



# Association of Baseline Characteristics With Insulin Sensitivity and $\beta$ -Cell Function in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study Cohort

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Neda Rasouli,<sup>1,2</sup> Naji Younes,<sup>3</sup>  
Kristina M. Utzschneider,<sup>4</sup>  
Silvio E. Inzucchi,<sup>5</sup>  
Ashok Balasubramanyam,<sup>6</sup>  
Andrea L. Cherrington,<sup>7</sup>  
Faramarz Ismail-Beigi,<sup>8</sup> Robert M. Cohen,<sup>9</sup>  
Darin E. Olson,<sup>10</sup> Ralph A. DeFronzo,<sup>11</sup>  
William H. Herman,<sup>12</sup> John M. Lachin,<sup>3</sup>  
Steven E. Kahn,<sup>4</sup> and the GRADE Research Group\*

<sup>1</sup>Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado School of Medicine, Aurora, CO

<sup>2</sup>VA Eastern Colorado Health Care System, Aurora, CO

<sup>3</sup>The Biostatistics Center, Department of Biostatistics and Bioinformatics, Milken Institute School of Public Health, The George Washington University, Rockville, MD

<sup>4</sup>Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and the University of Washington, Seattle, WA

<sup>5</sup>Yale School of Medicine, New Haven, CT

<sup>6</sup>Division of Diabetes, Endocrinology and Metabolism, Baylor College of Medicine, Houston, TX

<sup>7</sup>Department of Medicine, The University of Alabama at Birmingham, Birmingham, AL

<sup>8</sup>Department of Medicine, Case Western Reserve University and Louis Stokes Cleveland VA Medical Center, Cleveland, OH

<sup>9</sup>Division of Endocrinology, Diabetes and Metabolism, University of Cincinnati College of Medicine and Cincinnati VA Medical Center, Cincinnati, OH

<sup>10</sup>Atlanta VA Health Care System and Division of Endocrinology, Metabolism, and Lipids, Department of Medicine, Emory University School of Medicine, Atlanta, GA

<sup>11</sup>University of Texas Health Science Center at San Antonio, San Antonio, TX

<sup>12</sup>Departments of Internal Medicine and Epidemiology, University of Michigan, Ann Arbor, MI

Corresponding author: Neda Rasouli, [grademail@bsc.gwu.edu](mailto:grademail@bsc.gwu.edu)

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\*A complete list of GRADE Research Group members is included in the supplementary material online.

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## OBJECTIVE

We investigated sex and racial differences in insulin sensitivity,  $\beta$ -cell function, and glycated hemoglobin (HbA<sub>1c</sub>) and the associations with selected phenotypic characteristics.

## RESEARCH DESIGN AND METHODS

This is a cross-sectional analysis of baseline data from 3,108 GRADE (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study) participants. All had type 2 diabetes diagnosed <10 years earlier and were on metformin monotherapy. Insulin sensitivity and  $\beta$ -cell function were evaluated using the HOMA of insulin sensitivity and estimates from oral glucose tolerance tests, including the Matsuda Index, insulinogenic index, C-peptide index, and oral disposition index (DI).

## RESULTS

The cohort was  $56.6 \pm 10$  years of age (mean  $\pm$  SD), 63.8% male, with BMI  $34.2 \pm 6.7$  kg/m<sup>2</sup>, HbA<sub>1c</sub>  $7.5 \pm 0.5\%$ , and type 2 diabetes duration  $4.0 \pm 2.8$  years. Women had higher DI than men but similar insulin sensitivity. DI was the highest in Black/African Americans, followed by American Indians/Alaska Natives, Asians, and Whites in descending order. Compared with Whites, American Indians/Alaska Natives had significantly higher HbA<sub>1c</sub>, but Black/African Americans and Asians had lower HbA<sub>1c</sub>. However, when adjusted for glucose levels, Black/African Americans had higher HbA<sub>1c</sub> than Whites. Insulin sensitivity correlated inversely with BMI, waist-to-hip ratio, triglyceride-to-HDL-cholesterol ratio (TG/HDL-C), and the presence of metabolic syndrome, whereas DI was associated directly with age and inversely with BMI, HbA<sub>1c</sub>, and TG/HDL-C.

## CONCLUSIONS

In the GRADE cohort,  $\beta$ -cell function differed by sex and race and was associated with the concurrent level of HbA<sub>1c</sub>. HbA<sub>1c</sub> also differed among the races, but not by sex. Age, BMI, and TG/HDL-C were associated with multiple measures of  $\beta$ -cell function and insulin sensitivity.

$\beta$ -Cell function declines progressively during the transition from normal glucose tolerance to impaired glucose tolerance and ultimately to type 2 diabetes (1). The UK Prospective Diabetes Study (UKPDS) showed that  $\beta$ -cell function, as evaluated by the HOMA2-B index, was already diminished by  $\geq 50\%$  at the time of diagnosis of type 2 diabetes and continued to decline over the 6-year trial despite ongoing glucose-lowering medication (2). Since progressive loss of  $\beta$ -cell function represents one of the most important challenges to maintenance of glycemic control in people with long-term type 2 diabetes (1), identifying factors associated with  $\beta$ -cell function and interventions to delay or prevent its deterioration would be of great value.

Previous studies have reported several potential mechanisms underlying progressive  $\beta$ -cell dysfunction, including metabolic abnormalities such as glucotoxicity and lipotoxicity, local or systemic inflammation, oxidative and endoplasmic reticulum stress, and amyloid deposition (3). The phenotypic characteristics associated with  $\beta$ -cell dysfunction in patients with type 2 diabetes have not been clearly defined. The results vary depending on the method of measuring  $\beta$ -cell function and the cohort studied. Previous cross-sectional studies showed that  $\beta$ -cell function differed by sex and type of glucose-lowering medication (4). Insulin treatment initiation as an indirect measure of more severe  $\beta$ -cell dysfunction was associated with diabetes duration, levels of glycated hemoglobin (HbA<sub>1c</sub>), triglycerides (TG), and HDL cholesterol (HDL-C) (5).

Other studies have reported racial differences in the relationship between HbA<sub>1c</sub> and plasma glucose concentration, notably that Black/African Americans have higher HbA<sub>1c</sub> compared with Whites for similar blood glucose levels (6–8). In studies of patients with diabetes, this difference persisted when adjusted for sociodemographic and lifestyle factors (9) and adherence to glycemic-lowering medications (10). In this study, we studied the racial and ethnic differences in HbA<sub>1c</sub> in a large and well-characterized cohort of patients with type 2 diabetes and also assessed whether such differences were associated with measures of  $\beta$ -cell function.

