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Genetic European Ancestry and Incident Diabetes in Black Individuals: Insights from the SPRINT Trial

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Abstract

Background: Black individuals have high incident diabetes risk, despite having paradoxically lower triglyceride (TG) and higher high-density lipoprotein cholesterol (HDL-C) levels. The basis of this is poorly understood. We evaluated the participants of the Systolic Blood Pressure Intervention Trial (SPRINT) to assess the association of estimated European genetic ancestry with the risk of incident diabetes in self-identified Black individuals.

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Supplementary Material:
Supplementary Tables I–VII
Supplementary Figures I–VII
Supplementary References.[53–65]

Methods: Self-identified non-Hispanic Black SPRINT participants free of diabetes at baseline were included. Black participants were stratified into tertiles (T1-T3) of European ancestry proportions estimated using 106 biallelic ancestry informative genetic markers. The multivariable-adjusted association of European ancestry proportion with indices of baseline metabolic syndrome (i.e., fasting plasma glucose [FPG], triglycerides, high-density lipoprotein-cholesterol [HDL-C], body mass index [BMI], and blood pressure [BP]) was assessed. Multivariable-adjusted Cox regression determined the risk of incident diabetes (FPG ≥126 mg/dL or self-reported diabetes treatment) across tertiles of European ancestry proportion.

Results: Among 2,466 Black SPRINT participants, a higher European ancestry proportion was independently associated with higher baseline TG and lower HDL-C levels ($p<0.001$ for both). European ancestry proportion was not associated with baseline FPG, BMI, and BP ($p>0.05$). Compared with the first tertile, those in the second (HR:0.64 [95%CI:0.45–0.90]) and third tertiles (HR:0.61 [95%CI:0.44–0.89]) of European ancestry proportion had a lower risk of incident diabetes. A 5 percentage point higher European ancestry was associated with a 29% lower risk of incident diabetes (HR:0.71 [95%CI:0.55–0.93]). There was no evidence of a differential association between European ancestry proportion tertiles and incident diabetes between those randomized to intensive vs. standard BP treatment.

Conclusions: The higher risk of incident diabetes in Black individuals may have genetic determinants in addition to adverse social factors. Further research may help understand the interplay between biological and social determinants of cardiometabolic health in Black individuals.

Clinical Trial Registration: NCT01206062 registered at Clinicaltrials.gov.

Keywords

Blood Pressure; Diabetes Mellitus; Genetics; Health Disparities; Metabolic Syndrome; Race

Introduction

Non-Hispanic Black individuals are at a higher risk of incident diabetes, which is primarily believed to be driven by the differences in lived experience and social determinants of health.[1] Non-Hispanic Black individuals also have a disproportionately higher prevalence of insulin resistance, diabetes, and diabetes-associated cardiovascular mortality.[2–10] However, the prevalence of metabolic syndrome, which is defined by abdominal obesity, elevated triglyceride levels, reduced high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and elevated plasma glucose,[11, 12] is relatively lower among non-Hispanic Black individuals.[13] This incongruence is attributed to lower triglyceride levels, higher HDL-C, and metabolic paradox in Black individuals.[14–16]

While the social determinants of health explain much of the racial disparity for incident diabetes risk, the biological basis has also previously been explored.[17–19] Self-reported non-Hispanic Black individuals have a wide variation of European admixture ranging from ~1–70%.[20, 21] Lower European genetic ancestry in Black Americans has been associated with higher glycated hemoglobin, decreased adiponectin, increased C-reactive protein, and a lower resting metabolic rate, all of which are predictors of incident diabetes.[17–19, 22]

Genetic ancestry proportions have been previously noted to be associated with poor cardiometabolic phenotype and with adverse cardiovascular events.[23, 24] Importantly, the relationship between the genetic ancestry proportion and incident diabetes among high-risk, hypertensive African-American individuals has not been previously evaluated.

We sought to evaluate the association between genetic European ancestry proportion and 1) metabolic syndrome components at baseline, and 2) incident diabetes, in self-identified Black participants of the Systolic Blood Pressure Intervention Trial (SPRINT), who were free of diabetes at baseline. We also assessed the risk of incident diabetes in non-Hispanic Black individuals relative to non-Hispanic White individuals in SPRINT.

Methods

The anonymized study data used for this analysis are publicly available at the National Heart, Lung, and Blood Institute's BioLINCC data repository and can be accessed at https://biolincc.nhlbi.nih.gov/home/. The SPRINT study protocol was approved by the local Institutional Review Boards at the respective trial sites. Written informed consent was obtained from all SPRINT participants. The study complied with principles detailed in the Declaration of Helsinki. This analysis was approved by the University of Alabama at Birmingham Institutional Review Board. The full study methods are available as Supplementary Methods.

