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Race-Dependent Association of High-Density Lipoprotein Cholesterol Levels With Incident Coronary Artery Disease

Neil A. Zakai, MD,[a,b] Jessica Minnier, PhD,[c] Monika M. Safford, MD,[d] Insu Koh, PhD,[a] Marguerite R. Irvin, PhD,[e] Sergio Fazio, MD, PhD,[f] Mary Cushman, MD,[a,b] Virginia J. Howard, PhD,[e] Nathalie Pamir, PhD[f]

ABSTRACT

BACKGROUND Plasma lipids are risk factors for coronary heart disease (CHD) in part because of race-specific associations of lipids with CHD.

OBJECTIVES The purpose of this study was to understand why CHD risk equations underperform in Black adults.

METHODS Between 2003 and 2007, the REGARDS (REasons for Geographic and Racial Differences in Stroke) cohort recruited 30,239 Black and White individuals aged ≥45 years from the contiguous United States. We used Cox regression models adjusted for clinical and behavioral risk factors to estimate the race-specific hazard of plasma lipid levels with incident CHD (myocardial infarction or CHD death).

RESULTS Among 23,901 CHD-free participants (57.8% White and 58.4% women, mean age 64 ± 9 years) over a median 10 years of follow-up, 664 and 951 CHD events occurred among Black and White adults, respectively. Low-density lipoprotein cholesterol and triglycerides were associated with increased risk of CHD in both races (*P* interaction by race >0.10). For sex-specific clinical HDL-C categories: low HDL-C was associated with increased CHD risk in White (HR: 1.22; 95% CI: 1.05-1.43) but not in Black (HR: 0.94; 95% CI: 0.78-1.14) adults (*P* interaction by race = 0.08); high HDL-C was not associated with decreased CHD events in either race (HR: 0.96; 95% CI: 0.79-1.16 for White participants and HR: 0.91; 95% CI: 0.74-1.12 for Black adults).

CONCLUSIONS Low-density lipoprotein cholesterol and triglycerides modestly predicted CHD risk in Black and White adults. Low HDL-C was associated with increased CHD risk in White but not Black adults, and high HDL-C was not protective in either group. Current high-density lipoprotein cholesterol–based risk calculations could lead to inaccurate risk assessment in Black adults. (J Am Coll Cardiol 2022;80:2104–2115) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Coronary heart disease (CHD) remains a leading cause of morbidity and mortality in the United States, accounting for approximately 13% of all deaths in 2017.[1] Black Americans have a lower risk of overall CHD, although fatal CHD events are more common compared with White Americans.[2-4] Despite heterogeneity by race in the frequency of CHD risk factors and CHD outcomes, little is known as to the specific reasons for this disparity; thus, the American Heart Association, the U.S. Department of Health and Human Services, and the Institute of Medicine have called for further

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From the [a]Department of Medicine, Department of Pathology and Laboratory Medicine, Larner College of Medicine, University of Vermont, Burlington, Vermont, USA; [b]Larner College of Medicine, University of Vermont, Burlington, Vermont, USA; [c]OHSU-PSU School of Public Health, Oregon Health and Science University, Portland, Oregon, USA; [d]General Internal Medicine, Weill Cornell Medicine, New York, New York, USA; [e]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama, USA; and the [f]Knight Cardiovascular Institute, Department of Medicine, Oregon Health and Science University, Portland, Oregon, USA.

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community-based populations studies addressing this knowledge gap.[5-8]

Clinical risk factors for CHD include dyslipidemia, diabetes mellitus, hypertension, adiposity, cigarette smoking, and physical inactivity.[9] Growing evidence indicates that some of these risk factors display race-specific associations with CHD among Black Americans.[10-13] Therefore, available risk assessment models, developed primarily in cohorts of White Europeans, may misclassify risk in Black adults,[2] potentially hindering optimal cardiovascular disease prevention and management programs for this group.

In the 1970s, the Framingham Heart Study discovered the now well-established inverse and linear association between plasma high-density lipoprotein cholesterol (HDL-C) concentration and CHD risk.[14]

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The association was confirmed in other mostly White European cohorts,[15-19] whereas it was weaker[20-22] or even absent[23-25] in racially diverse cohorts. For example, in a subcohort with incident cancer of the REGARDS (Reasons for Geographic and Racial Differences in Stroke) (the same biracial cohort we have investigated in this study), low HDL-C levels (30-40 mg/dL) were associated with reduced risk of incident CHD in Black adults.[26] However, this analysis did not examine the association with higher HDL-C levels—an important question considering that in some cohorts (mostly Caucasian), very high HDL-C levels are directly associated with CHD risk.[27] Data from >300,000 multiethnic participants in the Emerging Risk Factors Collaboration challenged the understanding of a linear inverse association between HDL-C and CHD even further by demonstrating that individuals with HDL-C <40 mg/dL (the clinical threshold for low HDL-C for men) have increased risk of cardiovascular events, whereas those with levels >60 mg/dL are not afforded protection.[28] Because these studies did not focus on race differences, the need remains to determine whether clinical risk categories for CHD using HDL-C levels are appropriate for all people.

To determine whether lipid parameters predicted CHD risk in a contemporary population of Black and White Americans, we assessed the impact of race on the association of lipid levels with incident CHD in REGARDS (**Central Illustration**).

