



High triglyceride to HDL cholesterol ratio is associated with increased coronary heart disease among White but not Black adults ^{☆,☆☆}



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ABSTRACT

Objective: Black adults are less likely than White adults to present with adverse lipid profiles and more likely to present with low-grade inflammation. The impact of race on the association between atherogenic lipid profiles, inflammation, and coronary heart disease (CHD) is unknown.

Methods: We evaluated the association between high levels (>50th percentile) of high-sensitivity C-reactive protein (hsCRP) and of triglycerides to high density lipoprotein ratio (TG/HDL-C) and CHD events by race in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort with 30,239 Black and White participants aged 45 and older.

Results: Participants with both high hsCRP and high TG/HDL-C had highest rates of CHD (HR 1.84; 95% CI: 1.48, 2.29 vs HR 1.52; 95% CI: 1.19, 1.94 in White vs Black participants respectively). Whereas isolated high hsCRP was associated with increased CHD risk in both races (HR 1.68; 95% CI: 1.31, 2.15 and HR 1.43; 95% CI: 1.13, 1.81 for White and Black participants respectively), isolated high TG/HDL was associated with increased CHD risk only in White participants (HR 1.44; 95% CI: 1.15, 1.79 vs HR 1.01; 95% CI: 0.74, 1.38). Further, the effects of high hsCRP and high TG/HDL-C were additive, with inflammation being the driving variable for the association in both races.

Conclusion: In both races, higher inflammation combined with adverse lipid profile is associated with greater CHD risk. Therefore, inflammation increases CHD risk in both races whereas dyslipidemia alone is associated with a greater risk in White but not in Black adults. hsCRP testing should be a standard feature of CHD risk assessment, particularly in Black patients.

1. Introduction

Despite decades of research and improvements in treatment, coronary heart disease (CHD) remains the leading cause of death in the United States, accounting for 1 of every 7 deaths in 2017—more than 600,000 deaths in total [1]. Common risk factors for CHD, include dyslipidemia, diabetes mellitus, hypertension, obesity, cigarette smoking, and physical inactivity [2] and have race-specific associations. A grow-

ing body of evidence indicates higher cardiovascular disease burden among African Americans (Black adults) [3,4].

Although low-density lipoprotein cholesterol (LDL-C) remains the primary treatment target to reduce cardiovascular disease risk, several large-scale epidemiological studies have demonstrated that elevated TG levels are independently associated with increased incidence of cardiovascular events, even in patients treated effectively with statins [5–7]. Hypertriglyceridemia is an independent predictor of CHD risk and may be a stronger risk factor among women than men [8,9]. Atherogenic

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dyslipidemia, the joint occurrence of high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C) in association with elevated apoprotein B and small dense LDL particle levels, is an important component of the metabolic syndrome and a strong risk factor for CHD [10–14]. A high TG/HDL-C ratio correlates with higher LDL-C, small HDL particles, and insulin resistance [15–17]. The ratio strongly predicts risk of myocardial infarction [18], impaired heart rate recovery after exercise [19], the extent of coronary atherosclerosis [20–22], CHD incidence [23], and cardiovascular and all-cause mortality [19,21,24].

In recent trials, such as JUPITER, CANTOS, and COLCOT, hsCRP levels have been convincingly linked to vascular events [25–27]. The CANTOS trial showed that directly reducing inflammation with canakinumab, an interleukin (IL)–1 β neutralizing monoclonal antibody, reduced the hsCRP levels, rate of recurrent cardiovascular events, independent of lipid-level lowering. These studies did not examine race and sex-dependent associations of lipid and inflammation measures with CVD outcomes.

To our knowledge, no study has evaluated the presence of biological interactions (e.g., synergism) between race, inflammation and dyslipidemia on the risk of coronary events. In this paper, we will refer to synergism as the situation in which the joint effect of two risk factors is greater than the sum of their isolated effects [28]. We analyzed data from the national Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort to examine racial differences, TG/HDL-C ratios, and hsCRP levels as predictors of fatal and non-fatal CHD with the intent to identify interactions of lipid and inflammation profiles with CHD risk.