Results

There were 5,256 non-Hispanic White and 2,673 non-Hispanic Black individuals free of diabetes at baseline. Supplementary Table II depicts the baseline characteristics of the study participants stratified by race. The distribution of social determinants of health (education status, employment status, and health insurance status) in Black and White individuals are depicted in Supplementary Figure II.

Risk of Incident Diabetes Mellitus: Stratified by Race

The incidence of diabetes mellitus was 2.0 (95% CI: 1.8–2.3) per 1000-person years (event frequency: 10.0%) among non-Hispanic Black participants and 1.5 (95% CI: 1.3–1.6) per 1000-person years (event frequency: 7.5%) among non-Hispanic White participants. Non-Hispanic Black participants in SPRINT had a higher risk of incident diabetes (HR: 1.43 [95% CI: 1.14–1.80]) compared with non-Hispanic White participants after accounting for various clinical and socioeconomic factors (Figure 1). The relative strength of the association of various clinical and socioeconomic factors with incident diabetes is depicted in Supplementary Figure III. Baseline blood glucose, BMI, age, presence of clinical or subclinical cardiovascular disease, health insurance status, education status, employment status, and race were the strongest correlates of incident diabetes. The estimates from individual model variables are described in Supplementary Figure IV and Supplementary Table III. There was a significant interaction between sex and race on the risk of incident diabetes mellitus (p=0.01). In the sex-stratified analyses, among females, the hazard for incident diabetes was 1.67 (95% CI: 1.07–2.60) for non-Hispanic Black participants. Among

males, the hazard for incident diabetes was 1.35 (95% CI: 1.03–1.78) for non-Hispanic Black participants (Supplementary Figure V).

In the competing risk analysis, the hazard for incident diabetes among non-Hispanic Black participants was 1.50 (95% CI: 1.23–1.84) (Supplementary Table IV). In the sensitivity analysis, taking age as the time-scale, the hazard for non-Hispanic Black participants was 2.65 (95% CI: 2.19–3.21) compared with non-Hispanic White participants (Supplementary Table V).

Baseline Characteristics Across European Ancestry Tertiles

There were 2,466 self-identified Black participants without baseline diabetes who provided consent for genetic analysis, had their DNA analyzed, and for whom European ancestry admixture data was available. Supplementary Table VI depicts the differences in baseline characteristics of these individuals with the rest of the SPRINT participants. The participants were categorized into three tertiles of European ancestry (T1: ≤15%; T2: 16–24%; T3: ≥25%). Participants in the first tertile (T1) had a median European ancestry proportion of 11%, those in the second tertile (T2) had a median ancestry proportion of 20%, and those in the third tertile (T3) had a median ancestry proportion of 32%. The baseline characteristics of the participants, grouped by tertiles of European ancestry, are presented in Table 1. The distribution of social determinants of health (education status, employment status, and health insurance status) across tertiles of European ancestry proportion are depicted in Figure 2.

Participants in the first tertile had lower baseline fasting triglyceride levels (T1: 89 [IQR: 67–120] mg/dL, T2: 93 [IQR: 69–126] mg/dL, T3: 94 [IQR: 70–131] mg/dL), and higher HDL cholesterol levels (T1: 55 [IQR: 46–65] mg/dL, T2: 53 [IQR: 45–62] mg/dL, T3: 52 [IQR: 44–62] mg/dL). Fasting total cholesterol, systolic and diastolic blood pressure, and BMI were not different between the tertiles. There was a trend for higher fasting plasma glucose across the European ancestry proportion tertiles (p=0.03). In multivariable-adjusted models, an increase in European ancestry proportion among non-Hispanic Black participants was associated with higher triglyceride levels (β=0.32, SE: 0.08; p<0.001) and lower HDL-C levels (β=−0.18, SE: 0.04; p<0.001)(Figure 3). The remaining metabolic syndrome parameters (blood glucose, systolic blood pressure, diastolic blood pressure, BMI) were not significantly associated with increasing European ancestry proportion (p>0.05 for all)(Supplementary Figure VI).

Risk of Incident Diabetes Mellitus Among Non-Hispanic Black Participants Across European Ancestry Tertiles