METHODS

STUDY POPULATION. REGARDS is a national prospective cohort of 30,239 participants that was designed to examine potential reasons underlying regional and racial differences in stroke mortality. Details on the design and methods of REGARDS have been previously described.[29,30] Briefly, REGARDS is composed of community-dwelling Black and White women and men aged ≥45 years, identified via mail and telephone using commercially available lists of U.S. residents, and enrolled from 2003 to 2007. The final sample included 21% of participants from the "stroke buckle" (counties within the coastal plain of North Carolina, South Carolina, and Georgia), 35% from the rest of the southeastern U.S. "stroke belt" (North Carolina, South Carolina, Georgia, Tennessee, Alabama, Mississippi, Arkansas, and Louisiana), and 44% from elsewhere in the contiguous United States. The resulting cohort was 42% Black and 55% women. Exclusion criteria included race other than White or Black, active treatment for cancer in the previous year, chronic medical conditions precluding long-term participation, cognitive impairment, current or impending residence in a nursing home, or inability to communicate in English. An initial telephone interview was used to survey participants, establish eligibility, and obtain verbal consent.[31] Demographic information and medical history (including risk factor evaluation) was collected by computer-assisted telephone interview.[31] Race was self-classified by participants and included the following options: White or Black/African American (referred henceforth as Black). An in-home examination was conducted to perform anthropometric measurements (eg, blood pressure) an electrocardiogram, medication inventory, phlebotomy, urine collection, and written informed consent. Follow-up telephone interviews are performed every 6 months to detect possible cardiovascular events. The study was approved by the Institutional Review Boards of all participating institutions. To report the clinical variables, we followed the STROBE (Strengthening The Reporting of OBservational studies in Epidemiology) guidelines.[32]

CHD OUTCOMES. Baseline CHD was defined as either participant-reported history of CHD or diagnostic electrocardiographic changes at baseline. Incident CHD was defined as a definite or probable nonfatal myocardial infarction (MI) or CHD death after the baseline in-person visit or on or before December 31, 2017.[33] The definition of "CHD death" includes definite or probable fatal MI (expert-adjudicated, with death within 28 days from event) or death from MI not meeting the criteria for definite, probable, or sudden death preceded by cardiac symptoms or signs

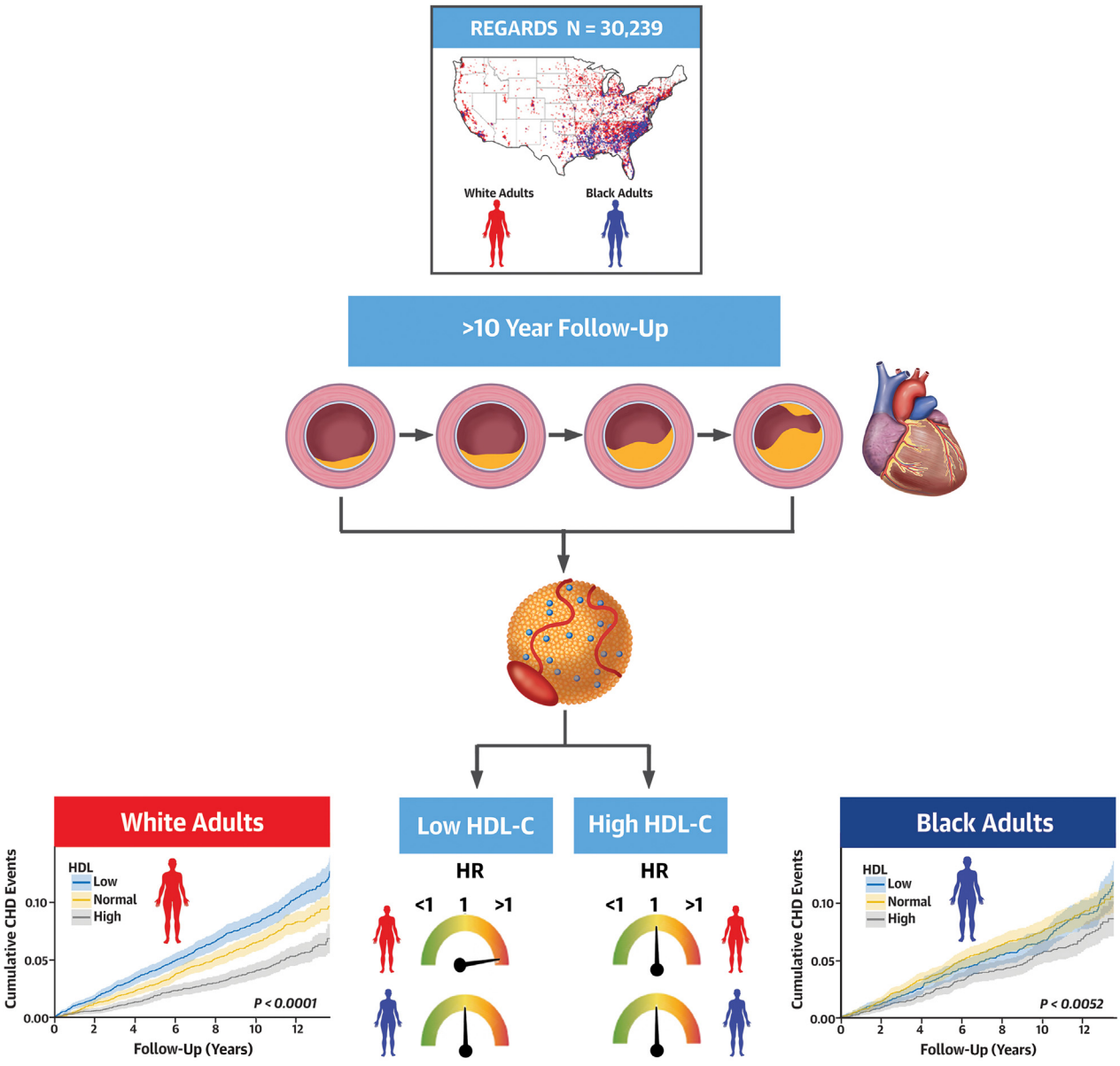
ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

CENTRAL ILLUSTRATION The Race-Specific Association of HDL-C With CHD Risk



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Low high-density lipoprotein cholesterol (HDL-C) levels were detrimental only in White adults; high HDL-C levels were not protective in either race. CHD = coronary heart disease; REGARDS = REasons for Geographic and Racial Differences in Stroke.

without evidence of noncoronary causes.[3] Non-CHD or MI-related deaths were censored.[4] When nonfatal events were reported, medical records were retrieved for adjudication by trained clinicians following published guidelines.[34,35] When fatal CHD events were reported, interviews with next of kin or proxies, review of medical records in the last year of life, death certificates, and autopsy reports were used to determine whether the CHD event was the ultimate cause of death.