Our objective was to describe the sex and racial differences in  $\beta$ -cell function,

insulin sensitivity, and glycemia. In addition, we investigated the association of selected participant characteristics with  $\beta$ -cell function, insulin sensitivity, and glycemia in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) cohort comprised of participants with a relatively recent diagnosis of type 2 diabetes (mean duration  $\sim 4$  years) using metformin monotherapy.

## RESEARCH DESIGN AND METHODS

GRADE is a National Institutes of Health–funded multicenter study designed to compare the effectiveness of four different glucose-lowering medications, each from a different class: glimepiride (sulfonylurea), sitagliptin (dipeptidyl peptidase 4 inhibitor), liraglutide (glucagon-like peptide 1 receptor agonist), or insulin glargine on glycemic control when added to metformin. The study randomly assigned 5,047 adults with type 2 diabetes at 36 clinical centers and 9 additional subsites across the U.S. We present in this study cross-sectional analyses on a subgroup of this cohort with complete baseline data. The rationale and full details of the study design are found elsewhere (11). All participants provided written informed consent, and the study was approved by each center's institutional review board.

### Eligibility

Participants were eligible to participate in the GRADE Study if they had been diagnosed with type 2 diabetes for  $< 10$  years at the time of screening and were  $\geq 30$  years of age ( $\geq 20$  years if American Indian) at the time of diagnosis, with HbA<sub>1c</sub> 6.8–8.5%, and taking at least 1,000 mg of metformin/day at the end of the run-in period. Exclusion criteria included: suspected type 1 diabetes, treatment with glucose-lowering medications other than metformin within the previous 6 months, use of medications that could impact glucose metabolism such as systemic corticosteroids, and significant medical illness or organ failure (11).

### Study Procedures

Eligible participants completed a 4–14-week run-in, during which they were provided metformin, and the dose was increased to 2,000 mg/day or a maximal tolerated dose  $\geq 1,000$  mg/day. At the end of the run-in, after an 8-h overnight

fast, eligible participants (HbA<sub>1c</sub> between 6.8 and 8.5%) underwent an oral glucose tolerance test (OGTT) with metformin held the morning of the test. The participant consumed a 75-g glucose drink within 5 min, and blood samples were drawn at 0, 15, 30, 60, 90, and 120 min relative to the start of glucose ingestion. Samples were collected on ice, spun and aliquoted promptly, and frozen at  $-80^{\circ}\text{C}$  before being shipped on dry ice to the central laboratory (University of Minnesota Advanced Research and Diagnostic Laboratory, Minneapolis, MN), where they were assayed.

### Assays

HbA<sub>1c</sub> was measured in EDTA whole blood on the Automated Glycohemoglobin Analyzer HLC-723G8 (Tosoh Medics, Inc., San Francisco, CA) using an automated high-performance liquid chromatography method. Calibration of this method was evaluated using standard values derived by the NGSP. Glucose was measured in EDTA plasma by a hexokinase method on a Cobas c501 chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Insulin and C-peptide were measured in EDTA plasma on a Cobas e601 immunoassay analyzer using a sandwich immunoassay (Roche Diagnostics). Baseline samples for those randomized to the glargine group ( $n = 1,263$ ) have not yet been assayed for insulin. These baseline samples are being reserved for potential measurement by mass spectrometry owing to difficulties in measuring insulin with immunoassays in patients treated with glargine.

### Measures of Insulin Sensitivity and $\beta$ -Cell Function

The HOMA of insulin sensitivity (HOMA2-S) was calculated using the HOMA2 Calculator version 2.2.3 (Diabetes Trials Unit, University of Oxford, Oxford, U.K.) (12,13). Mean plasma glucose ( $G_m$ ) in milligrams per deciliter and mean insulin ( $I_m$ ) in millinternational units per liter were calculated from the values at 0, 30, 60, 90, and 120 min during the OGTT (14). The Matsuda Index of insulin sensitivity was calculated as  $10^4 / (I_0 \times G_0 \times I_m \times G_m)^{1/2}$ , where  $G_0$  and  $I_0$  are the fasting glucose and insulin.

Early insulin and C-peptide responses to glucose during the OGTT were calculated using the insulinogenic index (IGI) and the C-peptide index, respectively.

They were calculated as the increment in insulin or C-peptide values over the first 30 min, respectively, divided by the increment in glucose over 30 min as follows (15):  $IGI = 100(I_{30} - I_0)/(G_{30} - G_0)$  and  $C\text{-peptide index} = 100(C_{30} - C_0)/(G_{30} - G_0)$ . The late insulin response to glucose was calculated as the ratio of the area under the curve (AUC) for insulin divided by the AUC of glucose values from 60 to 120 minutes:  $100 \times (InsulinAUC_{60-120}/60 - I_0)/(GlucoseAUC_{60-120}/60 - G_0)$ . The oral disposition index (DI), as a measure of  $\beta$ -cell function, was calculated as the ratio of IGI over fasting insulin ( $DI = IGI/I_0$ ) (16).

We used the ratio of fasting C-peptide to fasting insulin ( $1,000 \times C_0/I_0$ ) as a measure of basal insulin clearance based on the assumption that insulin and C-peptide are secreted into the portal vein in a 1:1 molar ratio, and C-peptide is cleared primarily by the kidney (17).

The International Diabetes Federation definition of metabolic syndrome was used to categorize participants in this cohort (18).

### Participants

Of a total of 5,047 GRADE participants, a subgroup with complete data on glucose, insulin, and C-peptide values during the baseline OGTT was included in this study. Insulin was not measured in the 1,263 participants randomized to the glargine group, and thus, this group was excluded from the analysis. Also excluded were 321 participants with incomplete glucose data, 350 with incomplete insulin data, and 5 with incomplete C-peptide data. Thus, data from a total of 3,108 were available for this analysis. There was no significant difference in baseline characteristics of participants included in this study compared with those excluded (data not shown).

Among the 3,108 participants, 2,083 participants (67%) were White, including 423 (14%) Hispanic and 1,651 (53%) non-Hispanic, 553 (18%) Black/African American, 119 (4%) Asian, 103 (3%) American Indian/Alaska Native, and 250 (8%) other.