The incidence of diabetes mellitus in the first, second, and third tertiles was 3.12 (95% CI: 26.6–38.8) per 1000-person years (event frequency: 12.1%), 22.7 (95% CI: 17.9–28.7) per 1000-person years (event frequency: 8.8%), and 23.8 (95% CI: 19.1–29.7) per 1000-person years (event frequency: 9.3%), respectively (Figure 4). After multivariable adjustment, participants in the second (HR: 0.64 [95% CI: 0.45–0.90]) and third (HR: 0.61 [95% CI: 0.44–0.89]) tertiles of European ancestry proportion had a lower risk of incident diabetes mellitus compared with those in the first tertile (Supplementary Table VII, Supplementary Figure VII). Each 5% increment in European ancestry proportion in non-Hispanic Black

participants was independently associated with a 29% lower hazard of incident diabetes (HR: 0.71 [95% CI: 0.55–0.93]). There was no interaction between blood pressure control strategies and European ancestry proportion on incident diabetes (p=0.69). There was no interaction between sex and European ancestry proportion in incident diabetes (p=0.88). In the competing risk analysis, Black participants in second (HR: 0.69 [95% CI:0.49–0.96]) and third tertiles of European ancestry proportion (HR: 0.67 [95% CI:0.49–0.93]) have a lower risk of incident diabetes compared with those in the first tertile (Supplementary Table IV). Similar results were obtained in sensitivity analysis taking age as the time-scale (Supplementary Table V).

Discussion

In this study, we observed that among high-risk, hypertensive non-Hispanic Black individuals from the United States, a higher European ancestry proportion was associated with a lower risk of incident diabetes after accounting for numerous clinical and social factors. The lower incidence of diabetes, which was associated with higher European ancestry, was not different by sex or blood pressure control strategy. Among non-Hispanic Black individuals, a higher European ancestry proportion was associated with higher triglyceride levels and lower HDL-C levels. The distribution of social determinants of health is well understood to influence the higher risk of incident diabetes among Black individuals. However, our findings suggest that genetic factors may also contribute to a higher risk of incident diabetes and a paradoxically favorable baseline lipid profile (lower triglycerides and higher HDL-C) among non-Hispanic Black individuals.

While both biological and social factors clearly contribute to the development of cardiometabolic diseases, the relative contribution is difficult to evaluate on an individual level. Race is a social construct. However, there are many genetic variants with large differences in allele frequency by ethnic ancestry, with some contributing to disease and drug response.[1, 5, 9, 24–27] We reiterate that apart from clinical factors (age, BMI, blood glucose, clinical or subclinical cardiovascular disease), social factors such as all of the downstream effects of structural and interpersonal racism on education status, health insurance status, and employment status are key correlates of incident diabetes in our study population. While our analyses accounted for the common social factors, our analyses cannot completely capture the adverse life experience of Black Americans attributed to systemic structural and interpersonal racism in healthcare and society.[1, 7–10, 24] While these factors are important in driving the cardiometabolic disease burden, the higher risk of incident diabetes among non-Hispanic Black individuals may have genetic contributions that require evaluation. Given the strong association between European ancestry, metabolic profiles, and incident diabetes that we demonstrated, our investigation advocates for comprehensive genetic assessment to explore the various individual-level genetic determinants of incident diabetes among racial minorities while simultaneously mitigating the numerous extrinsic factors that are disproportionately impacting Black Americans.[9] Large-scale genetic association studies in Black individuals will help improve our understanding of the biological determinants contributing to cardiometabolic disease. Such investigations coupled with an examination of approaches for mitigating the

social determinants of health may help improve the cardiometabolic disease burden disproportionately impacting Black individuals.[1, 7–9, 11, 2]

Prior studies have noted the paradoxical finding that Black individuals have a more favorable lipid profile, a marker that is associated with a lower risk of cardiometabolic disease but is still predisposed to a higher risk of incident diabetes.[28–31] Previous studies have shown that triglyceride and HDL-C levels to be predictive of insulin resistance in self-identified White individuals, but not in self-identified Black individuals.[32, 33] We found that lower triglyceride and higher HDL-C levels track independently with the increasing genetic European ancestry proportion. Several genetic factors have been previously associated with the lower triglycerides, and higher HDL-C noted with lower European ancestry.[18, 31, 34–36] Prior investigations indicate that variants in the *LPL* gene (lipoprotein lipase gene) such as rs12678919 (occurring in tight linkage disequilibrium with rs328) result in a favorable lipid profile (higher HDL-C, lower triglycerides), and these genetic findings have been validated among Black Americans.[18, 36] Similarly, genetic variants in *NRXN3, TTC7B* and, *GCKR* have been suggested as potential contributors to racial differences in triglyceride levels.[11, 18] Further research is needed to understand the contribution of these and other genetic variants to the eventual higher risk of incident diabetes in Black individuals. Our findings add to the growing body of evidence that the current definition of metabolic syndrome inadequately characterizes the burden of cardiometabolic disease among non-Hispanic Black individuals because it relies on HDL-C and triglyceride levels.[15, 37–39]