2. Methods

2.1. Study population

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is a national prospective cohort of 30,239 participants established to determine the reasons for regional and racial differences in stroke mortality. 56 people dropped out and 30,183 participants with follow-up constitute the analytical cohort. Details on the design and methods of REGARDS have been previously described [29,30]. Briefly, REGARDS recruited community-dwelling Black and White women and men ≥ 45 years of age, identified via mail and telephone using commercially available lists of residents in the contiguous United States, and enrolled from 2003 to 2007. The sampling scheme included 30% of participants from the “stroke belt” (North Carolina, South Carolina, Georgia, Tennessee, Alabama, Mississippi, Arkansas, and Louisiana), 20% from the “stroke buckle” (the coastal plain of North Carolina, South Carolina, and Georgia), and 50% from elsewhere in the United States. The baseline cohort was 42% Black and 55% women (goal was 50% of each). Exclusion criteria included self-identified race other than White or Black/ African American, active treatment for cancer, chronic medical conditions precluding long-term participation, cognitive impairment as judged by the interviewer, current or impending residence in a nursing home, or inability to communicate in English. An initial telephone interview was used to survey participants and establish eligibility [31]. Following verbal consent, demographic information and medical history (including risk factor evaluation) was collected by a computer-assisted telephone interview [31]. Race was self-classified by participants and included the following options defined by the investigators: White and Black/African American (referred henceforth as Black). An in-home examination was conducted to perform anthropometric measurements (e.g., height, weight, waist circumference, blood pressure), and an electrocardiogram (ECG), medication inventory, phlebotomy, and urine collection among those eligible. Follow-up telephone interviews were performed every 6 months with the participant or designated next contact in order to detect the suspect of a cardiovascular event. The study design was approved by the institutional review boards of all partici-

pating institutions. Written informed consent was obtained from each participant.

2.2. Laboratory assessments

Blood samples were obtained in the morning after a 10 to 12 hour fast [32]. Samples were centrifugated within 2 h of collection; serum and plasma were separated and sent to the University of Vermont for analysis. Upon arrival, samples were re-centrifuged at 30,000 g at 4 C and either analyzed or stored at below -80 C. CRP was analyzed in batches by particle enhanced immunonephelometry using the BNII nephelometer (N High Sensitivity CRP; Dade Behring, Deerfield, IL) with interassay coefficients of variation of 2.1–5.7%. Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and glucose were measured by colorimetric reflectance spectrophotometry using the Ortho Vitros Clinical Chemistry System 950IRC instrument (Johnson & Johnson Clinical Diagnostics, Rochester, NY) [29,30].

2.3. CHD outcomes

Our study focused on CHD events defined as first definite or probable myocardial infarction (MI) or acute CHD death on/before 12/31/2016 [33]. Baseline CHD is defined as self-reported myocardial infarction (MI), coronary artery bypass grafting (CABG), angioplasty or stenting, or study baseline ECG evidence of a prior MI [33]. REGARDS study participants or proxy respondents were contacted every 6 months via telephone to assess incident CHD events. The primary study outcome was incident CHD, defined as an incident definite or probable non-fatal MI or CHD death [34]. Incident CHD events were adjudicated by a team of experts who used published guidelines [35,36]. When non-fatal events were reported, medical records were retrieved for adjudication. When fatal CHD events were reported or the participant died, interviews with next of kin or proxies, medical records in the last year of life, death certificates and autopsy reports were examined to determine if a CHD event was the main underlying cause of death. Deaths not captured by other means were captured using the national death index. A secondary study outcome was defined as definite or probable CHD death. For the current analysis, participants were followed through the date of their incident CHD event, death, last study contact or December 31, 2016, whichever occurred first.