### Statistical Analysis

Participant characteristics are presented using means and SDs for quantitative variables and counts and column percentages for qualitative variables. Comparisons between men and women used the  $\chi^2$  test of independence for qualitative variables and the Student *t* test with unequal variances using the Welch-Satterthwaite approximation to the df for quantitative variables. Comparisons of

the race categories used the  $\chi^2$  test of independence for qualitative variables and the ANOVA *F* test for quantitative variables. In Table 1, only racial groups with at least 100 members were considered for analysis.

The *P* values for the sex-based difference in Fig. 1A are from a least-squares regression of the ranks of each of the responses on sex adjusted for age, race, and diabetes duration in the combined cohort. The box plots are based on the residuals from ordinary regression models of each response on age, race, and diabetes duration. The *P* values in Fig. 1B are from a least-squares regression of the ranks of each of the responses on racial categories adjusted for sex, age, and diabetes duration. The box plots are based on the residuals from ordinary regression models of each response on age, sex, and diabetes duration. In Fig. 2, the Spearman correlation between two responses is computed as the Pearson correlation of the residuals from separate linear regression models of the ranks of each response on age, sex, race, and diabetes duration. Correlations with the IGI, C-peptide index, and late insulin response are adjusted for insulin sensitivity (HOMA2-S). In order to eliminate significant correlations that are not clinically meaningful, any correlations with  $r < 0.1$  in absolute value are considered clinically nonsignificant even if they were statistically significant at the 0.05 level.

Measures of insulin, HOMA2-S, HOMA2-B, Matsuda Index, insulinogenic and C-peptide indices, late insulin response, and the DI included some extreme outliers. To reduce the influence of outliers on analyses, these variables were winsorized (i.e., values above or below specified cutoffs were replaced by cutoffs) (19). For each variable, the winsorization upper (lower) cutoff was set to the median plus (minus) 8.9 times the distance from the median to the upper (lower) quartiles. For a normally distributed variable, this would result in cutoffs 6 SDs above and below the mean. The number of winsorized values ranged from 5 (0.2%) to 26 (0.8%). Analyses were performed using R version 3.6.0.

## RESULTS

### Differences in Phenotypic and Metabolic Characteristics by Sex and Race

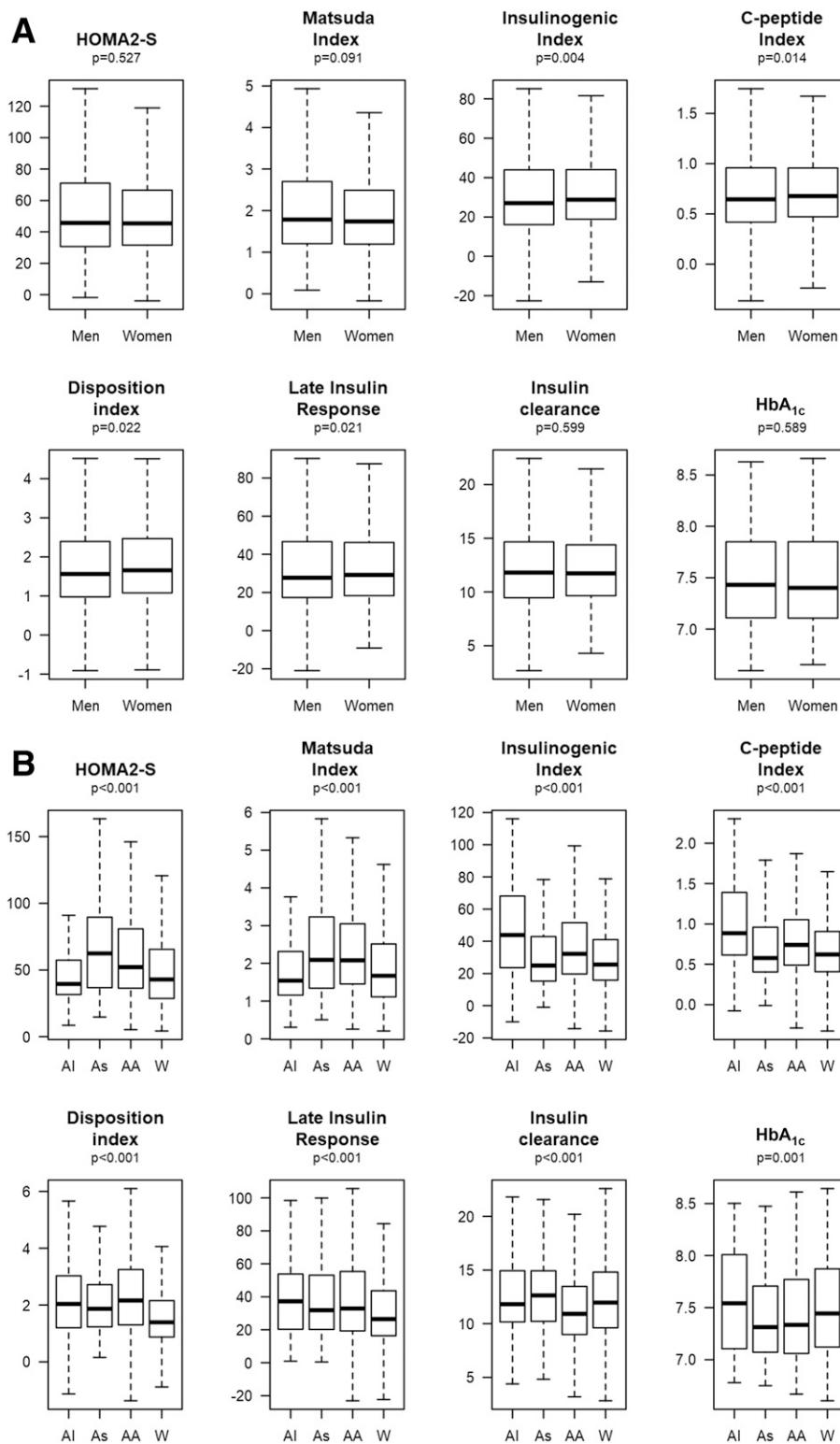
Table 1 shows characteristics of the cohort stratified by sex and race. Overall,

the majority were male, on average middle-aged, obese, and had known diabetes for  $4.0 \pm 2.8$  years. There were no differences between men and women in HbA<sub>1c</sub> or fasting insulin, but men had significantly higher fasting but lower 2-h glucoses and higher HOMA2-S but lower IGI (Table 1). Adjusting for all of these factors yields mean HbA<sub>1c</sub> values of  $7.55 \pm 0.02$  (mean  $\pm$  SE) among men versus  $7.54 \pm 0.02$  among women ( $P \leq 0.83$ ). Men had lower BMI but greater waist-to-hip ratio (WHR) compared with women. In addition, men had higher systolic and diastolic blood pressures, despite reporting more prevalent use of blood pressure-lowering medications. They also had higher TG levels but lower cholesterol levels (total, LDL, and HDL) and reported more prevalent use of lipid-lowering medications (Table 1).