RISK FACTORS. Baseline blood samples were obtained after a 10- to 12-hour overnight fast. Samples were centrifuged within 2 hours of collection; serum and plasma were separated and shipped overnight to

the study biorepository at University of Vermont for storage or analysis. Upon arrival, samples were centrifuged at 30,000 *g* at 4 °C and either analyzed or stored at below −80 °C. Cholesterol, HDL-C, triglycerides and glucose were measured by colorimetric reflectance spectrophotometry using the Ortho Vitros Clinical Chemistry System 950IRC (Johnson and Johnson Clinical Diagnostics).[31] LDL-C was calculated using the Friedewald equation.[36]

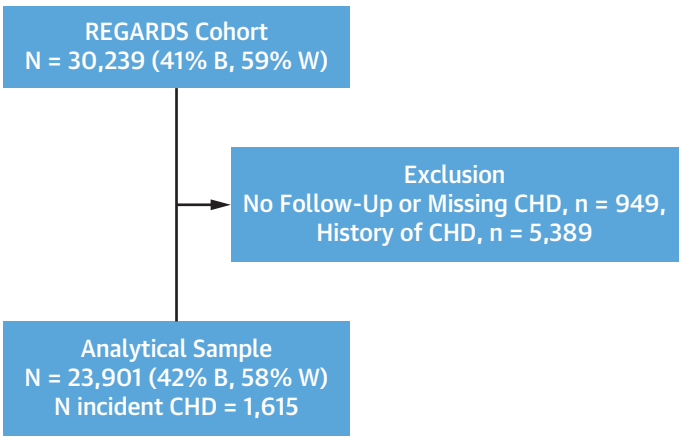
Smoking status was modeled as current vs former/never, and body mass index was defined as the mass in kilograms divided by the height in meters squared measured at the in-home visit. Medications (statins and blood pressure medications) were defined from a medication inventory collected at the in-home visit. Blood pressure was the average or 2 measures after resting for 5 minutes at the in-home visit. Diabetes was self-reported diagnosis of diabetes, a fasting glucose ≥126, a nonfasting glucose ≥200, or use of antidiabetic medications including insulin.

STATISTICAL ANALYSIS. Participants with prior CHD were excluded. Baseline characteristics were summarized with mean ± SD for continuous variables and n (%) for categorical variables. The standardized mean difference was calculated between Black and White participants as the difference in mean divided by the SD. Time to first CHD event, loss to follow-up (unable to contact because of illness, dementia, move, or withdrawal of consent by participant or proxy) or death was calculated from the baseline visit to compute the follow-up time for survival analyses. Details of the analytical approach are presented in the Supplemental Appendix.

RESULTS

COHORT CHARACTERISTICS. Among 29,290 participants with follow-up in REGARDS, we excluded 5,389 participants with baseline CHD, thus leaving 23,901 participants in the analytical sample. Race-specific missingness is presented in Supplemental Table 1. Of these, 57.7% identified as White and 58.3% as female (**Figure 1**). Black and White participants had comparable mean age, lipid profiles, smoking status, and hypertension and diabetes medication use (**Table 1**). Over a median follow-up of 10.7 years (IQR: 6.4-12.7 years), 1,615 CHD events occurred, of which 41.1% occurred among Black participants and 45.5% occurred among women (**Table 1**). Black and White men had comparable incident CHD rates, whereas Black women had a higher incident CHD rate than White women. More CHD events were fatal in Black men and women than in White men and women (**Table 1**).

FIGURE 1 The Flowchart of the Study Cohort



REGARDS (REasons for Geographic and Racial Differences in Stroke) is a national prospective cohort of 30,239 participants composed of community-dwelling Black (B) and White (W) women and men aged ≥45 years, identified via mail and telephone using commercially available lists of U.S. residents, and enrolled from 2003 to 2007. Incident coronary heart disease (CHD) was defined as a definite or probable nonfatal myocardial infarction or CHD death after the baseline in-person visit or on or before December 31, 2017.

LIPIDS PROFILES AND CHD RISK. We determined the association of plasma LDL-C, HDL-C, and triglycerides levels with CHD incidence. In model 2, every 1 SD increase in LDL-C (34 mg/dL) and triglyceride (82 mg/dL) levels were associated with a modest increase in CHD risk (HR: 1.05; 95% CI: 0.99-1.10, and HR: 1.09; 95% CI: 1.05-1.12, respectively) (**Table 2**). The detrimental association between increased LDL-C and triglycerides and CHD was maintained when the models were further adjusted for clinical factors (Model 3). In the unadjusted model, every 1-SD (16 mg/dL) increase in HDL-C levels was associated with decreased CHD risk (HR: 0.78; 95% CI: 0.74-0.83), although adjustment for clinical risk factors in Model 3 attenuated the association (HR: 0.95; 95% CI: 0.89-1.02) (**Table 2**).

