BMJ Open Diabetes Research & Care

Racial differences in measures of glycemia in the Vitamin D and Type 2 Diabetes (D2d) Study: a secondary analysis of a randomized trial

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To cite: LeBlanc ES, Pittas AG, Nelson J, *et al*. Racial differences in measures of glycemia in the Vitamin D and Type 2 Diabetes (D2d) Study: a secondary analysis of a randomized trial. *BMJ Open Diab Res Care* 2024;**12**:e003613. doi:10.1136/bmjdrc-2023-003613

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjdrc-2023-003613).

Received 14 July 2023
Accepted 12 January 2024

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ABSTRACT

Introduction Understanding how race may influence the association between A1c and glycemia can improve diabetes screening. We sought to determine whether, for a given A1c level, glucose levels during an oral glucose tolerance test (OGTT) differed by race.

Research design and methods From data collected at 22 US clinical sites, we conducted a cross-sectional study of concurrently measured A1c and OGTT and observational longitudinal follow-up of the subset with high-risk pre-diabetes. Numerical integration methods were used to calculate area under the glycemic curve (AUC_{glu}) during OGTT and least squares regression model to estimate A1c for a given AUC_{glu} by race, controlling for potential confounders.

Results 1016 black, 2658 white, and 193 Asian persons at risk of diabetes were included in cross-sectional analysis. Of these, 2154 with high-risk pre-diabetes were followed for 2.5 years. For a given A1c level, AUC_{glu} was lower in black versus white participants. After adjustment for potential confounders, A1c levels for a given AUC_{glu} quintile were 0.15–0.20 and 0.02–0.19 percentage points higher in black and Asian compared with white participants, respectively ($p<0.05$). In longitudinal analyses, black participants were more likely to be diagnosed with diabetes by A1c than white participants (28% vs 10%, respectively; $p<0.01$). Black and Asian participants were less likely to be diagnosed by fasting glucose than white participants (16% vs 15% vs 37%, respectively; $p<0.05$). Black participants with A1c levels in the lower-level quintiles had greater increase in A1c over time compared with white participants.

Conclusions Use of additional testing beyond A1c to screen for diabetes may better stratify diabetes risk in the diverse US population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have found that the relationships between glucose and A1c vary between different racial and ethnic groups. However, whether this impacts diabetes diagnosis has not been fully evaluated.

WHAT THIS STUDY ADDS

⇒ We found that A1c levels for a given area under the glycemic curve were higher in black and Asian compared with white participants and that, during follow-up, the test used to diagnose type 2 diabetes varied by race.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that use of additional testing beyond A1c to screen for diabetes may better stratify diabetes risk in the diverse US population.

Hemoglobin A1c (A1c), fasting plasma glucose (FPG), and 2-hour post-load glucose (2hPG) can all be used to diagnose pre-diabetes and diabetes. The relationship of A1c with FPG and the glucose peak and area under the curve during an oral glucose tolerance test (OGTT) was established in the 1970s. Twenty years later, the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study reported that A1c levels were associated with diabetic microvascular complications.[1 2] These findings led to the adoption of A1c as a method of diagnosing diabetes and pre-diabetes by American Diabetes Association (ADA) and WHO guidelines in 2010 and 2011.[3 4] Compared with FPG and 2hPG, A1c is unaffected by factors such as exercise and acute stress, does not require fasting or glucose drink consumption, and reflects longer-term glycemic exposure.[5] A1c also has greater pre-analytical stability, less biological variability, and international standardization.[5]

However, previous studies have found that the relationships between FPG, 2hPG, and A1c vary from person to person and between different racial and ethnic groups. In

particular, A1c has been shown to be 0.1–0.6 percentage points higher in black compared with white individuals for the same degree of glycemia as measured by OGTT, FPG, continuous glucose monitoring, and self-monitored plasma glucose profiles.[6–11] Differences in the association between A1c and glycemia among people of different races can have an impact on diabetes diagnosis, and this has not been fully evaluated.