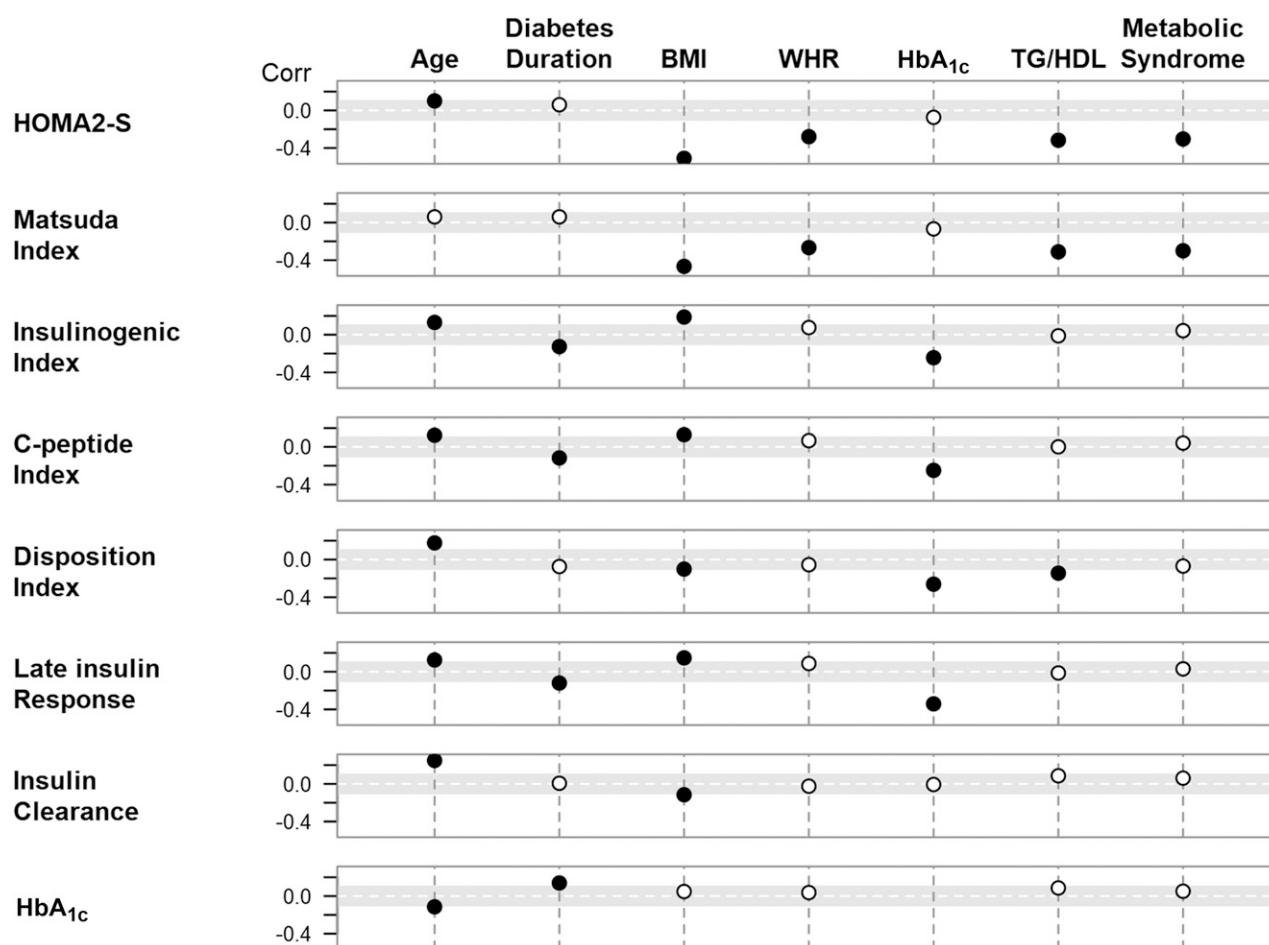
There were also racial differences in characteristics (Table 1). American Indians/Alaska Natives were the youngest, reflecting their lower age inclusion criterion, and they had the shortest duration of diabetes. Asians had the lowest BMI, and American Indians/Alaska Natives had the highest BMI. There were also significant differences in the use of blood pressure and lipid medications among races (Table 1).

There were small but significant racial differences in HbA<sub>1c</sub> ( $\leq 0.2\%$ ;  $P = 0.004$ ) (Table 1) and differences in fasting and 2-h glucose, fasting insulin, HOMA2-S, and IGI (Fig. 1B). Unadjusted, the American Indians/Alaska Natives had the highest HbA<sub>1c</sub> value (7.59%). This was followed by White (7.51%) and Black/African American (7.44%). The pairwise comparisons of Black/African American versus American Indians/Alaska Natives ( $P = 0.006$ ) and versus White ( $P = 0.004$ ) were significant. However, when adjusted for the fasting and 2-h glucoses, the Black/African American had higher HbA<sub>1c</sub> than Whites (7.53% vs. 7.48%;  $P = 0.009$ ). These results were virtually unchanged with further adjustment for sex, fasting insulin, HOMA2-S, and the IGI.

In additional analyses, the 423 Hispanic White and 1,651 non-Hispanic White groups had mean HbA<sub>1c</sub> of  $\sim 7.5\%$ , but the estimates differed significantly when adjusted for fasting and 2-h glucose levels (7.46% vs. 7.56%;  $P < 0.001$ ). Adjusted for glucoses, the mean HbA<sub>1c</sub> among the Black/African American (7.54%) was not different from that of the Hispanic



**Figure 1—A:** Distributions of insulin sensitivity, insulin and C-peptide responses, insulin clearance, and HbA<sub>1c</sub> for men and women. The box plots are adjusted for age, race, and diabetes duration. The P values are for comparisons between men and women adjusted for covariates including age, race, and diabetes duration. **B:** Distributions of insulin sensitivity, insulin and C-peptide responses, insulin clearance, and HbA<sub>1c</sub> by race for American Indian (AI), Asian (As), Black/African American (AA), and White (W). The box plots are adjusted for age, sex, and diabetes duration. The P values are for comparisons among different races adjusted for covariates including age, sex, and diabetes duration.