The race-stratified survival estimates per sex-specific low, normal, and high HDL-C clinical categories displayed distinct profiles for White and Black participants (**Figure 2**). Low HDL-C levels were associated with poor CHD-free survival rates in White but not in Black participants (global log-rank $P < 0.001$). High HDL-C levels were associated with favorable CHD-free survival rates in White but not in Black participants ($P = 0.0052$) (**Figure 2**).

In unadjusted race-stratified spline models, the point estimate for lower HDL-C levels were associated with increased CHD risk in White but not in Black participants, and the race-specific association was

TABLE 1 Characteristics of REGARDS Participants

	Overall (N = 23,901)	Black (n =10,095)	White (n = 13,806)
Male	9,949 (41.6)	3,661 (36.3)	6,288 (45.5)
Region			
Belt	8,262 (34.6)	3,388 (33.6)	4,874 (35.3)
Buckle	5,020 (21.0)	1,837 (18.2)	3,183 (23.1)
Nonbelt	10,619 (44.4)	4,870 (48.2)	5,749 (41.6)
Education			
Less than high school	2,733 (11.4)	1,872 (18.6)	861 (6.2)
High school	6,064 (25.4)	2,805 (27.8)	3,259 (23.6)
Some college	6,470 (27.1)	2,735 (27.1)	3,735 (27.1)
College and above	8,619 (36.1)	2,675 (26.5)	5,944 (43.1)
Age, y	64.1 ± 9.32	63.6 ± 9.25	64.4 ± 9.36
HDL, mg/dL	52.7 ± 16.25	53.9 ± 15.97	51.9 ± 16.40
HDL, mg/dL, M/F	46.17 ± 13.83/57.60 ± 16.19	48.33 ± 14.52/57.19 ± 15.87	44.94 ± 13.27/57.94 ± 16.44
LDL, mg/dL	116.5 ± 34.35	118.2 ± 36.05	115.3 ± 33.03
Triglycerides, mg/dL	129.7 ± 82.77	112.1 ± 73.68	142.2 ± 86.55
Cholesterol, mg/dL	195.2 ± 39.23	194.6 ± 40.48	195.6 ± 38.31
SBP, mm Hg	127.06 ± 16.46	130.29 ± 17.14	124.70 ± 15.52
DBP, mm Hg	76.70 ± 9.60	78.48 ± 9.96	75.40 ± 9.12
BMI, kg/m^2	29.2 ± 6.23	30.7 ± 6.70	28.2 ± 5.63
Sex-specific HDL categories			
Low	7,878 (34.6)	3,094 (32.6)	4,784 (35.9)
Normal	8,278 (36.3)	3,457 (36.5)	4,821 (36.2)
High	6,643 (29.1)	2,933 (30.9)	3,710 (27.9)
Current smoker	3,382 (14.2)	1,711 (17.0)	1,671 (12.1)
Taking hypertension medication	11,495 (50.1)	6,123 (63.0)	5,372 (40.6)
Diabetes	4,460 (19.4)	2,745 (28.4)	1,715 (12.8)
Taking dyslipidemia medication	6,672 (28.2)	2,728 (27.3)	3,944 (28.9)
Median follow-up, y	10.7	10.8	10.4
Total person-y follow-up	225,269	91,112	134,156
CHD events (women)	1,615 (736)	664 (358)	951 (378)
Total fatal CHD events (women)	555 (255)	280 (142)	275 (113)

Values are n (%) or median ± SD, unless otherwise indicated. HDL categories: Low ≤40 mg/dL for men, <50 mg/dL for women; normal 40-60mg/dL for men, 50-60 mg/dL for women; high >60 mg/dL. The table was constructed according to the STROBE (Strengthening The Reporting of OBservational studies in Epidemiology) guidelines and omits *P* values.[59]

BMI = body mass index; CHD = coronary heart disease; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; REGARDS = REasons for Geographic and Racial Differences in Stroke; SBP = systolic blood pressure.

maintained after adjusting for clinical and behavioral factors (**Figure 3**) (*P* values for race-spline term interaction: Model 1 $P = 0.018$, Model 2 $P = 0.056$, Model 3 $P = 0.067$).

In the unadjusted model, higher HDL-C levels were associated with reduced CHD risk in both White and Black individuals; after adjustment for clinical and behavioral factors, there was no association of higher HDL-C levels with CHD risk in both White and Black participants.

We next examined the association of clinical HDL-C categories with CHD risk stratified by race (**Figure 4**, Supplemental Table 2). Low HDL-C was associated with increased CHD risk in White (HR: 1.30; 95% CI: 1.13-1.50) but not in Black (HR: 0.97; 95% CI: 0.81-1.17) participants, whereas high HDL-C was associated with reduced CHD risk in both Black (HR: 0.74; 95% CI: 0.61-0.91) and White (HR: 0.67; 95% CI: 0.56-0.81) participants only in the unadjusted model (*P* interaction = 0.007). After adjusting for clinical risk factors (Model 3), low HDL-C was associated with increased risk of CHD in White (HR: 1.22; 95% CI: 1.05-1.43) but not in Black (HR: 0.94; 95% CI: 0.78-1.14) individuals (*P* interaction = 0.08) and high HDL-C was no longer protective in either Black (HR: 0.91; 95% CI: 0.74-1.12) or White (HR: 0.96; 95% CI: 0.79-1.16) participants. We found no evidence for sex interaction in race stratified models (Supplemental Table 3).

SENSITIVITY ANALYSES. We fit the Model 2 within race strata separately to determine whether the differences observed remained when allowing other

predictors to vary between the race subgroups (Supplemental Table 4). Consistent with the imputation-derived results, the high HDL-C clinical category translated to protection in White but not in Black participants.