The higher incidence of diabetes mellitus among Black Americans has been previously noted in community cohort-based studies and was shown to be driven by socioeconomic, psychosocial, behavioral, and neighborhood factors alongside the clinical factors.[1] The higher risk of incident diabetes among Black individuals is attenuated by ~96% on the inclusion of biological factors and further attenuated by 17% after accounting for the neighborhood, psychosocial, socioeconomic, and behavioral factors.[1] We observed that Black participants have a greater risk of incident diabetes, and this may be driven primarily by their clinical profile and social factors. Older individuals are at a greater risk of development of diabetes.[40] Age was one of the strongest correlates of incident diabetes in our study population. Our sensitivity analyses taking age as the time-scale yielded similar results of a higher risk of incident diabetes among non-Hispanic Black participants. Epidemiological evidence from American population cohorts suggests that a lower proportion of European ancestry is associated with higher odds of having diabetes mellitus after accounting for age, sex, BMI, and socioeconomic factors.[27] Our study advances this finding by noting a strikingly higher risk of incident diabetes with lower European ancestry proportions among non-Hispanic Black individuals after accounting for numerous clinical, biological, and social factors. This suggests that there may be genetic variants that contribute to the higher risk of developing diabetes mellitus among non-Hispanic Black individuals, which have not yet been discovered. Prior genome-wide association studies (GWASs) have identified several genetic loci for diabetes.[41–45] These findings are derived primarily from European populations and have not been validated in those with African ancestry. This may be due to smaller sample sizes in African ancestry studies, racial/ethnic differences in allele frequency or linkage disequilibrium, or smaller effect sizes in certain populations.[31] Further research is needed to improve the

understanding of the various genetic determinants of incident diabetes in Black individuals, alongside addressing the numerous social determinants of health driving the disproportionate cardiometabolic disease burden.

There are several limitations to our study. Our study was performed in the SPRINT population, which included high-risk hypertensive Americans, and this may introduce a collider bias in our investigation. We evaluated a subset of the SPRINT participants who represent a high-risk and hypertensive American population. Hence, these findings require validation in larger, more generalized populations.[39] Our study included only Black Americans from the SPRINT and did not include Hispanic participants due to lack of data on ancestry proportion in the Hispanic participants of the study. Recently, higher African and Native American ancestry and lower European ancestry have been found to be associated with a higher genetic risk of diabetes mellitus in Hispanic/Latino populations.[46] These findings strengthen our observed association of ancestry proportion with incident diabetes. While we used the available data regarding possible socioeconomic confounders, there are likely other unmeasured residual confounders, either extrinsic societal or biological, that may affect the observed results. Furthermore, though we utilized 106 biallelic AIMs for this analysis,[38] prior studies have shown a strong correlation (correlation coefficient>0.9) between true individual ancestry and the estimated ancestry computed using at least 100 AIMs.[47, 48] We also lacked data regarding the place of birth, acculturation status, and the impact of time spent in the United States on the development of incident diabetes.[21, 49–52] We did not have access to the geographical location of the randomization site, and the geographical heterogeneity in the genetic ancestry proportion, socioeconomic, cultural, dietary, and cardiometabolic risk factors of the study population may have also contributed to the observed results.[7, 8, 10, 21, 49–52] Due to the lack of availability of genetic data, the current investigation did not account for genetic variants that may be associated with the development of diabetes. The lack of interaction may result from inadequate power for the given sample size to detect a significant interaction. Notwithstanding these limitations, the randomized clinical trial setting provided a rigorous assessment of the clinical measures and study outcome in this study.

Conclusions

Among non-Hispanic Black SPRINT participants, higher levels of European genetic ancestry were associated with a less favorable lipid profile at baseline but with a lower risk of incident diabetes mellitus. Large-scale genetic association studies in Black Americans will help improve our understanding of the biological determinants contributing to the development of cardiometabolic diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

We would like to thank the SPRINT trial investigators for making the study data available for public use through the NHLBI Biologic Specimen and Data Repository.

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Non-Standard Abbreviations and Acronyms

AIM	Ancestry Informative Markers
BMI	Body Mass Index
HDL-C	High-Density Lipoprotein Cholesterol
LDL-C	Low-Density Lipoprotein Cholesterol
SPRINT	Systolic Blood Pressure Intervention Trial