**Figure 2**—Partial Spearman correlations (Corr) of measures of insulin sensitivity and insulin/C-peptide response with participant characteristics. Correlations are adjusted for age, sex, race, and diabetes duration (excluding the variable being correlated with insulin response or sensitivity). Insulin and C-peptide responses (IGI, C-peptide index, late insulin response, and insulin clearance) are also adjusted for HOMA2-S. The gray band marks correlations that are smaller than  $\pm 0.1$ , and the dotted line marks the correlation of 0. Partial correlations are shown as a black dot if they are nominally significant at the 0.05 level and at least 0.1 in absolute value and as a white dot otherwise. There were no meaningful correlations with diuretics,  $\beta$ -blockers, calcium channel blockers, statins, or fibrates.

White (7.56%) but was significantly higher than that of the non-Hispanic White (7.46%;  $P < 0.001$ ).

#### Differences in Insulin Sensitivity and $\beta$ -Cell Function by Sex and Race

After adjustment for age, race, and diabetes duration, DI was higher in women than men ( $P = 0.022$ ) (Fig. 1A). The IGI ( $P = 0.004$ ), C-peptide index ( $P = 0.014$ ), and late insulin responses ( $P = 0.021$ ) were also higher in women ( $P = 0.045$ ) (Fig. 1A). There were no differences between men and women in insulin sensitivity quantified as HOMA2-S ( $P = 0.527$ ) and the Matsuda index ( $P = 0.091$ ), basal insulin clearance ( $P = 0.138$ ), or HbA<sub>1c</sub> ( $P = 0.460$ ) (Fig. 1A).

After adjustment for age, sex, and diabetes duration, DI was the highest in Black/African Americans followed by American Indians/Alaska Natives, Asians,

and Whites in descending order (Fig. 1B). Asians had the highest insulin sensitivity (by HOMA2-S). Black/African Americans and American Indians/Alaska Natives had higher insulin and C-peptide responses than the others (Fig. 1B). Whites had the lowest late insulin response, while Black/African Americans had the lowest insulin clearance (Fig. 1B).

#### Association of Insulin Sensitivity and $\beta$ -Cell Function With Selected Phenotypic Characteristics

Figure 2 presents the correlations of participant characteristics with measures of insulin sensitivity and  $\beta$ -cell function. BMI and WHR were inversely correlated with insulin sensitivity ( $r = -0.51$  and  $r = -0.47$  for HOMA2-S and Matsuda with BMI, respectively;  $r = -0.28$  and  $r = 0.27$  for WHR,  $P < 0.001$  for both). The correlation of both BMI and WHR with

insulin sensitivity was greater in men than women ( $r = -0.55$  vs.  $r = -0.44$  and  $r = -0.53$  vs.  $r = -0.36$  for HOMA2-S and Matsuda index, respectively,  $P < 0.001$  for both) (Supplementary Tables 1 and 2). Insulin sensitivity also correlated inversely with the triglyceride-to-HDL-cholesterol ratio (TG/HDL-C) ( $r = -0.32$  with HOMA2-S and  $r = -0.31$  with Matsuda,  $P < 0.001$  for both) and presence of metabolic syndrome ( $r = -0.30$  for both HOMA2-S and Matsuda,  $P < 0.001$ ) (Fig. 2 and Supplementary Tables 1 and 2). Again, the association of insulin sensitivity with either lower TG/HDL-C ratio or the absence of metabolic syndrome was greater in men (Supplementary Tables 1 and 2). The correlations of metabolic syndrome and TG/HDL-C ratio with insulin sensitivity were greater in Black/African Americans than Whites (Supplementary Tables 1 and 2). Age, diabetes