The Vitamin D and Type 2 Diabetes (D2d) Study, a diabetes prevention trial conducted from October 2013 to November 2018, included a range of participants by age, gender, race, ethnicity, and spectrum of glycemia (normal glucose regulation, pre-diabetes, diabetes).[12] We collected concurrent data on A1c and glucose measurements during an OGTT, allowing us to examine associations between A1c and both fasting and post-glucose load glycemia. In addition, trial participants underwent repeat glucose testing during follow-up, allowing examination of the potential impact of race on diagnostic testing for diabetes. The D2d cohort, which also collected data on social determinants of health, offers a unique opportunity to examine associations between measures of glycemia by race and ethnicity cross-sectionally and longitudinally.

We hypothesized that for a given area under the glycemic curve (AUC_{glu}) level, A1c would be higher in black individuals compared with individuals who identified as white or Asian, even after controlling for potential confounders. We also hypothesized that the association would remain stable over time and would lead to more black participants being diagnosed with diabetes based on the standard A1c criterion compared with white and Asian participants. We hypothesized that there would be no difference by ethnicity.

RESEARCH DESIGN AND METHODS

Overview of the D2d Study

D2d was a multicenter, randomized, double-blind, placebo-controlled primary prevention clinical trial comparing the effect of 4000 IU of vitamin D_3 versus matching placebo, randomized in a 1:1 ratio, on the incidence of diabetes in people at high risk of diabetes, followed over a median of 2.5 years (ClinicalTrials.gov NCT01942694). The design, including eligibility criteria, when and where data were collected, a description of the intervention, and how randomization was implemented, and main results of D2d have been published.[12 13]

Baseline characteristics, including social determinants of health and vitamin D level

Self-administered questionnaires were used to collect data on age, gender, smoking status (never, former, current), annual household income (<$75 000 vs ≥$75 000), and education (no high school, no post-high school, some post-high school, bachelor's degree, graduate degree). Other self-administered questionnaires included the International Physical Activity Questionnaire[14] to determine total physical activity per week (metabolic equivalents-hours/week) and the Multicultural Food Frequency Questionnaire to determine alcohol use (g/day) and dietary glycemic index. Body mass index (BMI) (kg/m^2) was calculated using weight and height measured using standardized procedures. The 25-hydroxyvitamin D level (25(OH)D) was measured by liquid chromatography–tandem mass spectrometry, as previously described.[12]

Race and ethnicity

Reporting race and ethnicity in this study was mandated by the US National Institutes of Health (NIH). Race and ethnicity were self-reported by study participants. Per NIH guidance, race was categorized as American Indian or Alaska Native, Asian, black or African American, Native Hawaiian or Other Pacific Islander, white, or more than one race. Due to the low number of participants in certain racial categories, our analytical sample for the analysis by race was restricted to participants who self-identified their race as black, white, or Asian (online supplemental figure 1). Ethnicity was categorized as Hispanic or not Hispanic.

Glycemic testing

D2d used a two-step screening process (online supplemental figure 1). At screening step 1, FPG and A1c were measured. If results suggested participants were likely to meet D2d glycemic enrollment criteria, they were invited for a full screening visit. At the full screening visit, which also served as the baseline visit for participants who were randomized, participants underwent a 75-gram OGTT to measure FPG, glucose at 30 min (Glu-30) and 2hPG, along with A1c. Participants were instructed not to change physical activity and diet for the 3 days before the OGTT. All tests were analyzed by the D2d central laboratory to determine final eligibility for the trial. A1c was measured by an ion-exchange high-performance liquid chromatography method certified by the National Glycohemoglobin Standardization Program.[15] Plasma glucose was measured with the use of a hexokinase method (Roche Cobas Integra at the University of Vermont Laboratory for Clinical Biochemistry Research).[12]

Participants

Cross-sectional

The cross-sectional analyses include participants who underwent glycemic testing at the full screening visit (online supplemental figure 1; n=3876), regardless of their randomization status in the trial.

