# Type 2 Diabetes Genetic Risk Scores Are Associated With Increased Type 2 Diabetes Risk Among African Americans by Cardiometabolic Status

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**ABSTRACT:** The relationship between genetic risk variants associated with glucose homeostasis and type 2 diabetes risk has yet to be fully explored in African American populations. We pooled data from 4 prospective studies including 4622 African Americans to assess whether β-cell dysfunction (BCD) and/or insulin resistance (IR) genetic variants were associated with increased type 2 diabetes risk. The BCD genetic risk score (GRS) and combined BCD/IR GRS were significantly associated with increased type 2 diabetes risk. In cardiometabolic-stratified models, the BCD and IR GRS were associated with increased type 2 diabetes risk among 5 cardiometabolic strata: 3 clinically healthy strata and 2 clinically unhealthy strata. Genetic risk scores related to BCD and IR were associated with increased risk of type 2 diabetes in African Americans. Notably, the GRSs were significant predictors of type 2 diabetes among individuals in clinically normal ranges of cardiometabolic traits.

**KEYWORDS:** Type 2 diabetes, genetic risk factors, genetic epidemiology, African American health, risk prediction

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## Introduction

Type 2 diabetes is a significant public health issue.[1,2] As of 2012, approximately 26 million US adults aged 20 years or older have been diagnosed with diabetes; African Americans are disproportionately affected compared with non-Hispanic whites with 18.7% (4.9 million) of all African Americans diagnosed with type 2 diabetes compared with only 7.1% of non-Hispanic whites.[2] In addition, African Americans are also more likely to experience increased morbidity related to type 2 diabetes such as diabetic retinopathy and kidney disease.[2]

Although the cause of type 2 diabetes is not completely understood, there is a strong genetic component to type 2 diabetes risk as evidenced by family history and concordance studies among twins.[3] The advent of genome-wide association studies (GWAS) has resulted in the identification of robust associations with common genetic risk variants for type 2 diabetes and related traits; risk prediction models incorporating these variants have only improved risk prediction marginally.[4–21] A better understanding of how these known genetic variants affect type 2 diabetes, for example, via β-cell dysfunction (BCD) or increased insulin resistance (IR) has allowed for the development of pathway-specific genetic risk scores (GRSs); yet, few studies have evaluated their association with type 2 diabetes risk.[7] Cardiometabolic traits such as obesity, hypertension, hyperlipidemia, and hyperglycemia are established type 2 diabetes risk factors; however, it remains to be seen whether type 2 diabetes risk is modified in the presence of both cardiometabolic and genetic risk factors.[22] With the high prevalence of IR and lower insulin sensitivity in African Americans, risk variants related to glucose homeostasis may be of particular importance among those with existing cardiometabolic risk factors.[23–25] Given the current public health crisis posed by type 2 diabetes coupled with the difficulty in lowering and maintaining cardiometabolic risk factors, the early identification of at-risk individuals prior to the onset of cardiometabolic risk factors is an important public health goal.

In this study, we combined data from 4 prospective cohort studies to (1) determine whether the cumulative effect of 22 glucose homeostasis genetic risk variants combined into GRSs related to BCD, IR, or both (BCD/IR) is associated with incident type 2 diabetes; (2) evaluate the association of each GRS on type 2 diabetes risk within cardiometabolic strata; and (3) assess whether the GRSs improve type 2 diabetes risk prediction beyond established risk factors.

## Methods

### *Description of studies*

Data from the Jackson Heart Study (JHS), the Multi-Ethnic Study of Atherosclerosis (MESA), the Atherosclerosis Risk in Communities Candidate Gene Association Resource (ARIC_CARe), and the Coronary Artery Risk Development in Young Adults (CARDIA) were obtained from the database of Genotypes and Phenotypes (dbGaP). All 4 studies have been previously described elsewhere.[26–29] Briefly, JHS is one of the largest prospective cohort studies assessing cardiovascular risk in African Americans. Noninstitutionalized participants aged 35 to 84 years living in the Jackson, Mississippi metropolitan statistical area, were eligible at the time of enrollment. Data were available for 934 participants for the initial examination and a second follow-up examination in addition to yearly follow-up contact information yielding 12 years of follow-up.[26] MESA included community-dwelling participants aged 45 to 84 years without any known clinical cardiovascular disease at the time of enrollment. Recruited from 6 different field centers throughout the United States, MESA participants were identified as European American, African American, Hispanic, or of Chinese descent. Complete data for 940 African Americans were available from 4 clinic examinations beginning in 2000.[27] ARIC_CARe is a part of the larger ARIC study assessing cardiovascular disease risk in close to 15 000 African Americans and European Americans. Participants aged 45 to 64 years were recruited from 4 US communities and have undergone 4 clinical examinations over a 10-year period as well as yearly follow-up via telephone for a total of 25 years.[28] Complete follow-up data were available for 1991 African American participants. Finally, beginning in 1985-1986, CARDIA has enrolled African Americans and European Americans from 4 US communities. Participants' ages ranged from 18 to 30 years at enrollment, and data were available from 7 clinical examinations spanning 20 years for 757 African American participants.[29] Participants of all 4 studies provided informed consent and each original study had institutional review board approval. Our study was approved by the Indiana University Institutional Review Board.