DISCUSSION

In REGARDS—a large contemporary biracial cohort—after adjusting for other risk factors, low HDL-C was associated with increased CHD risk in White but not Black participants, whereas high HDL-C was not associated with CHD risk in either group. Other lipid parameters, such as LDL-C and triglycerides, did not display race-specific behavior and were comparably associated with CHD risk in Black and White participants. Our race-dependent observations indicate that the underlying biologic mechanism by which HDL-C associates with incident CHD in White and Black participants is different from that of other lipid risk factors. Although HDL-C clinical risk category cutoffs are well established for White populations, our findings expose the weaknesses in their use, because such categories might not apply to Black men and women, reducing their value in CHD risk assessment.

Previous epidemiological studies including mostly White participants established that higher HDL-C is associated with a reduced risk of incident CHD, although the strength of this association is unclear for other populations. Although the inverse relationship between HDL-C and CHD was believed to be linear,[14,28] several cohorts have revealed a leveling of risk at around 40 mg/dL.[37] Recent evidence from 2 large population-based Danish cohorts[38] and in the MESA (Multi-Ethnic Study of Atherosclerosis)[39] supports a U-shaped association between HDL-C and CHD risk. Most evidence stems from ethnically White-enriched cohorts; therefore, it is unknown whether the U-shaped association applies to all races and ethnicities. In the Dallas Heart Study, with 46% Black participants, HDL-C was inversely associated with incident CHD among non-Black but not in Black participants.[25] A prior analysis in a cancer-focused REGARDS substudy did report that HDL-C of 30 to 40 mg/dL—compared with HDL-C >40 mg/dL—was associated with lower CHD risk in Black but not in White adults, but did not report on the association of all established HDL-C clinical categories with CHD risk.[26]

Further, we reported that triglycerides to HDL-C ratio was a CHD risk predictor in White but not in Black adults of the REGARDS—an effect driven by the lack of association of HDL-C with CHD in Black adults.[40] LDL-C rather than total cholesterol is more likely to display racial differences because it is a metric sensitive to access to care. In our cohort, lipid-lowering medication use revealed modest but significant disparities between White and Black adults: among all of the adults on medication, 27.3% were Black participants vs 28.9% White participants. This aligns with the slightly elevated plasma LDL-C levels in Black participants. Although the adjustment for calculated LDL-C (which uses a formula inclusive of triglycerides) might mask the true point estimates for triglycerides, the fact that the point estimates do not vary between univariate and the most complex model suggests that the LDL-C adjusting has a minor or null effect.

Collectively, the results support the presence of racial differences that affect the inverse association of HDL-C and incident CHD.

What we have learned from the spline models and from the clinical cutoff point estimates aligns with low HDL-C being detrimental in White adults and not predictive in Black adults.

So far, data from multiethnic population-based studies and clinical cohorts have not provided a consistent conclusion on the role of HDL-C as predictor of CVD risk in Black participants. In some cohorts, HDL-C levels were lower,[41] similar,[3] or higher in Black than in White participants.[42-44] Although Mendelian randomization studies demonstrate that mutations in several genes linked to elevated HDL-C concentrations are not associated with reduced risk of CHD,[45] most of these studies were conducted with European cohorts using 5-point ancestry principal component adjustment to correct for population architecture.[46,47] Causal variants at individual loci can be specific for certain ethnicities.[48] Of the identified HDL-C-related loci, only cholesteryl ester transfer protein has been validated in a Japanese cohort[49]—interestingly, in cholesteryl ester transfer protein mutation. Race- and ethnicity-specific Mendelian

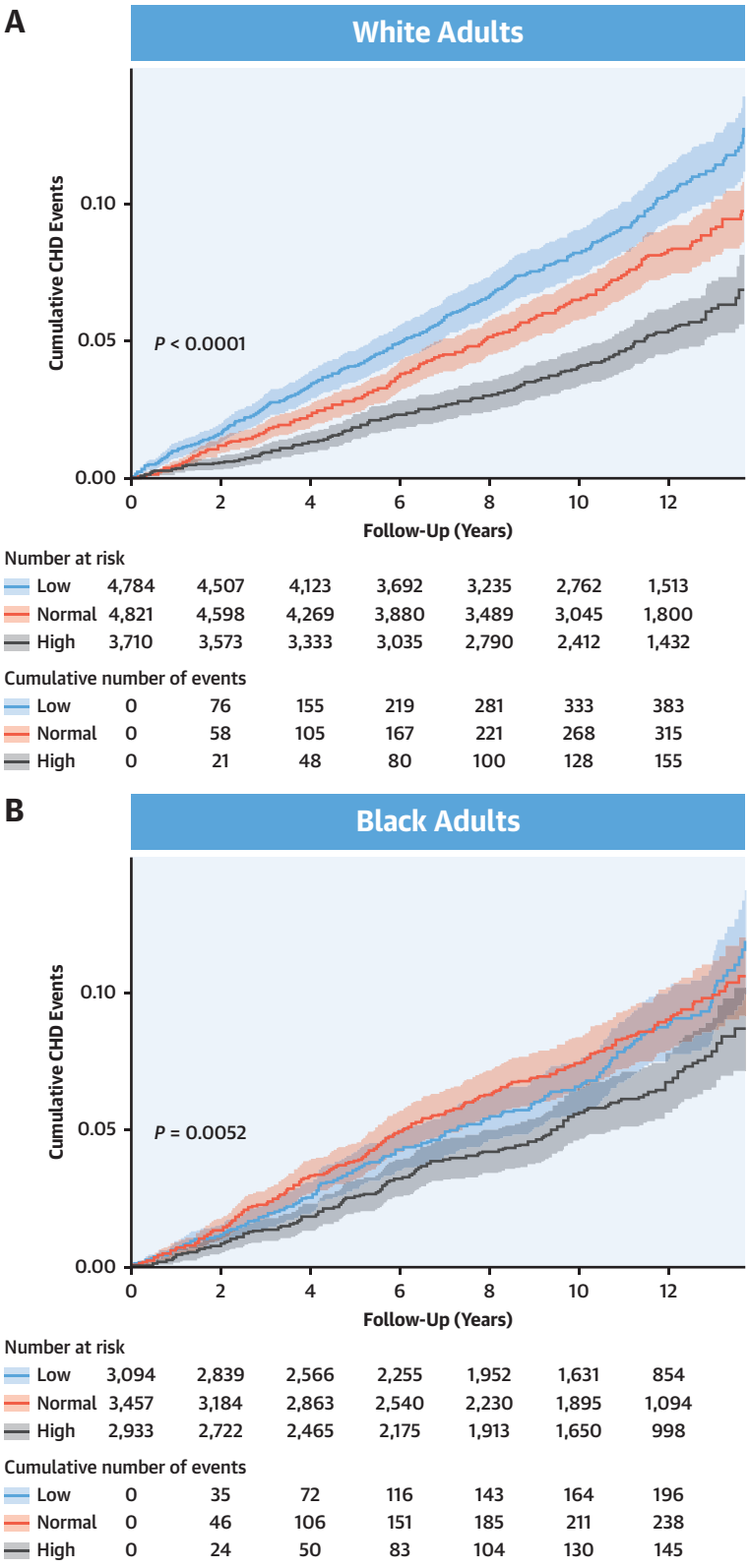
TABLE 2 Association of HDL-C per SD and Common Risk Factors With CHD