Longitudinal

Eligibility criteria for D2d included meeting at least two of the glycemic criteria for pre-diabetes per the 2010 ADA guidelines: FPG 100–125 mg/dL (5.6–6.9 mmol/L), 2hPG 140–199 mg/dL (7.8–11.0 mmol/L), or A1c 5.7–6.4% (39–46 mmol/mol).[16 17] Participants were also required to be age ≥30 years (≥25 years for American Indians, Alaska Natives, Native Hawaiians, or other Pacific Islanders) and have a BMI 24–42 kg/m^2 (22.5–42 kg/m^2

for Asian). Exclusion criteria included use of medications approved for treatment of diabetes, history of bariatric surgery, chronic kidney disease (estimated glomerular filtration rate <50 mL/min/1.73 m^2)[13] and presence of hemoglobin variants identified during screening that are known to interfere with the A1c assay, such as hemoglobin E, but not hemoglobin S or hemoglobin C.[18]

Participants who were randomized in D2d and self-reported to be of black, white or Asian race are included in the present longitudinal analyses if they had at least one follow-up glycemic measure (online supplemental figure 1; n=2154). Glycemic status was assessed annually with FPG, A1c and 2hPG, and semiannually with FPG and A1c. During the trial, if at least two of the glycemic measures met the ADA thresholds for diabetes,[16] the participant was considered to have met the diabetes outcome. When only one glycemic measure met the threshold, confirmatory testing was performed. A diagnosis of diabetes made outside of D2d that was not confirmed by the D2d central laboratory testing was not considered in the present analysis.

Derived glycemic values

To measure the glucose excursion during an OGTT, we used optimum numerical integration methods to estimate AUC_{glu} from FPG and plasma glucose at 30 min and at 2 hours.[19] We then categorized participants into AUC_{glu} quintiles. The integration of 3 glucose points provides a better picture of the overall glycemia versus examining individual time points.

Statistical analysis

Baseline difference in potential confounders

Descriptive statistics included percentage, means±SD, or medians (IQR: Q1–Q3) for non-normally distributed data. Comparisons between racial and ethnic groups at baseline used Fisher's exact test, the X^2 test, the Wilcoxon rank-sum test, or the pooled-variance t-test. Given the large Ns in our population, we used standard mean difference (SMD) to examine the strength of the association with racial and ethnic categories (>0.2 or <−0.2 indicates a moderate association; SMD >0.5 or <−0.5 indicates a large association).

Cross-sectional analysis

We examined the relationship between A1c and AUC_{glu} and component glucose measures (FPG, Glu-30 and 2hPG) stratified by self-identified race (black, white, or Asian). The linear intercept and slope with 95% CIs between glucose measures and A1c were plotted for each race. Linearity was evaluated by adding higher-order polynomial terms to the model and considered statistically significant at p<0.05. We repeated the analysis using ethnicity instead of race. In addition, we repeated the race analyses excluding those with hemoglobin variants. The primary analysis was a least squares regression model with A1c as the dependent variable and AUC_{glu}, race, and the interaction between them as independent variables. All reported p values were two-sided. To account for potential confounders in the association between A1c and AUC_{glu}, we then estimated racial and ethnic mean differences and 95% CIs in A1c for a given AUC_{glu}, controlling for the following potential confounders: age, gender, BMI, the interaction between age and gender and BMI, alcohol use, education, income, presence of hemoglobin variants, smoking status, physical activity, dietary glycemic index, and baseline 25(OH)D level; we refer to this as adjusted A1c.

Longitudinal analysis

We tested whether the distribution of diabetes diagnoses differed by race and ethnicity using X^2 tests of association. We also examined the change in A1c over time in black and white participants. We estimated the average per cent change from baseline (and 95% CIs) of A1c in each AUC_{glu} quintile for each race and the difference between race groups using linear mixed-effects regression models to account for repeated measurements over time. The unadjusted and adjusted models used A1c as the dependent variable and AUC_{glu}, baseline A1c, race, and the interaction between race and AUC_{glu} as independent variables. All reported p values were two-sided. The adjusted model controlled for the same potential confounders as the primary analysis.