### *Eligibility criteria*

To be included in this study, participants were required to self-identify as African American, be at least 18 years of age, and be free of type 2 diabetes at baseline. Those with baseline type 2 diabetes or missing type 2 diabetes status were excluded. In addition, participants with missing genetic, demographic, and clinical risk factors at baseline were excluded.

### *Type 2 diabetes outcome*

Incident type 2 diabetes was the main outcome variable in the study and was measured in follow-up examinations or questionnaires. The studies MESA, ARIC, JHS, and CARDIA determined type 2 diabetes status at baseline and during follow-up examinations using fasting plasma glucose (FPG) with a cutoff greater than 126 mg/dL (7.0 mmol/L). JHS also used annual follow-up questionnaires to establish type 2 diabetes status in between examinations by asking participants whether they had diabetes.

### *Clinical risk factors*

Baseline cardiometabolic risk factor cut points were determined using clinically meaningful standards and were defined as high body mass index (BMI) (≥30 kg/m$^2$), hypertension (≥140 mm Hg systolic blood pressure [SBP]), low fasting high-density lipoprotein (HDL) (≤40 mg/dL in men and ≤50 mg/dL in women), fasting hypertriglyceridemia (≥150 mg/dL), and fasting hyperglycemia (≥100 mg/dL).[30] A positive family history of type 2 diabetes was noted if one or both parents were reported to have type 2 diabetes. Race was determined via self-report.

### *Genetic risk score*

We chose 22 GWAS-identified type 2 diabetes single-nucleotide polymorphisms reported to affect β-cell function (15 SNPs) or IR (7 SNPs). Previously reported results from either homeostasis model assessment-B or β-cell function indices such as the insulinogenic index or acute insulin response were used to determine the potential physiologic impact of each SNP on β-cell function and/or IR.[7,10] Each of the 4 studies used the Affymetrix 6.0 platform; when the original SNPs reported in GWAS were not available, suitable proxy SNPs with an $r^2$ value greater than or equal to 0.8 in HapMap African Ancestry in Southwest USA (ASW) or Yoruba in Ibadan, Nigeria (YRI) populations were chosen. Assuming an additive genetic model for each SNP, the number of risk alleles present for each SNP (ranging from 0 to 2 risk alleles) was summed across all loci to create a GRS for each individual. Similarly, both the BCD and IR GRSs were created as the sum of the number of risk loci related to BCD and IR, respectively. Due to the lack of sufficiently large GWAS studies to determine locus effect sizes for type 2 diabetes risk variants in African Americans, we were not able to use weighted GRSs. However, previous studies have shown no difference between weighted and unweighted GRSs.[7]

### *Admixture analysis*

To control for potential confounding due to admixture in African Americans, 47 ancestry informative markers (AIMs) common across all 4 studies were used to determine individual admixture using Frappe (version 1.1) in a 2-population model.[31,32] These AIMs were chosen based on their availability on Affymetrix 6.0 platform in addition to their

**Table 1.** Baseline characteristics of study participants by cohort after exclusion of those with baseline type 2 diabetes.

