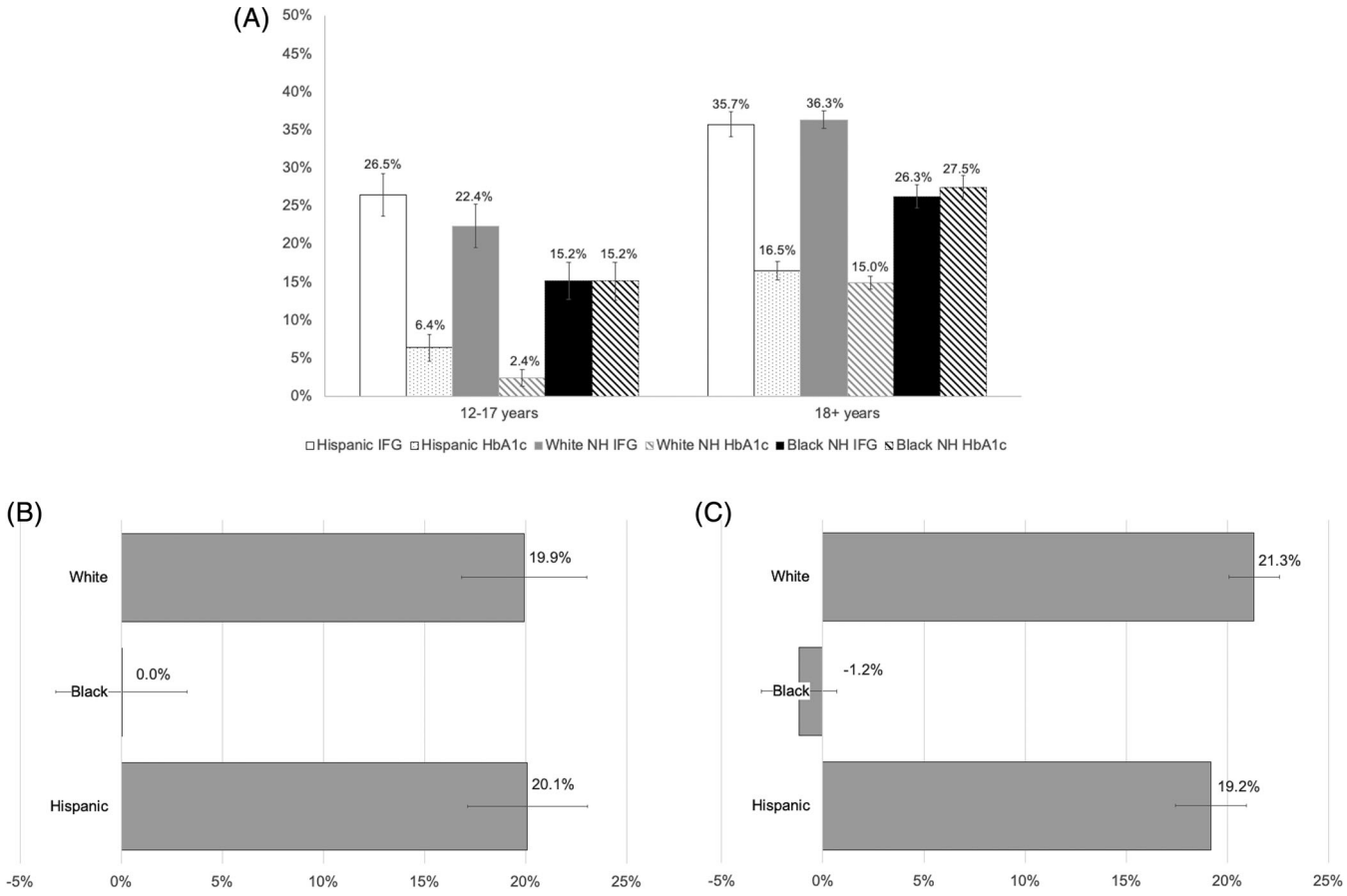

FIGURE 2 A, Estimates of the proportion of prediabetes by IFG and HbA1c by race/ethnicity and test type, for children 12 to 17 years and adults 18+ years. Solid white, Hispanic based on impaired fasting glucose; dots, Hispanic based on HbA1c; solid gray, White non-Hispanic based on impaired fasting glucose; striped gray, White non-Hispanic based on HbA1c; solid black, Black non-Hispanic based on impaired fasting glucose; striped black, Black non-Hispanic based on HbA1c. B, Difference in prediabetes prevalence (fasting plasma glucose-HbA1c) by test type, race among children, 12 to 17 years. *Comparison of white NH vs black NH (P = .0004); Hispanic vs black NH (P = .0004); white NH vs Hispanic (P = .017). C, Difference in prediabetes prevalence (fasting plasma glucose-HbA1c) by test type, race among adults. *Comparison of white NH vs black NH (P = .0004); Hispanic vs black NH (P = .0004); white NH vs Hispanic (P = .02). NH, non-Hispanic

acknowledge differences between our findings and the Menke and Andes papers may be attributed to the difference in sampling demographics and objectives. The objective of our study was unique, as we were unaware of studies that have focused on differences in prediabetes detection rates by test type, age, race/ethnicity using a nationally representative sample.

Our findings are relevant for informing studies of epidemiologic burden and trends for prediabetes in youth, particularly as it relates to racial differences in diabetes risk. Studies like the SEARCH for Diabetes in Youth Study have shown that minority youth are at elevated risk for type 2 diabetes.[17] Our study reveals that racial differences in diabetes risk may be impacted by test type, which gains even more relevance as an increasing number of pediatricians are ordering HbA1c in accordance with the ADA guidelines.[18] Will increasing use of HbA1c lead to overdiagnosis of diabetes risk in minority children, (given known non-glycemic racial differences in HbA1c) or appropriate identification of a population at high risk for developing diabetes, and what will be the impact on healthcare delivery and health outcomes? Additional longitudinal studies are needed to assess the ability of different screening tests to predict later development of diabetes, both in the healthcare delivery system as well as in population-based cohorts.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Carly R. Runge participated in the interpretation of the data and writing of the original manuscript. Michelle Ng contributed to the discussion and participated in revising the manuscript. William H. Herman participated in the interpretation of the data. Acham Gebremariam performed the statistical analyses of the data. Emily Hirschfeld contributed to discussion and critiquing the manuscript. Joyce M. Lee was involved in the study concept and design, interpretation of the

data, and writing of the original manuscript. All authors critically reviewed, edited, and approved the final manuscript. Joyce M. Lee 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.

PEER REVIEW

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