RESULTS

Baseline characteristics

The cross-sectional analysis included 1016 black, 2658 white, and 193 Asian participants with complete glycemic measurements (FPG, Glu-30, 2hPG), of whom 323 were Hispanic and 3544 were non-Hispanic. Their baseline characteristics are shown in online supplemental tables 1 and 2. White participants were older, had higher 25(OH)D levels, and consumed more alcohol than black and Asian participants. Black participants had lower hemoglobin levels, were more likely to have hemoglobin S trait, and were less likely to earn $75 000 or more per year or have a graduate or professional degree than white participants. Asian participants had lower BMIs, higher incomes, higher education levels, and lower physical activity levels than white participants. Compared with white participants, a larger proportion of black participants had an A1c in the pre-diabetes range and a smaller proportion had an FPG in the pre-diabetes range. Black participants were more likely than white participants to have all three tests in the normal range. Hispanic participants were younger than non-Hispanic participants (online supplemental table 2), relatively more women self-identified as Hispanic than non-Hispanic, and Hispanic participants had lower incomes and education levels than non-Hispanic participants.

The longitudinal analysis included 2359 participants (616 black, 1613 white, and 130 Asian) who were randomized and followed over time: of whom, 190 were Hispanic and 2169 were non-Hispanic. Differences in baseline

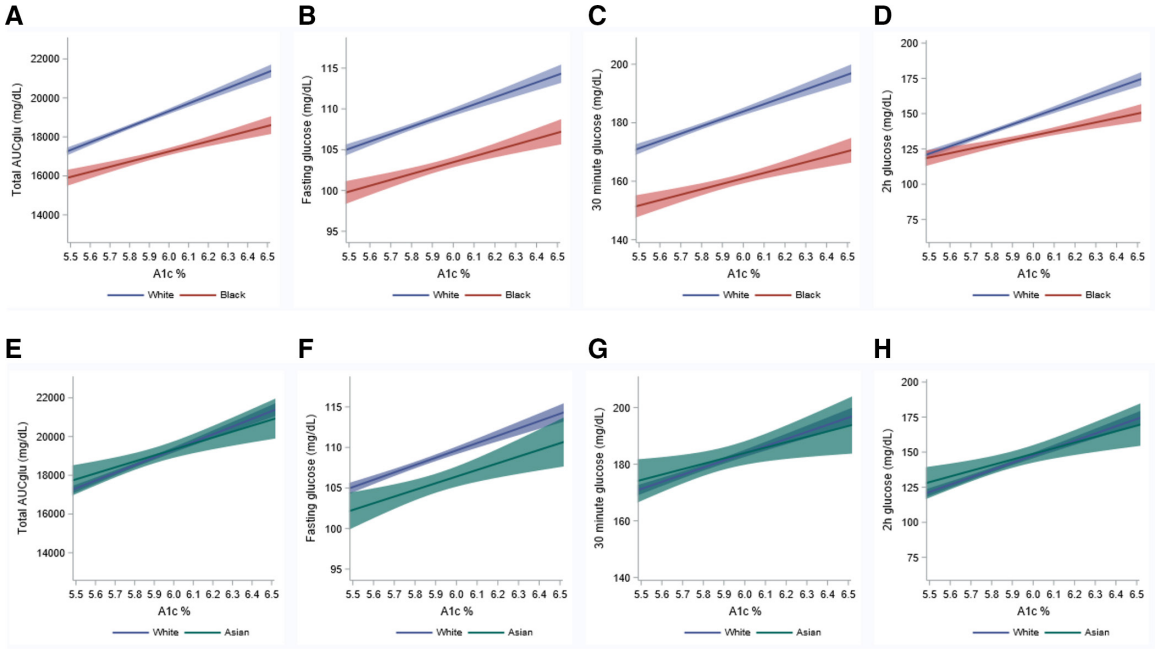

Figure 1 Cross-sectional association* between A1c and AUC_{glu}, and fasting, 30-minute, and 2-hour plasma glucose by race. (A) Association between A1c and AUC_{glu} in black versus white participants; (B) association between A1c and fasting glucose in black versus white participants; (C) association between A1c and 30-minute glucose in black versus white; (D) association between A1c and 2-hour glucose in black versus white participants; (E) association between A1c and AUC_{glu} in Asian versus white; (F) association between A1c and fasting glucose in Asian versus white participants; (G) association between A1c and 30-minute glucose in Asian versus white participants; (H) association between A1c and 2-hour glucose in Asian versus white participants. *Shaded areas represent 95% CIs of the regression curve. AUC_{glu}, area under the glycemic curve.

characteristics of those randomized in D2d by race were similar to those seen in the screening population (online supplemental tables 3 and 4).