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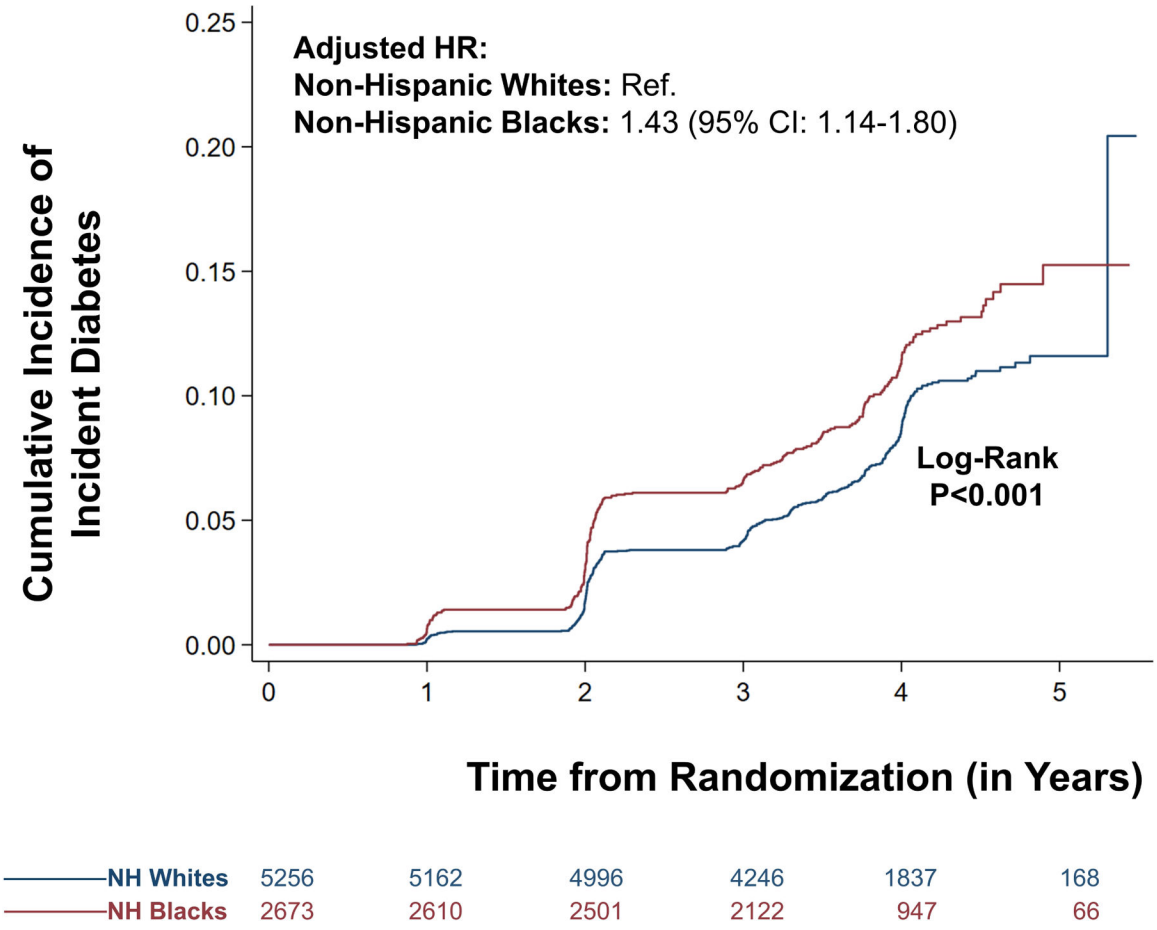


Figure 1. Risk of Incident Diabetes Mellitus in the SPRINT Trial: Stratified by Race

The curve in blue represents the non-Hispanic (NH) White population. The curve in red represents the NH Black population.