| VARIABLE NAME | OVERALL (N = 4622) | MESA (N = 940) | ARIC (N = 1991) | CARDIA (N = 757) | JHS (N = 934) | *P* VALUE FOR DIFFERENCE BETWEEN STUDIES |
|---|---|---|---|---|---|---|
| Gender (% male) | 1897 (41.0) | 446 (47.5) | 772 (38.8) | 313 (41.4) | 366 (39.2) | <.0001 |
| Family history of diabetes (% yes) | 1432 (31.0) | 394 (41.9) | 491 (24.7) | 128 (16.9) | 419 (44.9) | <.0001 |
| Age, y | 49.3 (14.3) | 61.6 (10.3) | 53.0 (5.7) | 24.4 (3.9) | 48.9 (11.7) | <.0001 |
| Systolic blood pressure, mm Hg | 124.6 (19.6) | 131.0 (21.1) | 127.3 (19.9) | 110.8 (11.0) | 123.5 (17.4) | <.0001 |
| HDL cholesterol, mg/dL | 54.2 (16.2) | 53.2 (15.4) | 56.2 (17.9) | 54.6 (13.1) | 50.5 (14.6) | <.0001 |
| Triglycerides, mg/dL | 97.0 (64.6) | 99.6 (56.26) | 106.3 (73.9) | 65.9 (35.3) | 99.7 (62.1) | <.0001 |
| Fasting plasma glucose, mg/dL | 92.3 (11.9) | 90.6 (10.8) | 98.6 (9.9) | 80.9 (8.8) | 89.6 (10.0) | <.0001 |
| BMI, kg/m$^2$ | 29.4 (6.5) | 30.0 (5.9) | 29.1 (5.9) | 26.2 (6.0) | 32.1 (7.4) | <.0001 |

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; HDL, high-density lipoprotein; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis.
Values are mean (SD) or counts (%).

ability to maximize European and African allele frequency differences. Admixture estimates were used as a covariate in all analyses.

### *Statistical analyses*

Baseline continuous variables were summarized by mean (SD) and compared using analysis of variance. Categorical variables were summarized by frequency (%) and compared using $\chi^2$ tests. Time to onset of type 2 diabetes (in months) was defined as the time from baseline to follow-up when type 2 diabetes was diagnosed. Logistic regression models were used to investigate the association between each individual SNP and incident type 2 diabetes, controlling for age, sex, and admixture. Cox proportional hazard models were used to associate baseline clinical covariates and GRSs to time of diabetes onset. The proportional hazard assumption was checked using the Schoenfeld residuals test.[33] The estimated linear term in the Cox model was treated as an overall risk score, which was used to discriminate people at high risk for diabetes from those who were not. Sensitivity, specificity, and area under the receiver operating characteristic curve of diabetes incidence were estimated using a nonparametric method, with confidence intervals constructed using the bootstrap method. C-statistics and continuous net reclassification improvement (NRI) for models with and without GRS were estimated and tested using the method by Pencina.[34,35] All analyses were performed in SAS 9.4 (SAS Inc., Cary, NC, USA) and R 3.0.[36]

## Results

### *Study sample characteristics*

Among all 4 studies used in these analyses, there were a total of 4622 African Americans free of type 2 diabetes at baseline. Table 1 shows baseline participant characteristics by study. Overall, the mean baseline age was 49.3 (SD: ±14.3) years and the mean FPG was 92.3 (SD: ±11.9) mg/dL. There were more women than men (59% vs 41%), and only 31% reported a family history of diabetes. Compared with the other 3 studies, CARDIA participants tended to be younger (mean age: 24.4 years, SD: ±3.9) and had a more favorable risk profile with respect to clinical risk factors and covariates such as family history of diabetes (16.9%) and FPG (80.9 mg/dL, SD: ±8.8). Over a mean follow-up time of 7.7 years, there were a total of 679 incident type 2 diabetes cases giving a cumulative incidence of 14.7%. Finally, the mean African ancestry proportion in the overall sample was 0.80 (SD: ±0.17).

### *Individual genetic risk variants*

Supplemental Table 1 lists the SNPs used in our analyses, their risk alleles and frequencies in the overall study population, and the association results. We assessed 22 SNPs related to glucose homeostasis (7 SNPs associated with IR and 15 SNPs related to BCD). Of these 22 SNPs, only CDC123 rs4747969 was significantly associated with type 2 diabetes after adjustment for age, sex, and African admixture (odds ratio = 1.176, 95% confidence interval [CI]: 1.031-1.342), although most of the remaining SNP results were consistent in direction and effect size with previously published results.

### *GRSs and type 2 diabetes*

Incident type 2 diabetes cases had a higher mean BCD GRS and BCD/IR GRS as compared with controls (19.4 vs 19.1 and 28.2 vs 27.8, $P < .05$ for both), whereas the mean IR GRS did not differ significantly between cases and controls (8.8 vs 8.7). Both the BCD GRS and the BCD/IR GRS were