Baseline AUC_{glu} categories

The quintiles of AUC_{glu} for the full screening cohort are shown in online supplemental figure 2, along with the mean FPG, Glu-30 and 2hPG values for each AUC_{glu} quintile. The mean FPG, Glu-30, and 2hPG level for the first quintile were 98.7, 140.2, and 95.2 mg/dL compared with 115.5, 208.6, and 198.3 mg/dL in the highest quintile, respectively.

Cross-sectional association between A1c and AUC_{glu}, FPG, 2hPG by race

For a given A1c level, the AUC_{glu} was lower in black versus white participants (figure 1A). A similar pattern emerged when we examined FPG, Glu-30, or 2hPG for a given A1c among black and white participants (figure 1B–D). Differences were less pronounced for 2hPG at lower A1c levels. When we excluded the 37 with hemoglobin variants (ie, hemoglobin S and hemoglobin C), the associations did not change (data not shown). When we compared Asian with white participants, overall AUC_{glu} for a given A1c was not different. However, Asian participants did have lower FPG for a given A1c compared with white participants, although there were no differences in AUC_{glu} levels by Glu-30 and 2hPG (figure 1E–H). There were no significant differences in AUC_{glu} for a given A1c between Hispanic versus non-Hispanic participants (data not shown).

When we estimated racial and ethnic mean differences and 95% CIs in A1c for a given AUC_{glu} controlling for potential confounders, the adjusted A1c levels for a given AUC_{glu} quintile were 0.15–0.20 and 0.02–0.19 percentage points higher in black ($p<0.01$ all quintiles) and Asian ($p<0.05$ for quintiles 1, 3–5; NS for quintile 2), compared with white, participants (table 1). In the highest AUC_{glu} quintile, Hispanic participants had a higher adjusted A1c compared with non-Hispanic participants (6.05 (5.98, 6.12) vs 5.96 (5.95, 5.98); $p<0.03$), but there were no A1c differences between ethnic groups in the other AUC_{glu} quintiles (online supplemental table 5).

Racial differences in tests confirming diagnosis of diabetes during follow-up

When the diagnosis of diabetes was made during study trial follow-up, the diagnostic tests confirming diagnosis differed by race. Of those who developed diabetes during the study, 27.5% of black participants vs 9.8% of white participants were diagnosed by two A1c values ($p<0.01$; table 2) and 19.2% vs 12.0% were diagnosed by simultaneously elevated A1c and FPG ($p=0.04$), respectively. A much larger proportion of white participants (37.3%) were diagnosed with diabetes by two FPG values compared with 15.8% and 15.2% of black and Asian participants ($p<0.01$ and $p=0.01$, respectively). There were no other differences between racial groups. These

Table 1 A1c level by AUC-glucose quintiles in screening cohort by race

AUC-glucose quintile*	Black		White		Asian	
Mean (range)	Observed	Adjusted†	Observed	Adjusted†	Observed	Adjusted†
Low—1	5.91 (5.89, 5.94)‡	5.94 (5.91, 5.97)‡	5.73 (5.71, 5.75)	5.74 (5.71, 5.76)	5.85 (5.74, 5.95)§	5.87 (5.77, 5.98)‡
2	5.96 (5.93, 5.99)‡	5.98 (5.95, 6.02)‡	5.78 (5.76, 5.81)	5.78 (5.76, 5.80)	5.78 (5.69, 5.86)	5.80 (5.71, 5.89)
3	5.96 (5.93, 6.00)‡	5.98 (5.94, 6.01)‡	5.82 (5.80, 5.84)	5.81 (5.79, 5.83)	5.94 (5.87, 6.01)‡	6.00 (5.92, 6.07)‡
4	6.02 (5.98, 6.06)‡	6.02 (5.98, 6.06)‡	5.86 (5.84, 5.88)	5.84 (5.82, 5.86)	5.91 (5.84, 5.98)	5.93 (5.86, 6.00)§
High—5	6.07 (6.03, 6.12)‡	6.09 (6.04, 6.14)‡	5.95 (5.93, 5.97)	5.94 (5.92, 5.96)	5.85 (5.74, 5.95)	6.03 (5.96, 6.10)§