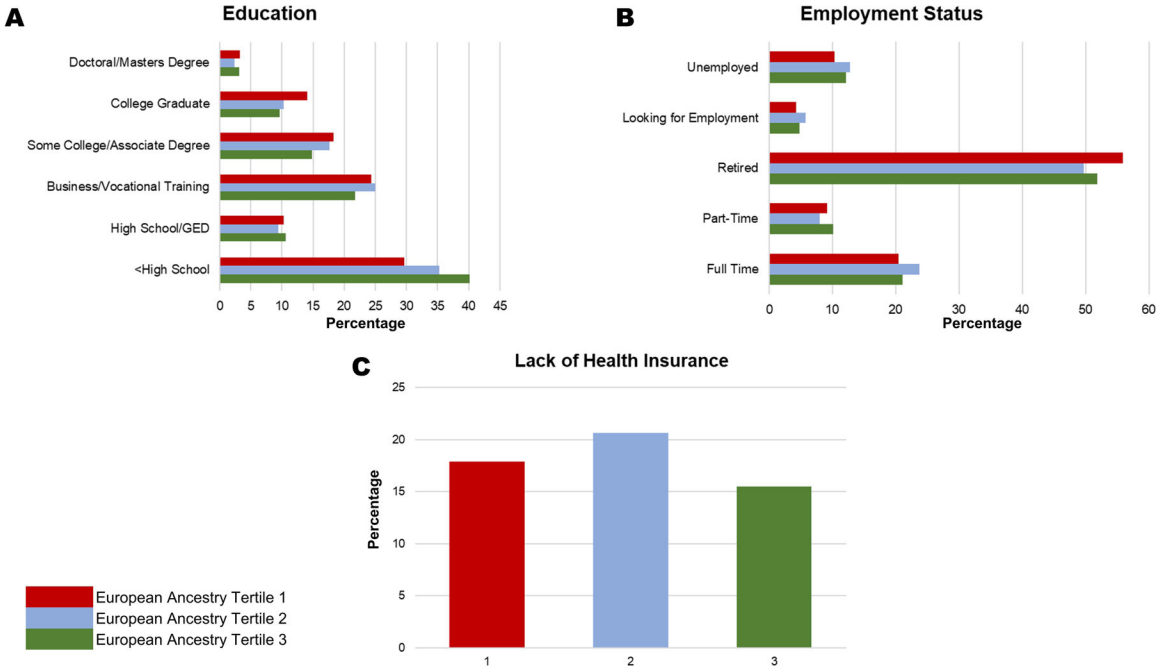


Figure 2. Social Determinants of Health Among Black Individuals Across Ancestry Proportion Tertiles

This figure depicts the distribution of the education status (Panel A), employment status (Panel B), and health insurance status (Panel C). P for education status=0.001. P for employment status=0.17. P for health insurance status=0.22.