**Table 1—Participant characteristics for all and stratified by sex and race**

	Sex				P value	Race				
	All	Men	Women			American Indian	Asian	African American	White	P value
N	3,108	1,984	1,124		103	119	553	2,084		
Age (years)	56.6 ± 10.0	57.7 ± 10.1	54.7 ± 9.7	<0.001	45.6 ± 10.4	53.9 ± 10.3	55.6 ± 8.9	57.9 ± 9.8	<0.001	
Female					63 (61.2)	28 (23.5)	268 (48.5)	661 (31.7)	<0.001	
Race				<0.001						
American Indian/Alaska Native	103 (3.3)	40 (2.0)	63 (5.6)							
Asian	119 (3.8)	91 (4.6)	28 (2.5)							
Hawaiian/Pacific Islander	20 (0.6)	15 (0.8)	5 (0.4)							
Black or African American	553 (17.8)	285 (14.4)	268 (23.8)							
White	2,084 (67.1)	1,423 (71.7)	661 (58.8)							
Other/multiple	189 (6.1)	107 (5.4)	82 (7.3)							
Unknown/not reported	40 (1.3)	23 (1.2)	17 (1.5)							
BMI (kg/m <sup>2</sup> )	34.2 ± 6.7	33.6 ± 6.2	35.2 ± 7.3	<0.001	36.5 ± 7.4	28.9 ± 5.2	34.2 ± 6.8	34.4 ± 6.5	<0.001	
100 * WHR	99.2 ± 8.3	102.2 ± 7.2	93.8 ± 7.3	<0.001	99.2 ± 8.8	96.7 ± 7.9	97.0 ± 8.2	99.9 ± 8.2	<0.001	
Diabetes duration (years)	4.0 ± 2.8	4.1 ± 2.8	3.9 ± 2.8	0.078	2.8 ± 2.6	4.3 ± 2.7	4.2 ± 2.7	4.1 ± 2.8	<0.001	
HbA <sub>1c</sub> (%)	7.5 ± 0.5	7.5 ± 0.5	7.5 ± 0.5	0.997	7.6 ± 0.5	7.4 ± 0.4	7.4 ± 0.5	7.5 ± 0.5	0.004	
Fasting glucose (mg/dL)	151.7 ± 30.9	153.1 ± 30.8	149.3 ± 30.9	<0.001	144.9 ± 34.6	141.2 ± 23.1	139.0 ± 29.2	156.4 ± 30.3	<0.001	
2-h glucose (mg/dL)	287.9 ± 55.2	283.4 ± 53.8	295.9 ± 56.7	<0.001	278.7 ± 62.8	285.6 ± 53.3	272.7 ± 59.3	292.6 ± 53.1	<0.001	
Fasting insulin (mU/L)	21.5 ± 14.8	21.4 ± 15.1	21.6 ± 14.4	0.847	27.0 ± 17.5	16.2 ± 10.1	18.6 ± 13.1	22.5 ± 15.5	<0.001	
Metformin dose at screening (mg/day)	1,586.6 ± 525.0	1,602.5 ± 521.7	1,558.3 ± 529.9	0.025	1,648.1 ± 499.9	1,558.0 ± 527.6	1,494.9 ± 544.7	1,623.9 ± 513.3	<0.001	
Systolic BP (mmHg)	128.1 ± 14.6	128.8 ± 14.6	126.9 ± 14.6	<0.001	122.3 ± 11.1	126.8 ± 15.2	128.6 ± 15.0	128.7 ± 14.3	<0.001	
Diastolic BP (mmHg)	77.2 ± 9.8	77.7 ± 9.7	76.3 ± 9.8	<0.001	78.2 ± 7.8	78.6 ± 10.1	78.3 ± 10.4	76.9 ± 9.6	0.005	
Total cholesterol (mg/dL)	162.8 ± 37.2	157.9 ± 37.3	171.6 ± 35.3	<0.001	161.0 ± 28.4	164.0 ± 35.9	166.7 ± 35.8	161.7 ± 38.0	0.038	
HDL (mg/dL)	43.4 ± 10.6	41.0 ± 9.3	47.6 ± 11.5	<0.001	41.8 ± 7.5	44.9 ± 9.7	48.2 ± 12.3	42.0 ± 10.0	<0.001	
LDL (mg/dL)	89.6 ± 31.3	86.1 ± 30.8	95.7 ± 31.1	<0.001	88.9 ± 24.1	92.4 ± 30.2	97.6 ± 31.5	86.9 ± 31.2	<0.001	
TG (mg/dL)	154.2 ± 124.1	160.1 ± 138.2	143.8 ± 93.3	<0.001	153.2 ± 73.3	136.2 ± 73.8	105.4 ± 69.7	169.5 ± 135.7	<0.001	
ACE/ARB	1,350 (43.4)	923 (46.5)	427 (38.0)	<0.001	49 (47.6)	35 (29.4)	240 (43.4)	925 (44.4)	0.012	
Diuretics	722 (23.2)	464 (23.4)	258 (23.0)	0.818	3 (2.9)	21 (17.6)	157 (28.4)	497 (23.8)	<0.001	
β-Blockers	560 (18.0)	396 (20.0)	164 (14.6)	<0.001	8 (7.8)	16 (13.4)	95 (17.2)	415 (19.9)	0.004	
Calcium channel blockers	428 (13.8)	292 (14.7)	136 (12.1)	0.048	4 (3.9)	15 (12.6)	125 (22.6)	263 (12.6)	<0.001	
Statins	1,950 (62.7)	1,333 (67.2)	617 (54.9)	<0.001	31 (30.1)	79 (66.4)	319 (57.7)	1,383 (66.4)	<0.001	
Fibrates	97 (3.1)	72 (3.6)	25 (2.2)	0.040	1 (1.0)	1 (0.8)	6 (1.1)	82 (3.9)	0.001	
Matsuda index (μU · mg/dL <sup>-2</sup> · min <sup>-1</sup> )	2.1 ± 1.4	2.2 ± 1.5	2.1 ± 1.4	0.015	1.7 ± 1.1	2.5 ± 1.4	2.5 ± 1.6	2.0 ± 1.4	<0.001	
HOMA2-S	56.5 ± 40.6	57.5 ± 41.7	54.8 ± 38.6	0.075	44.1 ± 31.4	69.9 ± 40.9	64.3 ± 42.6	54.2 ± 39.9	<0.001	
HOMA2-B	67.7 ± 37.0	66.5 ± 37.4	69.8 ± 36.1	0.015	90.7 ± 49.8	61.4 ± 29.5	71.6 ± 38.6	66.0 ± 36.2	<0.001	
IGI (μU/mg)	33.8 ± 27.9	32.6 ± 27.4	35.9 ± 28.8	0.002	52.7 ± 37.3	32.3 ± 28.4	40.0 ± 32.1	31.3 ± 25.0	<0.001	
CPI (nmol/β)	0.7 ± 0.5	0.7 ± 0.5	0.8 ± 0.5	0.046	1.1 ± 0.7	0.7 ± 0.5	0.9 ± 0.6	0.7 ± 0.5	<0.001	
Late insulin response (pmol/mol)	40.3 ± 35.0	39.1 ± 34.3	42.4 ± 36.0	0.013	54.6 ± 47.5	42.8 ± 33.6	45.8 ± 38.4	37.9 ± 33.0	<0.001	
DI (mU/mg)	1.91 ± 1.55	1.85 ± 1.51	2.01 ± 1.60	0.009	2.33 ± 1.82	2.20 ± 1.67	2.57 ± 1.95	1.69 ± 1.32	<0.001	
Insulin clearance (μmol/pmol)	12.5 ± 4.6	12.7 ± 4.6	12.2 ± 4.6	0.003	11.3 ± 4.0	12.6 ± 3.4	11.6 ± 4.2	12.9 ± 4.8	<0.001	

Data are mean ± SD or n (%), unless otherwise indicated. The  $\chi^2$  test of independence was used for qualitative variables. The Student t test with unequal variances was used for quantitative variables comparing men vs. women and the ANOVA F test for quantitative variables in racial groups. Any racial group with <100 members was excluded from this analysis. ARB, angiotensin receptor blocker; BP, blood pressure; CPI, C-peptide index.

duration, and HbA<sub>1c</sub> were not associated with insulin sensitivity (Fig. 2).

DI was positively associated with age ( $r = 0.18$ ;  $P < 0.001$ ) while negatively correlated with BMI, HbA<sub>1c</sub>, and the TG/HDL-C ratio ( $r = -0.10$ ,  $r = -0.26$ , and  $r = -0.15$  respectively,  $P < 0.001$  for all) (Fig. 2 and Supplementary Table 5). The association of DI with age, BMI, HbA<sub>1c</sub>, or the TG/HDL-C ratio was stronger in Whites than Black/African Americans (Supplementary Table 5).