*Quintiles were derived for the screening population (all races combined).
†Estimated linear regression for adjusted A1c; R^2=0.046 for observed model (no adjustment); R^2=0.119 for model adjusted for race+race×AUC quintile group; R^2=0.137 for model adjusted for race+AUC quintile groups+race×AUC quintile groups+age×gender×BMI; R^2=0.148 for fully adjusted model=(race)+AUC quintile groups+(race)×AUC quintile groups+adjusted variables (age, gender, BMI, age×gender×BMI, alcohol use, education, income, presence of hemoglobinopathy, smoking status, physical activity, dietary glycemic index, and 25(OH)D (R^2=0.148).
‡P<0.01 for white versus black participants or white versus Asian participants.
§P<0.05 for white versus Asian participants.
AUC, area under the curve; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D.

differences are likely attributable to black participants having higher A1c levels at diagnosis compared with white participants (mean (SD): 6.5 (0.6) vs 6.3 (0.5); p<0.001). FPG and 2hPG did not differ between racial groups at diabetes diagnosis. Although mean A1c (SD) was higher at diabetes diagnosis in Hispanic versus non-Hispanic participants (6.5 (0.6) vs 6.3 (0.5); p=0.02), FPG and 2hPG were not different between ethnic groups at diabetes diagnosis (data not shown).

Longitudinal change in A1c over time by baseline AUC_{glu} quintile by race

Average change in A1c compared with baseline did not differ by treatment group and so the vitamin D and placebo groups were combined in the longitudinal analysis. The absolute increase in A1c over time according to baseline AUC_{glu} quintiles differed by race (online supplemental table 6). Compared with white participants, black participants in lower baseline AUC_{glu} quintiles had greater increases in A1c over time (first quintile: 0.76 (0.29, 1.23) vs 0.03 (−0.37, 0.43); unadjusted p=0.02 and second quintile: 1.81 (1.23, 2.40) vs 0.85 (0.48, 1.21); unadjusted p=0.006, respectively). When adjusted for potential confounders, the p value for A1c change in the first quintile was no longer significant (adjusted p=0.057) but remained significant for those in the second quintile (adjusted p=0.027). A1c increased similarly in white and

Table 2 Glycemic tests at diabetes diagnosis by race in enrolled population (longitudinal analysis)

		Race				White vs black	White vs Asian
Observed level, mean (SD)	Overall n=563	Black n=120	White n=410	Asian n=33	P value	P value	P value
Fasting plasma glucose (FPG), mg/dL	127.6 (22.3)	128.7 (31.5)	127.7 (19.5)	121.8 (12.9)	0.28	0.91	0.30
2-hour post-load glucose (2hPG), mg/dL	205.7 (47.9)	215.7 (50.1)	202.3 (45.2)	213.5 (62.8)	0.10	0.12	0.50
Hemoglobin A1c, %	6.3 (0.5)	6.5 (0.6)	6.3 (0.5)	6.4 (0.3)	<0.01	<0.001	0.43
Diabetes confirmatory tests, no (%)					<0.001		
2 A1c tests	77 (13.7)	33 (27.5)	40 (9.8)	4 (12.1)		<0.01	0.66
2 FPG tests	177 (31.4)	19 (15.8)	153 (37.3)	5 (15.2)		<0.01	0.01
2 2hPG tests	109 (19.4)	16 (13.3)	83 (20.2)	10 (30.3)		0.09	0.17
A1c+FPG	77 (13.7)	23 (19.2)	49 (12.0)	5 (15.2)		0.04	0.59
FPG+2hPG	62 (11.0)	12 (10.0)	46 (11.2)	4 (12.1)		0.71	0.87
2hPG+A1c	34 (6.0)	10 (8.3)	21 (5.1)	3 (9.1)		0.19	0.33
A1c+FPG+2hPG	27 (4.8)	7 (5.8)	18 (4.4)	2 (6.1)		0.51	0.66

black persons in the three highest baseline AUC_{glu} quintiles before and after adjustment.