**Table 2.** Genetic risk scores associated with type 2 diabetes incidence and prediction performance.

| | WITHOUT GRS | GRS-IR | GRS-BCD | GRS-BCD/IR |
|---|---|---|---|---|
| Entire study cohort (n = 4622) | | | | |
| HR (95% CI) | — | 1.01 (0.96 to 1.06) | **1.037 (1.006 to 1.070)** | **1.029 (1.002 to 1.057)** |
| C-statistics (95% CI) | 0.811 (0.796 to 0.828) | 0.811 (0.795 to 0.829) | 0.812 (0.795 to 0.829) | 0.812 (0.795 to 0.829) |
| Continuous NRI (95% CI) | — | 0.014 (−0.076 to 0.068) | 0.014 (−0.068 to 0.065) | 0.002 (−0.104 to 0.056) |

Abbreviations: BCD, β-cell dysfunction; GRS, genetic risk score; HR, hazard ratio; IR, insulin resistance; NRI, net reclassification index.
A clinical model without the GRS is compared with 3 different GRSs in the whole cohort using Cox proportional hazards modeling and continuous net reclassification index analyses: GRS-IR includes SNPs associated with IR, GRS-BCD includes SNPs associated with β-cell function, and GRS-BCD/IR includes both IR and β-cell function SNPs. The clinical model includes the following baseline variables: age, sex, family history of diabetes, BMI, SBP, HDL, triglycerides and fasting glucose, cohort, and admixture.
Bold values signify *P* value < 0.05.

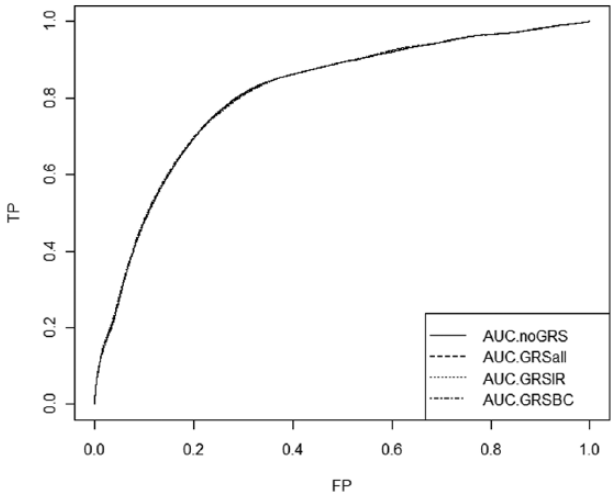


**Figure 1.** Receiver operating characteristic (ROC) curves for each of the GRS for the combined study population. Incident type 2 diabetes risk prediction is shown at 5 years without genetic risk information (noGRS) and with the addition of each of the 3 GRSs (GRSBC, genetic risk score β-cell dysfunction; GRSIR, genetic risk score insulin resistance; GRSall, genetic risk score BCD/IR). The graph plots sensitivity vs (1 – specificity). The area under the curve (AUC) corresponds to the C-statistics for each of the 4 models. The model without genetic risk information includes the following variables: age, sex, family history of diabetes, body mass index, systolic blood pressure, high-density lipoprotein, triglycerides and fasting glucose, cohort, and admixture.
TP: true positive (sensitivity); FP: false positive (1-specificity).

significantly associated with incident type 2 diabetes in models including standard clinical risk factors (hazard ratio [HR] = 1.037, 95% CI: 1.006-1.070 and HR = 1.029, 95% CI: 1.002-1.057, respectively; Table 2).

### *Predictive ability of GRSs*

The addition of any of the 3 GRS to a standard clinical risk factors–only model showed no improvement in the NRI or the C-statistics in the overall study cohort (Table 2 and Figure 1) or the cardiometabolic strata (Table 3) indicating no improvement in the ability to predict incident type 2 diabetes beyond that of standard clinical risk factors.

### *Cardiometabolic risk factor analyses*

We performed analyses stratified by cardiometabolic risk factors to determine whether the magnitude of the effect of the BCD or IR GRS differed within each cardiometabolic strata after adjusting for standard clinical risk factors (Table 3). In clinically healthy strata, the BCD GRS HRs were 1.054 (95% CI: 1.003-1.107) and 1.063 (95% CI: 1.026-1.101) in lean and normotensive individuals, respectively. In normoglycemic individuals, the IR GRS HR was 1.093 (95% CI: 1.001-1.194). In clinically unhealthy strata, the BCD GRS HRs were 1.060 (95% CI: 1.012-1.111) and 1.071 (95% CI: 1.004-1.143) in low HDL and hypertriglyceridemic individuals, respectively (Table 3).