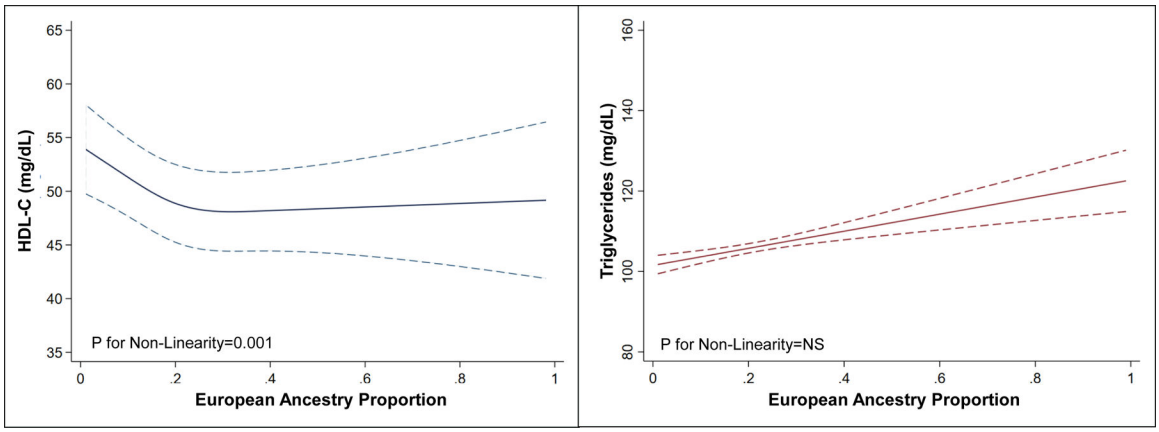
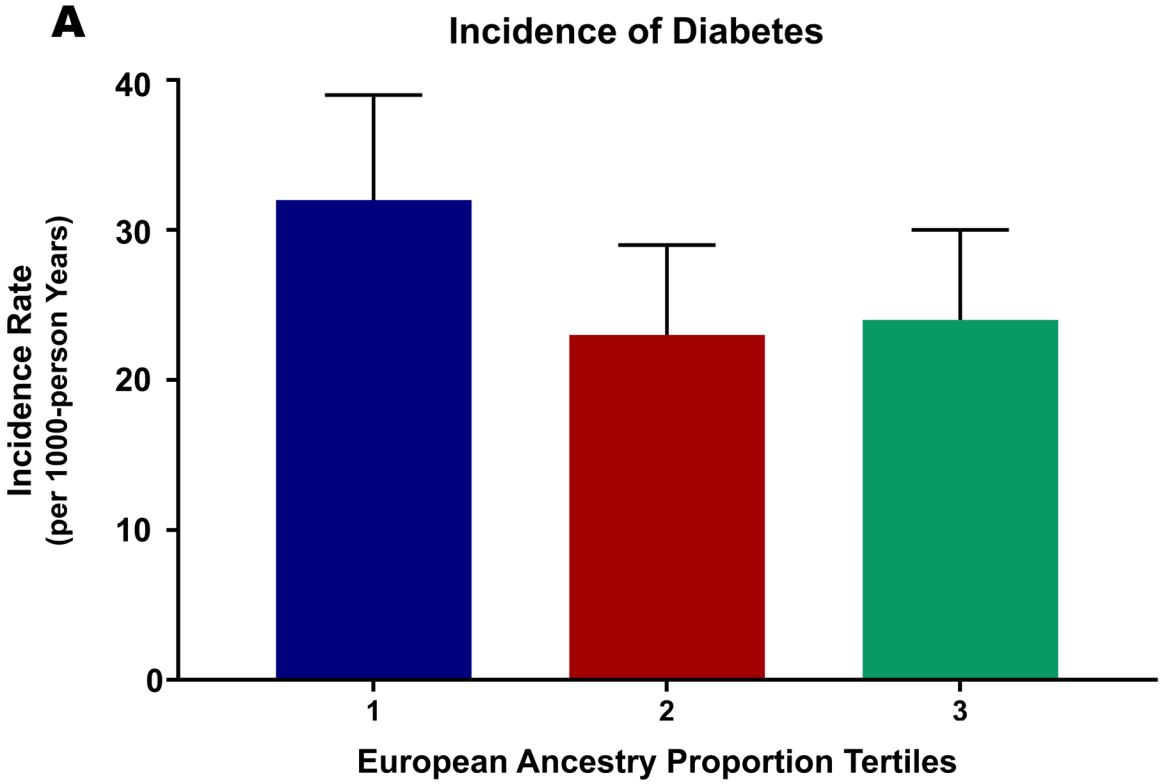
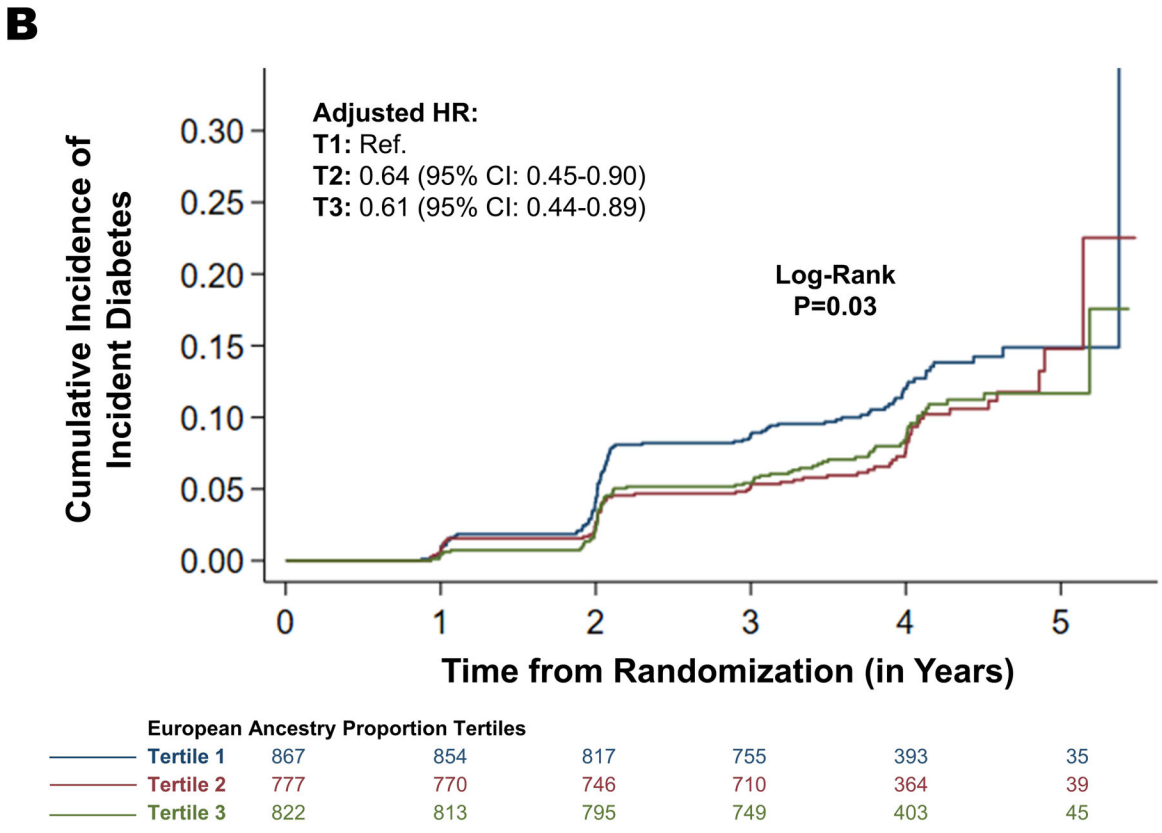


Figure 3.

Multivariable-Adjusted Relationship of Baseline High-Density Lipoprotein-Cholesterol and Triglycerides with European Ancestry Proportions





European Ancestry Proportion Tertiles						
Tertile 1	867	854	817	755	393	35
Tertile 2	777	770	746	710	364	39
Tertile 3	822	813	795	749	403	45

Figure 4. European Ancestry Proportion and the Risk of Incident Diabetes Among Black Individuals

This figure depicts the incidence rate of diabetes mellitus across increasing European ancestry proportion as tertiles (Panel A and Panel B).