CONCLUSIONS

This study confirms previous findings that black individuals have higher A1c levels than white participants and adds information about the association between glucose and A1c in the less well-studied Asian population. It also extends previous work by relating baseline A1c to incident diabetes and change in A1c over a 2.5-year period according to race.

The present analyses focused on understanding how race may impact the association between A1c and glycemia as measured by AUC_{glu} during an OGTT in a population with a range of glycemia (from normal to diabetes). Most of the prior work has examined the association between A1c and glycemia by race using adjustment of A1c by glucose levels. These studies have generally found that black participants have higher A1c levels compared with white participants.[6–8 10 20] A different analytic approach involving estimation of A1c for a given glucose level was used by this study, as well as two prior studies.[8 21] In one of these previous studies, which was conducted in those with type 1 diabetes, black individuals had a higher A1c for a given mean glucose as measured by continuous glucose monitoring (CGM).[8] In the other study, which consisted predominantly of those with type 1 and type 2 diabetes, association between A1c and mean glucose during fingerstick monitoring was found.[21] Our study adds to this prior work by estimating racial mean differences and 95% CIs in A1c for a given AUC_{glu} controlling for potential confounders in a population consisting predominantly of those with pre-diabetes. While we found that race had a small but significant association with A1c for a given level of mean glycemia, other factors beyond race may also contribute to explained variance. Because these study data were not specifically collected for this post-hoc analysis, the results are preliminary and can only suggest possible differences.

The association between A1c and glucose has been less well studied in other races and ethnic groups. We noted that Asian participants with a given A1c level had lower FPG levels, but not AUC_{glu}, compared with white participants and after adjustments for potential covariates, particularly BMI, A1c was generally higher for a given AUC_{glu} quintile. Previous work examining A1c levels in Asian compared with white individuals has been mostly in those with diabetes and has had mixed findings.[7 10 21] Our study adds important data on a possible clinically important difference in the A1c–glucose association among Asian and white individuals with pre-diabetes. Previous work from the National Health and Nutrition Examination Survey found that Mexican-Americans were more likely to have an elevated A1c than non-Hispanic white people.[22] In studies of those with high risk of diabetes and established diabetes, A1c levels were higher in Hispanic versus non-Hispanic participants after adjustment for glucose levels,[10] which matches our finding that adjusted A1c differed by ethnicity in the highest AUC_{glu} quintile.

It has been proposed that racial differences in the glucose–A1c relationship could be due to differences in prevalence of hemoglobin variants,[23] but when we excluded those with abnormal hemoglobin variants, the associations remained unchanged. Differences in how much glucose attaches to hemoglobin for a given blood glucose concentration have also been invoked as an explanation for the differences in associations between A1c and glucose measures by race. Other explanations for the racial and ethnic differences in the A1c–glucose relationship include differences in red blood cell, age and turnover, lower average hemoglobin levels, and genetic differences.[24–26] There may also be other factors that were not assessed in the present study (including social determinants and glucoregulatory function) that might impact long-term glycemic excursions that may not be captured by measurement of FPG or 2hPG.[26 27]

The most novel piece of our work is the longitudinal follow-up, which reveals that racial differences in the glucose–A1c relationship likely have a clinical impact. Among black participants, A1c was more likely than FPG or 2hPG to diagnose both high-risk pre-diabetes at baseline and incident diabetes during study follow-up. On the other hand, white participants were more likely to be diagnosed with diabetes using FPG compared with black and Asian participants. Therefore, if A1c alone is used to screen for pre-diabetes and diabetes, A1c differences in black and Asian compared with white individuals would lead to differential diabetes diagnoses. Descriptively, the 2-hour time point during the OGTT appeared a better approximation of A1c in black persons compared with the other concurrent time points. Use of additional testing beyond A1c to screen for diabetes may better stratify diabetes risk in the diverse US population, especially using the 2-hour OGTT which showed less divergence between black and white participants. While the choice of screening tests may influence when individuals in different ethnic groups are diagnosed with diabetes, it is unclear whether these differences in individual's glycemic testing at the time of diabetes diagnosis have long-term impact on the development of microvascular and macrovascular complications.[28]