We compared baseline cardiometabolic profiles between cases and controls in each of the strata where the GRSs were significantly associated with type 2 diabetes to gain insight into which clinical risk factors were influencing this increased risk using International Diabetes Federation (IDF) cutoff values for metabolic syndrome.[30] In the clinically unhealthy strata, cases had baseline cardiometabolic profiles that met the criteria for metabolic syndrome (Table 4). For example, within the low HDL and hypertriglyceridemia strata, cases had BMI values that met the abdominal obesity criterion in addition to 2 other factors; for the low HDL stratum, cases had reduced HDL and raised FPG, whereas cases in the hypertriglyceridemia stratum had both elevated triglycerides and FPG. In contrast, none of the cases within the clinically healthy strata met the IDF criteria for metabolic syndrome (Table 5). This suggests that GRSs alone are significant predictors before the onset of the clinical risk factors.

## Discussion

We observed a significant increase in type 2 diabetes risk with increased risk allele load in analyses using a GRS based on variants related to BCD but not IR in the overall study cohort. When we stratified our study cohort by cardiometabolic risk factors, we found that the IR GRS was significantly associated with 9% increased type 2 diabetes risk only among individuals

**Table 3.** Genetic risk scores associated with type 2 diabetes incidence and prediction performance within cardiometabolic strata.

| | WITHOUT GRS | GRS-IR | GRS-BCD |
|---|---|---|---|
| Lean (BMI < 30 kg/m$^2$) (n = 2819) | | | |
| HR (95% CI) | — | 1.010 (0.927 to 1.100) | **1.054 (1.003 to 1.107)** |
| C-statistics | 0.815 | 0.817 | 0.820 |
| Difference in AUC (95% CI) | — | −0.002 (−0.004 to 0.002) | −0.005 (−0.010 to 0.005) |
| Obese (BMI ≥ 30 kg/m$^2$) (n = 1803) | | | |
| HR (95% CI) | — | 1.004 (0.939 to 1.074) | 1.040 (1.000 to 1.081) |
| C-statistics | 0.770 | 0.770 | 0.770 |
| Difference in AUC (95% CI) | — | 0.000 (−0.001 to 0.001) | 0.000 (−0.005 to 0.008) |
| Normotensive (SBP < 140 mm Hg) (n = 3753) | | | |
| HR (95% CI) | — | 1.010 (0.950 to 1.074) | **1.063 (1.026 to 1.101)** |
| C-statistics | 0.809 | 0.809 | 0.811 |
| Difference in AUC (95% CI) | — | 0.000 (−0.001 to 0.001) | −0.002 (−0.006 to 0.003) |
| Hypertensive (SBP ≥ 140 mm Hg) (n = 869) | | | |
| HR (95% CI) | — | 1.017 (0.914 to 1.130) | 0.999 (0.937 to 1.064) |
| C-statistics | 0.781 | 0.781 | 0.779 |
| Difference in AUC (95% CI) | — | 0.000 (−0.004 to 0.003) | 0.002 (−0.008 to 0.014) |
| Normal HDL (≥40 mg/dL [men] and ≥50 mg/dL [women]) (n = 3218) | | | |
| HR (95% CI) | — | 0.997 (0.932 to 1.067) | 1.027 (0.986 to 1.070) |
| C-statistics | 0.805 | 0.805 | 0.802 |
| Difference in AUC (95% CI) | — | 0.000 (−0.002 to 0.001) | 0.003 (−0.003 to 0.008) |
| Low HDL (<40 mg/dL [men] and <50 mg/dL [women]) (n = 1404) | | | |
| HR (95% CI) | — | 1.034 (0.950 to 1.126) | **1.060 (1.012 to 1.111)** |
| C-statistics | 0.796 | 0.797 | 0.798 |
| Difference in AUC (95% CI) | — | −0.001 (−0.002 to 0.001) | −0.002 (−0.007 to 0.005) |
| Normal triglycerides (<150 mg/dL) (n = 4073) | | | |
| HR (95% CI) | — | 1.031 (0.970 to 1.097) | 1.034 (0.999 to 1.071) |
| C-statistics | 0.812 | 0.813 | 0.813 |
| Difference in AUC (95% CI) | — | −0.0004 (−0.0015 to 0.0007) | −0.001 (−0.005 to 0.004) |
| Hypertriglyceridemia (≥150 mg/dL) (n = 549) | | | |
| HR (95% CI) | — | 0.981 (0.882 to 1.090) | **1.071 (1.004 to 1.143)** |
| C-statistics | 0.742 | 0.741 | 0.752 |
| Difference in AUC (95% CI) | — | 0.0004 (−0.0029 to 0.0057) | −0.010 (−0.028 to 0.005) |
| Normoglycemia (FPG < 100 mg/dL) (n = 3437) | | | |
| HR (95% CI) | — | **1.093 (1.001 to 1.194)** | 1.040 (0.990 to 1.091) |
| C-statistics | 0.671 | 0.672 | 0.672 |
| Difference in AUC (95% CI) | — | −0.001 (−0.003 to 0.001) | −0.001 (−0.012 to 0.009) |