Age also had a positive association with markers of  $\beta$ -cell responses, including IGI ( $r = 0.13$ ), C-peptide index ( $r = 0.12$ ), late insulin response ( $r = 0.13$ ), and insulin clearance ( $r = 0.25$ ,  $P < 0.001$  for all) (Fig. 2 and Supplementary Tables 3–8). The association of age with measures of  $\beta$ -cell response (IGI, C-peptide index, and late insulin response) was stronger in Whites than Black/African Americans (Supplementary Tables 3, 4, and 6). BMI was associated directly with the IGI ( $r = 0.19$ ), C-peptide index ( $r = 0.13$ ), and late insulin response ( $r = 0.15$ ) but inversely with insulin clearance ( $r = -0.13$ ,  $P < 0.001$  for all) (Fig. 2 and Supplementary Table 3). The association of BMI with measures of  $\beta$ -cell response (IGI, C-peptide index, and late insulin response) was stronger in men than women and not different between Whites and Black/African Americans (Supplementary Tables 3, 4, and 6).

Diabetes duration was inversely correlated with markers of  $\beta$ -cell responses, including IGI ( $r = -0.13$ ), C-peptide index ( $r = -0.12$ ), and late insulin response ( $r = -0.12$ ,  $P < 0.001$  for all) (Fig. 2 and Supplementary Tables 2–6).

HbA<sub>1c</sub> was not correlated with insulin sensitivity, but was inversely correlated with other measures of  $\beta$ -cell function ( $r = -0.26$  for DI,  $r = -0.24$  for IGI,  $r = -0.25$  for C-peptide index, and  $r = -0.34$  for late insulin response,  $P < 0.001$ ) (Supplementary Tables 1–7). HbA<sub>1c</sub> was also negatively correlated with increasing age ( $r = -0.11$ ) and increasing diabetes duration ( $r = -0.14$ ,  $P < 0.001$  for both).

Neither treatment for hypertension (ACE/angiotensin receptor blocker, diuretics,  $\beta$ -blockers, or calcium channel blockers) nor dyslipidemia (statins or fibrates) was associated with insulin response or sensitivity (Supplementary Tables 1–7).

## CONCLUSIONS

In the GRADE cohort, there were modest differences between men and women in insulin sensitivity, insulin clearance, and  $\beta$ -cell function in unadjusted models (Table 1). However, with the exception of  $\beta$ -cell function, sex differences in insulin sensitivity and clearance attenuated when adjusted for age, race, and diabetes duration (Fig. 1A). There was also no sex difference in HbA<sub>1c</sub> even though men had a higher fasting glucose and lower 2-h glucose.

In unadjusted analyses, we observed small racial differences in HbA<sub>1c</sub> with higher levels among Whites. However, after adjusting for fasting and 2-h glucose levels, the Black/African Americans had a slightly higher mean HbA<sub>1c</sub> than Whites (7.53% vs. 7.48%). In an analysis of Hispanic and non-Hispanic White separately, adjusted for glucoses, the difference between Black/African American and non-Hispanic White was equivalent to that in the full cohort (7.54% vs. 7.46%). Others have also reported interracial and interethnic differences in the relationship of average glycemia and HbA<sub>1c</sub> (7,9,10,20,21). Most studies, with rare exceptions (22,23), have not collected reliable measures of average glycemia and have not evaluated differences in red blood cell turnover or genetic variation in hemoglobin glycation as plausible mechanisms (24,25). To further investigate the relationship of average glucose and HbA<sub>1c</sub> among different racial/ethnic groups, continuous glucose monitoring and evaluation of red blood cell age and turnover studies will be completed in a subgroup of the GRADE cohort, which should help to distinguish the contribution of abnormalities in red blood cell turnover from differences in glycation (26).

There were also significant racial differences in insulin sensitivity and  $\beta$ -cell function as well as the early insulin and C-peptide responses, late insulin response, and insulin clearance in the fasting state. Black/African Americans were more insulin sensitive than Whites, but Black/African Americans had higher insulin and C-peptide responses compared with others, resulting in the highest DI among different races. These racial differences in  $\beta$ -cell function, as well as HbA<sub>1c</sub>, persisted when adjusted for basic factors.

Racial differences in  $\beta$ -cell function have been previously reported (20,27–30). The ADOPT study (20) enrolled 4,360 participants with type 2 diabetes aged 30–75 years (mean 57 years) of  $<3$  years' duration on diet therapy alone with plasma glucose 7–10 mmol/L. In the subset of patients from North America, compared with the 1,815 Caucasians, Blacks had a higher HbA<sub>1c</sub> (8.0% vs. 7.3%) and lower fasting insulin and higher insulin secretory index despite no difference in fasting glucose.

In a systematic review, Kodama et al. (27) analyzed data from 74 study cohorts comprising 3,800 individuals, the majority being without diabetes, and reported that Black/African Americans without diabetes had robust insulin responses to reduced insulin sensitivity, while East Asians were insulin sensitive and thus required less robust insulin responses. However, racial differences in insulin sensitivity and  $\beta$ -cell responses were less prominent in individuals with type 2 diabetes, but the study was limited to relatively small number of individuals with type 2 diabetes (11 cohorts,  $n = 255$ ).

The etiology for these racial differences remains unknown. Decreased insulin clearance in Black/African Americans, as seen in our cohort, has been proposed as one of the mechanisms for the higher insulin response (31). This study suggested that the racial differences in insulin clearance were due to decreased hepatic extraction of insulin during the first pass and not the extrahepatic component of insulin clearance (31). Proposed mechanisms for this racial difference include decreased expression/activity of insulin-degrading enzyme and/or carcinoembryonic antigen-related cell adhesion molecule-1, which enhances the rate of uptake of the insulin receptor complex, and reduced hepatic insulin receptor number or activity (31,32). The higher C-peptide responses in Black/African Americans suggests that other mechanisms are also likely involved because C-peptide is not degraded by the liver (33,34). Racial differences in body size (height, weight, and BMI), body composition, and fat distribution have been proposed as potential contributors to racial differences in insulin sensitivity or insulin response (35). Whether the difference in DI in Black/African Americans

represents an adaptation to a reduction in glucose uptake or other mechanisms independent of insulin, such as genetic variation, cannot be discerned from these data. However, genome-wide association studies have reported that racial differences exist in the association between genetic variation and T2D risk (36,37).