	Univariate[a]	Model 2[b]	Model 3[c]
HDL-C, per 16 mg/dL	0.78 (0.74-0.83	0.86 (0.81-0.91)	0.95 (0.89-1.02)
LDL-C, per 34 mg/dL	1.01 (0.96-1.06)	1.05 (0.99-1.10)	1.10 (1.05-1.17)
Triglycerides, per 62 mg/dL	1.11 (1.08-1.14)	1.09 (1.05-1.12)	1.05 (1.01-1.10)
Age, y	1.05 (1.04-1.06)	1.05 (1.05-1.06)	1.05 (1.05-1.06)
Male	1.64 (1.49-1.81)	1.52 (1.36-1.70)	1.64 (1.46-1.84)
Black	1.03 (0.94-1.14)	1.19 (1.07-1.32)	0.88 (0.79-0.99)

Values are HR (95% CI). Staged Cox proportional hazards models for the association of HDL-C with incident CHD were applied, without race-lipid interactions. HR for HDL, LDL, and triglycerides were calculated per SD increment. Male HR is calculated in reference to female, and Black HR is calculated in reference to White. [a]Univariate unadjusted estimates for each predictor. [b]Model 2 estimates are adjusted for LDL-C, triglycerides, age, sex, race, and region. [c]Model 3 estimates are additionally adjusted for smoking, BMI, SBP, diabetes, statins, and hypertensive medication.

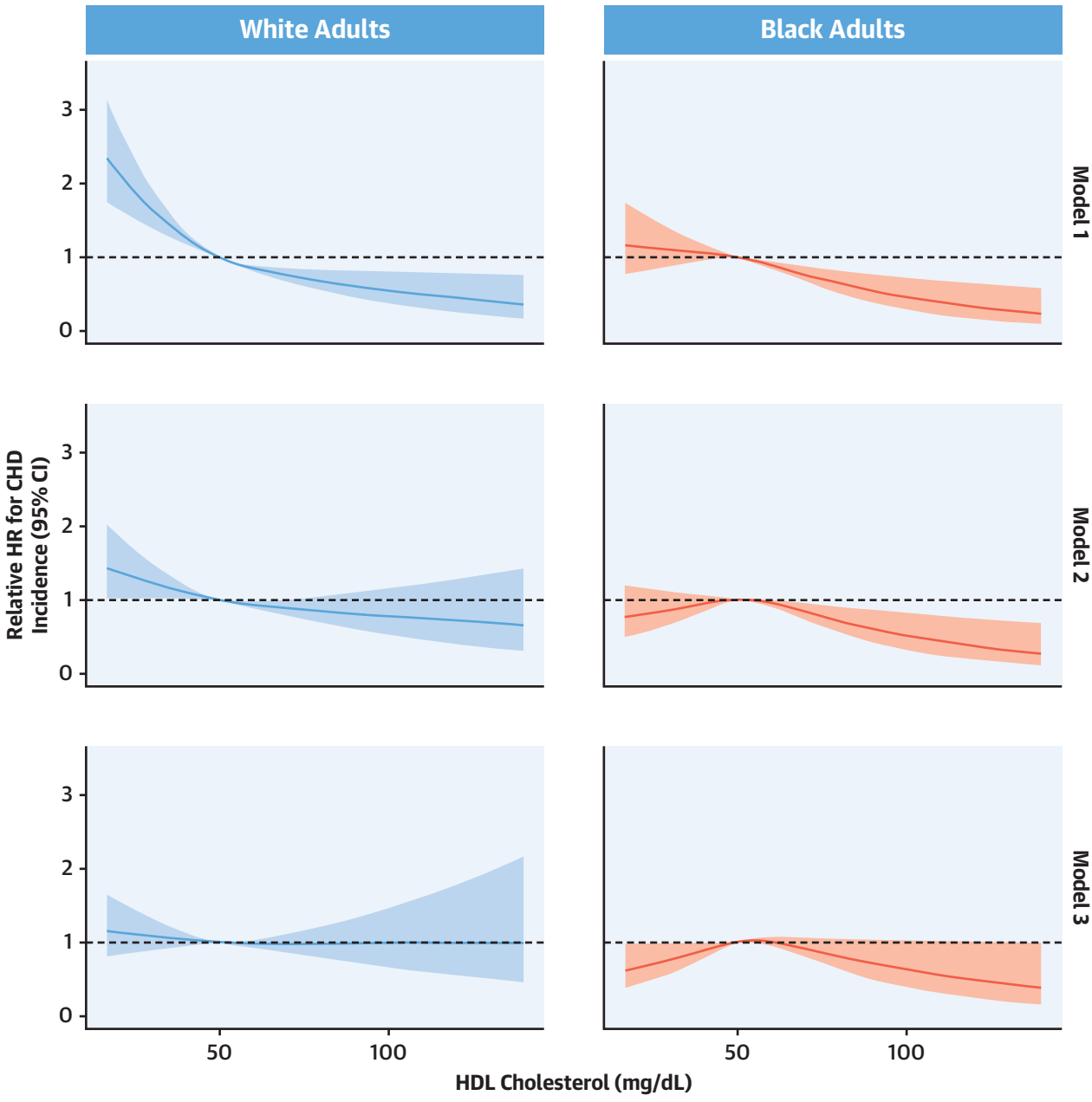
Abbreviations as in Table 1.