**Table 3.** (Continued)

| | WITHOUT GRS | GRS-IR | GRS-BCD |
|---|---|---|---|
| Hyperglycemia (FPG ≥ 100 mg/dL) (n = 1185) | | | |
| HR (95% CI) | — | 0.963 (0.901 to 1.030) | 1.034 (0.995 to 1.074) |
| C-statistics | 0.717 | 0.715 | 0.713 |
| Difference in AUC (95% CI) | — | 0.002 (−0.001 to 0.003) | 0.004 (−0.005 to 0.012) |

Abbreviations: AUC, area under the curve; BCD, β-cell dysfunction; BMI, body mass index; FPG, fasting plasma glucose; GRS, genetic risk score; HDL, high-density lipoprotein; HR, hazard ratio; IR, insulin resistance; SBP, systolic blood pressure; T2D, type 2 diabetes.
A clinical model without the GRS is compared with 2 different GRSs in the whole cohort using Cox proportional hazards modeling and continuous net reclassification index analyses: GRS-IR includes SNPs associated with insulin resistance and the GRS-BCD includes SNPs associated with β-cell function. The difference in AUC compares clinical models without a GRS to models with each individual GRS. Model without GRS includes the following variables at baseline: age, sex, family history of diabetes, BMI, SBP, HDL, triglycerides and fasting glucose, cohort, and admixture. Within each cardiometabolic strata, the trait corresponding to that strata was not included in the model.
Bold values signify P value < 0.05.

**Table 4.** Characteristics of participants by case/control status in clinically unhealthy cardiometabolic strata in which the genetic risk scores are associated with incident type 2 diabetes.

| CLINICAL RISK FACTOR | LOW HDL (<40 MG/DL [MEN] AND <50 MG/DL [WOMEN]) (N = 1404) (N = 289 T2D CASES VS N = 1115 CONTROLS) | *P* VALUE* | HYPERTRIGLYCERIDEMIA (≥150 MG/DL) (N = 549) (N = 161 T2D CASES VS N = 388 CONTROLS) | *P* VALUE* |
|---|---|---|---|---|
| Systolic blood pressure, mm Hg | 127.1 (19.3) vs 124.3 (19.6) | .0283 | 132.0 (20.8) vs 129.6 (19.2) | .1833 |
| HDL cholesterol, mg/dL | 38.1 (6.2) vs 39.4 (6.0) | .0010 | 44.5 (15.1) vs 43.6 (13.7) | .4981 |
| Triglycerides, mg/dL | 148.5 (143.2) vs 118.7 (71.9) | .0007 | 231.1 (171.3) vs 207.7 (77.0) | .0975 |
| Fasting plasma glucose, mg/dL | 102.8 (12.0) vs 91.8 (10.8) | <.0001 | 104.7 (11.2) vs 95.6 (10.5) | <.0001 |
| BMI, kg/m$^2$ | 33.3 (6.6) vs 30.7 (6.4) | <.0001 | 32.6 (5.7) vs 29.9 (5.6) | <.0001 |

Abbreviations: BCD, β-cell dysfunction; BMI, body mass index; GRS, genetic risk score; HDL: high-density lipoprotein; T2D, type 2 diabetes.
Only the BCD GRS was associated with incident type 2 diabetes within the low-HDL and hypertriglyceridemia strata.
**P* value is for comparison between cases and controls.

**Table 5.** Characteristics of participants by case/control status in clinically healthy cardiometabolic strata in which the genetic risk scores are associated with incident type 2 diabetes.