In the GRADE cohort, age (positively) and BMI, TG/HDL-C ratio, and HbA<sub>1c</sub> (inversely) were correlated with  $\beta$ -cell function. Among baseline characteristics, HbA<sub>1c</sub> had the strongest correlation with DI, consistent with the long-held belief that  $\beta$ -cell function plays an important role in determining glycemic control. This observation is in keeping with other studies, including a cross-sectional analysis comprising four ethnic groups in the U.S. with varying glucose tolerance in whom DI was most strongly associated with the 2-h glucose (28). It is also consistent with a study involving a large group of people with newly diagnosed, drug-naïve type 2 diabetes in whom more severe  $\beta$ -cell dysfunction was associated with a higher baseline HbA<sub>1c</sub> and a greater risk of glycemic progression (38). Older individuals with type 2 diabetes in the GRADE cohort had a higher insulin response and DI. Our finding of the direct association of age with  $\beta$ -cell function is not supported by epidemiologic studies that have shown a higher prevalence of diabetes with increasing age (39). This is likely the result of a decreased ability of the  $\beta$ -cells to maintain adequate insulin responses for metabolic demand over time (40). The most likely explanation is that older individuals in the GRADE Study had less severe disease, which is supported by the negative correlation between age and HbA<sub>1c</sub>, and thus may have better  $\beta$ -cell function at the time of the study. There is also the possibility that the inclusion criteria imposed by the study design excluded older individuals who had worse  $\beta$ -cell function and failed metformin earlier (39).

Although BMI correlated with DI inversely, there was direct association of BMI with IGI and C-peptide response. The association remained significant after adjusting for age, sex, race, diabetes duration, and HOMA2-S, suggesting that obesity might be associated with higher  $\beta$ -cell response beyond what was expected for decreased insulin sensitivity. The inverse association of BMI with DI

was likely driven by the stronger reverse association of insulin sensitivity with BMI dominating the direct association of BMI with  $\beta$ -cell response.

Similar to our findings, Ferrannini et al. (41) reported higher fasting insulin in obese compared with lean individuals without diabetes and the difference remained significant after adjusting for insulin sensitivity. They also reported significantly lower insulin clearance in obesity independent of insulin sensitivity (41), suggesting that peripheral hyperinsulinemia in obese subjects may reflect both insulin hypersecretion and reduced insulin clearance.

Although diabetes duration correlated inversely with insulin and C-peptide responses in this cohort, it did not correlate significantly with DI. This could be related to the relatively short duration of diabetes and narrow range of diabetes duration dictated by the GRADE Study inclusion criteria.

Similar to the previous studies (42,43), we confirm the inverse association between TG/HDL-C ratio and insulin sensitivity. Additionally, we report an inverse association of TG/HDL-C ratio with  $\beta$ -cell function. This association was previously reported only in a small study limited to Black/African American women (44). However, this information should be considered with some caution, as the majority of participants were treated with statins (63%) or other lipid-lowering medications such as fibrates (3%). Our study also investigated sex and racial differences in the correlation between baseline characteristics with insulin sensitivity and  $\beta$ -cell function. We reported that the association between insulin sensitivity and traditional clinical markers including BMI, presence of metabolic syndrome, and TG/HDL-C ratio is stronger in men than women.

In addition, correlation of BMI with  $\beta$ -cell function and insulin and C-peptide responses were stronger in men, suggesting that there might be a need for different BMI cutoffs for risk evaluation based on sex. Epidemiologic studies have also reported a sex-related disparity in the prevalence of metabolic syndrome and type 2 diabetes (45). Women are diagnosed with type 2 diabetes at a higher BMI than men (46), suggesting that obesity could be defined differently according to sex, similar to the different cutoff values of waist circumference for

men and women. We also reported racial differences in the correlation of  $\beta$ -cell function with baseline characteristics. The association of DI with HbA<sub>1c</sub> and TG/HDL-C ratio was stronger in Whites compared with Black/African Americans, which could be the result of racial variation in glycation (6) and racial differences in lipid metabolism (47). Furthermore, BMI and age correlated with DI in the entire cohort and in Whites, but were not associated with DI in Black/African Americans, suggesting racial differences in the regulation of  $\beta$ -cell function.

Our study has several strengths, including the large and racially diverse cohort of adults early in the course of diabetes with a relatively short duration of type 2 diabetes of <10 years and HbA<sub>1c</sub> of 6.8–8.5% while using metformin monotherapy. This cohort provided the opportunity to investigate the association of several characteristics with  $\beta$ -cell function, which was evaluated using both fasting and post-glucose load  $\beta$ -cell responses at several time points during an OGTT. Insulin and C-peptide assays were performed at a central laboratory, which minimized interassay variabilities. The study cohort also includes both men and women and adequate representation from a range of ethnic and racial groups. Further, the cohort represents a sample of subjects with early type 2 diabetes treated with metformin alone that is comparable to the general U.S. population selected to include individuals who meet the principal GRADE eligibility criteria (48).

However, a limitation is that the selective nature of the cohort may limit generalizability to the general population of those with longer diabetes duration who have already been treated with multiple glycemic-lowering medications. Another limitation is that  $\beta$ -cell function and insulin sensitivity were not evaluated using more precise methods such as the euglycemic/hyperglycemic clamp or the frequently sampled intravenous glucose tolerance test. However, measures of insulin sensitivity and  $\beta$ -cell function derived from the OGTT are reported to agree well with those from the euglycemic insulin clamp (14,49). The higher variability in  $\beta$ -cell function measures using an OGTT was likely mitigated by the large sample size in this study. We were unable to calculate hepatic insulin extraction using more sophisticated



methods and estimated only fasting hepatic clearance. In addition, information regarding menopausal status was unavailable, but the analysis was adjusted for age.

In conclusion, in a large cohort of participants with type 2 diabetes, insulin response measures were differentially correlated with age, BMI, and HbA<sub>1c</sub>. There were racial differences in these responses as well as insulin sensitivity and insulin clearance that jointly may explain previously observed racial differences in the level of HbA<sub>1c</sub>. The underlying mechanisms regulating the racial differences in insulin sensitivity,  $\beta$ -cell function, and insulin clearance are not totally clear. As such, more studies are needed addressing the mechanisms responsible for these differences. Understanding potential differences in these mechanisms could in time lead to more personalized approaches to diabetes care.

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