Table 1.

Baseline Characteristics of Self-Reported Black Individuals, Stratified by Tertile of European Admixture Proportion

Characteristics	Tertile 1 (n=867)	Tertile 2 (n=777)	Tertile 3 (n=822)	P-value
European Admixture Proportion	11% (8–13%)	20% (17–22%)	32% (27–38%)	<.001
Age	62 (57–71)	62 (57–69)	64 (58–72)	.01
Age ≥75 years	139 (16.0)	109 (14.0)	155 (18.9)	.13
Age ≥65 years	362 (41.8)	281 (36.2)	383 (46.6)	<.001
Female	406 (46.8)	352 (45.3)	366 (44.5)	.63
Framingham 10-year CHD Risk Score	18.2 (12.6–26.8)	18.9 (13.3–27.5)	19.6 (13.7–28.6)	.003
Framingham 10-year CHD risk ≥15%	541 (62.4)	506 (65.1)	583 (70.9)	<.001
Body Mass Index (kg/m^2)	30.0 (26.3–34.3)	30.5 (26.7–34.6)	29.6 (25.4–34.1)	.69
Systolic Blood Pressure (mmHg)	138 (129–150)	139 (130–150)	139 (129–149)	.44
Diastolic Blood Pressure (mmHg)	82 (73–90)	82 (74–90)	81 (72–89)	.13
Fasting Plasma Glucose (mg/dL)	94 (88–102)	95 (88–102)	96 (89–103)	.03
Total Cholesterol (mg/dL)	193 (170–220)	194 (173–222)	194 (166–219)	.39
LDL Cholesterol (mg/dL)	116 (95–140)	119 (98–144)	117 (93–139)	.87
HDL Cholesterol (mg/dL)	55 (46–65)	53 (45–62)	52 (44–62)	<.001
Triglycerides (mg/dL)	89 (67–120)	93 (69–126)	94 (70–131)	.02
Serum Creatinine (mg/dL)	1.08 (0.91–1.32)	1.06 (0.88–1.27)	1.04 (0.87–1.25)	
Urine Albumin to Creatinine Ratio (mg/gm)	9.5 (5.0–22.5)	9.1 (5.1–25.0)	8.9 (5.1–20.0)	.26
Estimated GFR (mL/min/1.73m^2)	73.3 (59.5–87.9)	76.4 (62.1–91.5)	78.3 (63.1–91.7)	<.001
CKD (eGFR <60 mL/min/1.73m^2)	27.1	22.1	21.2	.002
CKD Stage II (eGFR 45–59 mL/min/1.73m^2)	15.5	14.9	13.9	.007
CKD Stage III (eGFR 30–59 mL/min/1.73m^2)	8.8	4.9	5.7	
CKD Stage IV (eGFR 15–29 mL/min/1.73m^2)	2.9	2.5	1.5	
Aspirin Use	40.9	39.6	33.3	.29
Statin Use	31.7	32.6	37.0	.02
Antihypertensive Medications	2 (1–3)	2 (1–3)	2 (1–3)	.63
Smoking Status				
Never	47.3	41.2	41.6	.008
Former	29.4	33.7	37.2	
Current	23.2	25.1	20.9	
Education				
Less than High School	348 (40.1)	274 (35.3)	244 (29.7)	.001
High School or GED	92 (10.6)	73 (9.4)	85 (10.3)	
Business or Vocational Training	189 (21.8)	194 (25.0)	200 (24.3)	
Some College or Associate Degree	128 (14.8)	137 (17.6)	150 (18.3)	
College Graduate	83 (9.6)	80 (10.3)	116 (14.1)	

Characteristics	Tertile 1 (n=867)	Tertile 2 (n=777)	Tertile 3 (n=822)	P-value
Doctoral or Masters Degree	27 (3.1)	19 (2.4)	27 (3.3)	
Employment				
Full Time	176 (21.1)	179 (23.8)	163 (20.4)	.17
Part-Time	84 (10.1)	60 (8.0)	73 (9.2)	
Retired	432 (51.8)	374 (49.7)	446 (55.9)	
Looking for Employment	40 (4.8)	44 (5.8)	34 (4.3)	
Unemployed	102 (12.2)	96 (12.8)	82 (10.3)	
Lack of Health Insurance	155 (17.9)	160 (20.6)	127 (15.5)	.22

Categorical variables are represented as counts with proportions, and continuous variables are represented as medians with interquartile ranges. **Abbreviations:** GFR: Glomerular Filtration Rate; CKD: Chronic Kidney Disease; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; CHD: Coronary Heart Disease. Continuous variables are compared using the Jonckheere-Terpstra test. Categorical variables are compared using the Cochran-Armitage test.