| CLINICAL RISK FACTOR | LEAN (BMI < 26 KG/M$^2$) (N = 1504) (N = 92 T2D CASES VS N = 1412 CONTROLS) | *P* VALUE* | NORMOTENSIVE (SBP < 140 MM HG) (N = 3753) (N = 507 T2D CASES VS N = 3246 CONTROLS) | *P* VALUE* | NORMOGLYCEMIA (FPG < 100 MG/DL) (N = 3437) (N = 255 T2D CASES VS N = 3182 CONTROLS) | *P* VALUE* |
|---|---|---|---|---|---|---|
| Systolic blood pressure, mm Hg | 124.4 (18.4) vs 120.1 (19.2) | .0372 | 120.1 (10.8) vs 116.9 (11.9) | <.0001 | 126.6 (19.1) vs 122.6 (19.0) | .0011 |
| HDL cholesterol (mg/dL) | 52.1 (15.0) vs 59.7 (18.1) | <.0001 | 49.2 (14.1) vs 54.8 (16.0) | <.0001 | 50.2 (14.8) vs 55.5 (16.2) | <.0001 |
| Triglycerides, mg/dL | 111.4 (81.7) vs 81.2 (46.2) | .0007 | 125.4 (115.1) vs 89.4 (51.9) | <.0001 | 112.0 (92.1) vs 87.8 (50.1) | <.0001 |
| FPG, mg/dL | 98.5 (13.6) vs 87.7 (10.8) | <.0001 | 102.0 (13.0) vs 89.7 (10.6) | <.0001 | 89.2 (8.7) vs 86.8 (7.8) | <.0001 |
| BMI, kg/m$^2$ | 23.8 (1.9) vs 23.1 (2.2) | .0028 | 32.7 (6.8) vs 28.6 (6.1) | <.0001 | 32.6 (7.1) vs 28.6 (6.3) | <.0001 |

Abbreviations: BCD, β-cell dysfunction; BMI, body mass index; FPG: fasting plasma glucose; GRS, genetic risk score; HDL: high-density lipoprotein; IR, insulin resistance; SBP: systolic blood pressure; T2D, type 2 diabetes.
The BCD GRS was associated with incident type 2 diabetes within lean BMI and normotensive strata and the IR GRS was associated with incident type 2 diabetes within the normoglycemia stratum.
**P* value is for comparison between cases and controls.

who were normoglycemic at baseline. The BCD GRS was associated with 5% to 7% increased type 2 diabetes risk among those belonging to each of the following baseline-derived strata: lean, normotensive, low HDL, and hypertriglyceridemia. The C-statistics and net risk reclassification did not show the GRSs improved risk prediction over standard clinical risk

factors in both the overall study cohort and within each of the cardiometabolic strata.

Participants in the clinically healthy strata (lean, normotensive, or normoglycemic) where the BCD or IR GRS were significantly associated with increased type 2 diabetes risk overall demonstrated a more favorable clinical profile at baseline such as younger age, lower BMI, and lower triglycerides. Furthermore, the type 2 diabetes cases within these strata had clinical profiles which would not necessarily identify them as being at risk for type 2 diabetes. On average, their SBP, HDL, triglycerides, FPG, and BMI did not exceed metabolic syndrome cutoffs as determined by the IDF criteria. These results suggest that cases with healthier baseline characteristics such as lower BMI (<30 kg/m$^2$), normotension (<140 mm Hg), and normoglycemia (<100 mg/dL) may have a stronger genetic susceptibility to type 2 diabetes thus explaining why we observed an increased risk for type 2 diabetes in otherwise clinically healthy strata.

Conversely, type 2 diabetes cases in the 2 dyslipidemic strata (low HDL and high triglycerides) where the BCD GRS was also significantly associated with type 2 diabetes did have values meeting the IDF criteria for metabolic syndrome in addition to higher BCD GRSs. It is possible that in addition to having an increased genetic risk for BCD, cases in these unhealthy dyslipidemic strata may be experiencing glucolipotoxicity where the combined effects of increased fatty acid levels and elevated glucose negatively affect β-cell function and survival.[37] Thus, those with dyslipidemia in combination with increased genetic risk load related to BCD could potentially benefit from early interventions targeting cardiometabolic traits such as dyslipidemia to prevent or delay type 2 diabetes onset by potentially preserving β-cell function.

The Diabetes Prevention Program (DPP) has already demonstrated that type 2 diabetes can be delayed or prevented with interventions involving 5% to 7% weight loss through lifestyle and behavior changes.[38] More recently, a genetic risk intervention study of adults at high risk phenotypically for type 2 diabetes reported no significant difference in adherence to DPP by participants with elevated GRSs vs controls.[39] Indeed, changing type 2 diabetes risk behaviors and maintaining them is difficult.[40] Our results imply that genetic risk information could be used to identify at-risk individuals who appear to have a clinically favorable profile prior to the development of the risk factors for and the onset of type 2 diabetes. Thus, the potential public health impact could be significant given that early identification can delay or prevent type 2 diabetes onset through the use of prevention efforts tailored to individual specific cardiometabolic risk profiles.