FIGURE 2 Estimates for Cumulative Incidence of CHD Events and CHD Death



(A) White adults, **(B)** Black adults. Kaplan-Meier estimates were calculated per clinical high-density lipoprotein (HDL) categories. Participants were classified by sex: low (reference): <40 mg/dL for men and <50 mg/dL for women; normal: 40-59 mg/dL for men, 50-59 mg/dL for women; and high: ≥60 mg/dL. *P* values are from log-rank test. CHD = coronary heart disease.

FIGURE 3 **Predicted Relative HR Curves From Spline Regression Analyses**

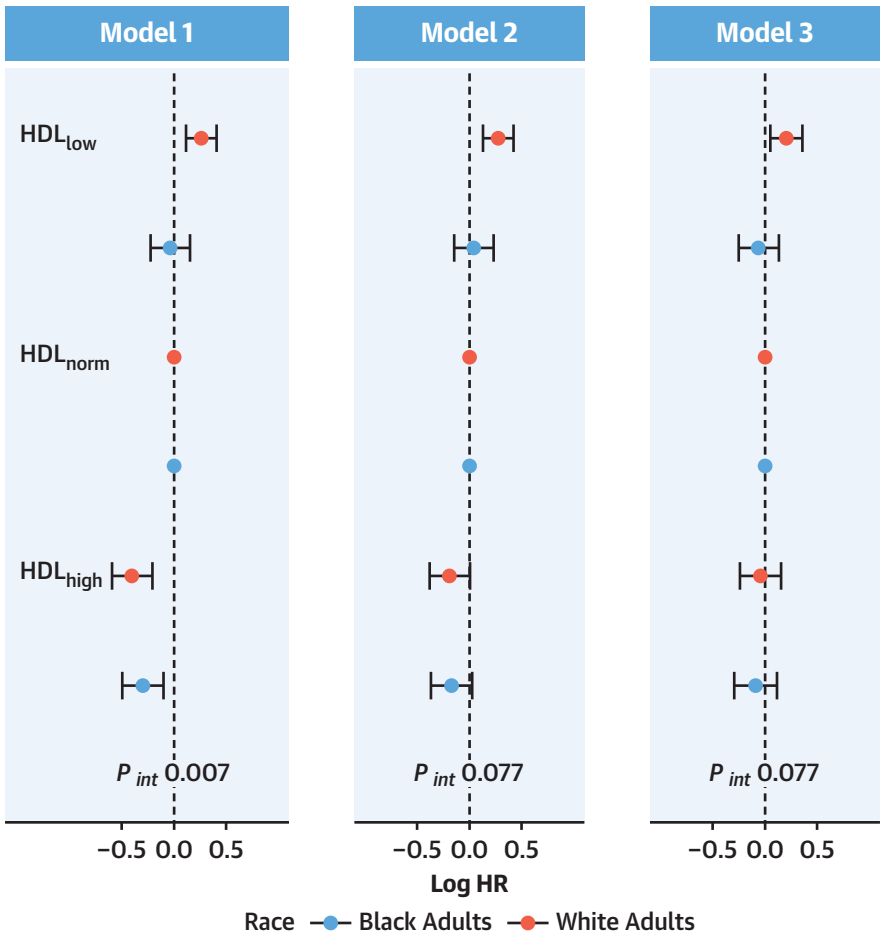


Cubic splines were fit for high-density lipoprotein (HDL) cholesterol within each race group, with relative hazard curves for coronary heart disease incidence compared with median HDL cholesterol of 50 mg/dL. HRs evaluated at median or reference groups of all other model predictors. **Shaded area** represents 95% CI. Model 1 is unadjusted. Model 2 estimates were adjusted for low-density lipoprotein cholesterol, triglycerides, age, sex, race, and region. Model 3 estimates were additionally adjusted for smoking, body mass index, systolic blood pressure, diabetes, statins, and hypertensive medication.

randomization studies may help extend and refine our understanding between plasma HDL-C levels and CHD risk in diverse populations.