We also examined longitudinal change in A1c by baseline AUC_{glu} quintile according to race. Our results suggest that black participants who have the lowest AUC_{glu} during an OGTT (and theoretically the least risk of progression to diabetes) have a more rapid rise of A1c than white participants who are in the same low AUC_{glu} category. This finding needs confirmation in other cohorts to better understand how frequently A1c needs to be monitored among the diverse US population who are in the early stages of hyperglycemia.

Our study has several strengths, including a large sample size, extensive phenotyping of people at risk of diabetes, and longitudinal follow-up from pre-diabetes

to diabetes. Our study also had some limitations. The screening cohort for the cross-sectional analysis had already been through a pre-screening process which likely resulted in a screened population at relatively higher risk than the general population. We were also limited by only having a single OGTT per person, while A1c reflects approximately 2 months of glycemia. Future research should examine racial differences in fasting and postprandial glucose levels over longer periods of time, with multiple test results and/or CGM, reflecting the same time window as A1c.

In conclusion, our work confirms previous studies reporting that A1c is higher for a given mean glucose level in those who self-identify as black compared with white even after adjustment for potential covariates. This finding indicates that choice of screening tests for pre-diabetes and diabetes may lead to different diagnostic outcomes in different racial groups, particularly between white and black individuals. Such differences in mean glycemia at the time of diabetes diagnosis may have important clinical implications with regard to how early diabetes is detected which can have an impact on management and development of long-term complications; these questions require additional study.

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Acknowledgements The authors thank the D2d investigators, staff, and trial participants for their outstanding dedication and commitment to the study. AGP is supported in part by generous donations to the Tupper Research Fund at Tufts Medical Center.

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Funding The conduct of the trial was supported primarily by the NIDDK and the Office of Dietary Supplements of the National Institutes of Health through the multicenter clinical study cooperative agreement (U01DK098245; principal investigator, AGP) to Tufts Medical Center, where the D2d Coordinating Center is based. The U01 grant mechanism establishes the NIDDK project scientist (Dr Staten) as a member of the D2d Research Group. The trial also received secondary funding from the American Diabetes Association to Tufts Medical Center (1-14-D2d-01; principal investigator, AGP).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants. The Tufts Health Sciences IRB served as IRB of the coordinating center, and each of the 22 participating sites' IRBs also approved the study: Tufts Health Sciences IRB Coordinating Center (10594); Maine Medical Center/MaineHealth IRB (958790-9); Tufts Health Sciences IRB, Clinical Site (10866); MedStar Health Research Institute IRB (2013-130); Duke Health IRB (47517); Medical University of South Carolina IRB for Human Research (24354); Florida Hospital IRB (481944); Emory University IRB (68082); Mt Sinai Program for the Protection of Human Subjects IRB (16-00216); Northwestern University IRB (78718); University of Tennessee Health Science Center IRB (13-02590); Pennington Biomedical Research Center IRB (2013-042-PBRC D2d); HealthPartners Institute IRB (A12-056); University of Kansas Medical Center IRB (13811); Baylor College of Medicine IRB (H-33130); University of Nebraska Medical Center IRB (411-13-FB); UT Southwestern IRB (8843); University of Southern California Health Sciences Campus IRB (13-00450); Stanford University IRB (27848); Omaha VA Medical Center IRB (874); Kaiser Permanente IRB (4927); Cleveland Clinic IRB (14-718); Colorado Multiple IRB (14-2402). All participants provided informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Datasets generated and/or analyzed during the current study and the associated data dictionary are not publicly available but are available from the D2d Coordinating Center at Tufts Medical Center on reasonable request by bona fide researchers after acceptance for publication. Protocol synopsis, contact details, publications, and the process for collaboration and data requests can be found on the website (d2dstudy.org).

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