Our results are consistent with previous research that has demonstrated increased type 2 diabetes risk with both pathway-specific and type 2 diabetes–related GRSs among African Americans.[7–9,16,20] Cooke et al,[9] one of the only identified studies solely conducted among African Americans (n = 4045), observed a significant association between their GRS comprising 17 SNPs and type 2 diabetes risk even after taking into account African American admixture. Waters et al[16] also observed an increased risk for type 2 diabetes with increasing risk alleles in both their multiethnic cohort and the African American subset. In contrast, after limiting their cohort to African Americans (n = 577), Hivert et al[20] found no association between their 34-SNP GRS and progression to diabetes among participants with baseline-impaired glycemic regulation (HR = 0.98 per risk allele, 95% CI: 0.94-1.03). A more recent study by Vassy et al[8] used a 38-variant GRS in the CARDIA study, including both white and black participants, and reported a genotype risk score that significantly predicted incident type 2 diabetes (HR = 1.08 per risk allele, 95% CI: 1.04-1.13). Nonetheless, when stratifying by race/ethnicity, discrimination did not improve.[8] However, only 34% of their study population was African American and therefore it is possible that this smaller sample size limited their ability to assess the discriminatory ability of their risk prediction model.

More recent studies have begun to focus on pathway-specific GRSs to improve predictive performance as well as to better understand the genetic influences that may affect the observed racial differences in type 2 diabetes risk. Vassy et al[7] and Klimentidis et al[11] both evaluated GRSs based on multiple pathways. Similar to the work by Vassy et al,[7] our BCD GRS predicted incident type 2 diabetes but only in the overall study cohort. Klimentidis et al[11] reported an association with their fasting insulin GRS and type 2 diabetes in African Americans but not with their fasting glucose GRS. This is consistent with our results of an increased type 2 diabetes risk with the IR GRS in the normoglycemic stratum in addition to findings of greater IR and secretion among African Americans.[23–25]

A limitation of the study was the use of baseline measurements of clinical characteristics. Many clinical variables are not static but change over time in contrast to genetic variants which are stable over the life course. However, established risk prediction models using clinical variables such as the Framingham Risk Score have used baseline measurements in their models achieving a high level of predictive power.[41] In addition, models containing only clinical risk factors should perform better over shorter time frames given their variable nature, whereas genetic-based models should do better with longer time frames. The mean follow-up time in our study was 7.5 years; therefore, it is not unreasonable that our models performed better with clinical variables. Other limitations involved the different study time periods during which diabetes classification criteria changed along with different methods used to determine type 2 diabetes status in the included studies. Although all of the studies used clinical measures of fasting glucose to determine type 2 diabetes status at baseline or later examinations, self-reported physician-diagnosed type 2 diabetes or self-reported diabetes medication use was also used to determine diabetes status. Although this could result in potential misclassification of diabetes status, validation studies in ARIC, for example, have shown that the reliability of self-reported diabetes status is more than 92%.[42] Finally, GRSs

themselves have limitations. For example, GRSs do not take into account the potential interactions between genes and the environment. Although we stratified our results by known cardiometabolic risk factors to evaluate the effect of the GRS within these subgroups, we were not able to evaluate how unhealthy lifestyle behaviors such as diet and physical activity may interact with genetic risk. This remains an important future research goal. Another limitation concerning our GRS is that the SNPs used in our study account for only a small proportion of diabetes heritability and may not include causal variants or SNPs in high linkage disequilibrium with causal variants in the African American population. Because African populations have shorter linkage disequilibrium blocks, it is possible that common variants may be missed in GWAS primarily conducted in European populations; identification of causal variants specific to African and African American populations may improve the GRS predictive ability in these populations.

## Conclusions

Our results suggest that SNPs related to BCD and IR pathways may be important in type 2 diabetes risk prediction in African Americans. In addition, there is evidence that a genetic predisposition for BCD and/or IR may result in an increased risk for type 2 diabetes despite having a more favorable clinical profile with respect to cardiometabolic risk factors. Further work is needed to better characterize the effect of pathway-specific genetic risk in these populations so that early identification and intervention can occur prior to type 2 diabetes onset.

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## Author Contributions

JW conceived and designed the experiments. JL, XL, and CS analyzed the data. JL wrote the first draft of the manuscript. JW and CS contributed to the writing of the manuscript. JW, JL, XL, CS, MdG, LL, and AC agree with manuscript results and conclusions. JW and JL jointly developed the structure and arguments for the paper. JW, JL, CS, MdG, LL, and AC made critical revisions and approved final version. All authors reviewed and approved the final manuscript.

## Disclosures and Ethics

As a requirement of publication, authors have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. The external blind peer reviewers report no conflicts of interest.

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