Measures other than HDL cholesterol content, such as HDL particle number, proteomic composition, and anti-inflammatory, antioxidant, and sterol efflux activities are all candidates to explain the race-specific association of HDL with CHD risk.[24,25,50-53] For example, greater HDL cholesterol efflux capacity, independent of either HDL-C or APOAI (the major structural protein of HDL), is associated with a lower prevalence and incidence of atherosclerotic vascular

FIGURE 4 Race-Specific HRs for CHD by Baseline HDL



Log-hazard ratio (95% CI); *P* value is calculated for race × lipid interaction. High-density lipoprotein (HDL)$_{low/norm/high}$ strata are defined by sex: low (reference): <40 mg/dL for men and <50 mg/dL for women; normal: 40-59 mg/dL for men, 50-59 mg/dL for women; and high: ≥60 mg/dL. Model 1 is unadjusted. Model 2 estimates were adjusted for low-density lipoprotein cholesterol, triglycerides, age, sex, race, and region. Model 3 estimates were additionally adjusted for smoking, body mass index, systolic blood pressure, diabetes, statins, and hypertensive medication.

disease in multiple cohorts.[24,51,52] More recently, in the PREVEND (Prevention of Renal and Vascular End Stage Disease) study, the anti-inflammatory capacity of HDL (independent of its sterol efflux capacity) was inversely associated with incident vascular events,[53] and the authors showed that inclusion of this metric in the risk prediction formula improves CHD risk assessment. It is yet to be determined, however, if these novel HDL measures display race-specific associations with CHD outcomes and whether they can indeed improve risk assessment in all ethnicities.

Race dependent associations of HDL-C with CHD risk may affect the performance of CHD risk prediction equations. Our findings using a contemporary cohort raise caution for the widely used CHD risk algorithms such as Framingham,[54] PROCAM,[55] Pooled Cohort,[56] and MESA.[20] Assuming a linear relationship, these algorithms reward for high HDL-C and penalize for low HDL-C. In addition, though race is a component of the formula, the interaction of specific components, such as HDL-C, is not. For example, according to the MESA risk calculator,[57] a 50-year-old woman with no clinical risk factors and no family history of heart disease, total cholesterol of 170 mg/dL, and systolic blood pressure of 120 mm Hg has a 10-year CHD risk of 1.3%, 1.0%, and 0.5% for HDL-C levels of 30, 50, and 105 mg/dL respectively—and race information does not change a risk estimate predicting >3-fold decrease in risk with the doubling of HDL-C. Our results suggest that although low

HDL-C is detrimental only in White adults, high HDL-C does not afford protection for both races.

Even though the possibility of chance influencing our findings cannot be completely excluded, it is more likely that our results really identify a race-specific effect and indicate a need for race-specific guidelines in CVD risk prediction. Future efforts to calibrate and validate risk algorithms require continuous data input encompassing all races and ethnicities.

The contribution of HDL-C to overall CHD risk has been variable and modest; yet, we have a poor understanding of the competing risk—which is not discussed in the clinic or in the CHD risk equations. Given that overall CHD deaths are low in REGARDS and favor Black participants, and that low HDL-C is not a leading risk factor for mortality, we are less likely to overestimate its contribution to CHD risk. Therefore, a competing risk analysis, which is conducted to address risk overestimation,[58] might be insightful in larger cohorts with higher event rates.

Our current understanding of how HDL-C contributes to CHD risk is primarily shaped by the Framingham heart study, where all cohorts (original, offspring, spouses) are 100% White American. Collective data from recent years suggest that we should develop a population-wide risk estimation algorithm that works in other races as well. Race is a complex metric defined both by a social construct and a genetic construct, making it challenging to capture its full spectrum in a risk prediction algorithm. Further, modeling the race-HDL-C interaction is particularly challenging given that the association of HDL-C with CHD risk is likely ethnicity-dependent. Our data suggest that the use of low HDL-C is informative in White adults but not in Black adults and the use of high HDL-C might not be helpful in either race. Although we need to gather further population-based evidence, our data support the notion that the value of high HDL-C in risk prediction algorithms should be demoted.

STUDY LIMITATIONS. Because of this study's observational design, caution must be applied when drawing causal inferences. Note that the original study[14] assessing HDL-C as a risk factor for CHD was also observational. The dispersed nature of the REGARDS cohort is both a strength and a weakness. The population in the REGARDS cohort was recruited from the entire contiguous United States, having participants in 62% of U.S. counties. Although this distribution allows for generalizability of the findings, participants were not clinically assessed as in-depth at baseline as they were in other cohorts with discrete coordinating centers.[39] The geographic breadth of REGARDS is its greatest strength, but it may have affected the completeness of CHD event ascertainment. However, the geographic and racial diversity of REGARDS allows greater generalizability of the current findings to the U.S. population. The limited number of fatal CHD events per race prevents from assessing race dependent association of HDL-C with fatal CHD.

CONCLUSIONS

In a contemporary biracial cohort, low HDL-C levels were associated with increased CHD risk in White but not in Black adults. High HDL-C levels were not protective for either race. Our findings support the need for the calibration of the current risk algorithms.

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ADDRESS FOR CORRESPONDENCE: Dr Nathalie Pamir, Knight Cardiovascular Institute, Oregon Health and Science University, 3181 Southwest Sam Jackson Park Road, HRC5N, Portland, Oregon 97239, USA. E-mail: pamir@ohsu.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: An inverse relationship between plasma levels of HDL-C and atherosclerotic risk does not apply uniformly across racially defined populations. High HDL-C levels may not be protective in either White or Black adults, and low HDL-C levels are associated with increased cardiovascular risk only in White adults.

TRANSLATIONAL OUTLOOK: Further research is needed to understand the mechanisms linking HDL-cholesterol to cardiovascular risk and how these are modified by race.

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KEY WORDS CHD, cholesterol, HDL, health disparities, myocardial infarction, public health

APPENDIX For details regarding a full list of participating REGARDS investigators, an expanded Methods section, and supplemental tables, please see the online version of this paper.