2.4. Risk factor ascertainment

Because enrollment in REGARDS occurred between 2003 and 2007 and we have analyzed event data up to December 2016, hypertension was defined following the ACC/AHA 2003 guidelines as systolic blood pressure (SBP) greater or equal to 140 mmHg or diastolic blood pressure (DBP) greater or equal to 90 mmHg, or self-reported current medication use to control BP. Diabetes was defined as fasting glucose greater or equal to 126 mg/dL, or non-fasting glucose greater or equal to 200 mg/dL, or the self-reported use of insulin, or medications for glucose control. Smoking status was defined as a dichotomous variable where the reference category denotes the absence of the risk factor (non-current-smokers). BMI was defined as a 3-level categorical variable: normal weight (reference category, BMI < 24.9 kg/m²), overweight (BMI between 25 kg/m² and 29.9 kg/m²), and obese (BMI > 30 kg/m²). High, low groups for TG/HDL and hsCRP were above or below median: 2.19 mg/dL for hsCRP and 2.17 for TG/HDL-C ratio. Sex, race, and smoking status were dichotomous variables with lower risk groups as reference value (woman, White, non-current-smokers). Household income was operationalized as a 5-level categorical variable describing ascending levels of the income strata (< \$20k, \$20k - \$34k, \$35k - \$74k, \$75k or above, or refused) where the reference category was the lowest income strata. Similarly, educational attainment was defined as a 4-level categorical variable in ascending order of educational attainment (less

than high school, high school graduate, some college, college graduate or above), the reference category was less than high school education.

2.5. Statistical analysis

To create a primary predictor representing the interaction between hsCRP and TG/HDL-C ratio we dichotomized both variables into low (below median) versus high-risk (above median) categories. We performed Pearson's χ^2 test to examine the association between our primary predictor (the interaction of the two dichotomized predictors hsCRP and TG/HDL-C ratio) with respect to our categorical covariates of interest. We calculated estimated proportions and 95% confidence intervals for each of the categories of our primary predictor. Similarly, we performed an F-test to examine whether age (continuous) was significantly associated with our primary predictor. Additionally, we stratified the analysis of proportions by race category to examine whether there was a differential pattern of association between our covariates, our primary predictor, and the two racial groups. We estimated Kaplan Meier (KM) survival curves for our primary predictor stratified by racial group. We used a log-rank test to determine whether the KM survival curves differed by levels of our primary predictor and by race stratification.

We fit Cox proportional hazard regression models to determine the hazard ratios (HRs) for our primary predictor. We built two hazard models: a crude model and a model adjusted for the aforementioned risk factors. These models were fit separately for each racial group in order to estimate whether the association between the interaction of hsCRP and TG/HDL-C ratio differed by race strata. Subsequently, we used the regression coefficients of our primary predictor from each of these models (adjusted and unadjusted) to calculate three different measures of interaction in the additive scale: 1) the excess risk due to interaction (RERI), 2) the proportion attributable to interaction (AP), and 3) the synergy index (SI), and their respective confidence intervals (95% CI) using the delta method [37]. Derivations of measures of interactions in the additive scale using HRs are provided in the appendix. The data were analyzed using Stata 14 statistical software and R [38].

3. Results

3.1. Cohort characteristics

After excluding 5918 participants with baseline CHD (19.6%) and 3311 subjects with missing values in covariates (13.7%), the analytic sample included 20,954 participants (Fig. 1). Black and White participants had a comparable mean age, but Black men and women were more likely to smoke and have diabetes mellitus, to earn less than \$20,000 a year, and to be overweight or obese. More than 20% of subjects in each race and sex group had abnormal levels of both TG/HDL and hsCRP at baseline (Table 1). Our primary predictor variable was formed by all four possible combinations of low/high hsCRP and low/high TG/HDL-C ratio (< or >50th percentile). The HDL-C distributions were comparable for both Black and White participants, but the mean TG was lower among Black adults (Fig. 2, Supplemental Figure 1). The median TG/HDL-C cutoff effectively categorized abnormal lipid profiles: Of the men with low TG/HDL-C, 6.9% had TG > 150 mg/dL or HDL-C below 40 mg/dL vs. 12.7% in women (where HDL < 50 mg/dL was used) with an overall average of 10.7% (Supplemental Table S1, Supplemental Figure S2).

3.2. CHD incidence

Over a mean follow-up time of 8.91 (± 3.6) years, a total of 1306 (6.23%) CHD events occurred, of which 530 (40.6%) were among Black adults and 569 (43.5%) were among women (Table S2). Black men had a higher rate of CHD and case fatality than White men (respectively, 9.48 vs 9.13 events per 1000-person years; 42.8% vs 27.3%). Similarly, CHD incidence and case fatality rates were higher for Black women vs.

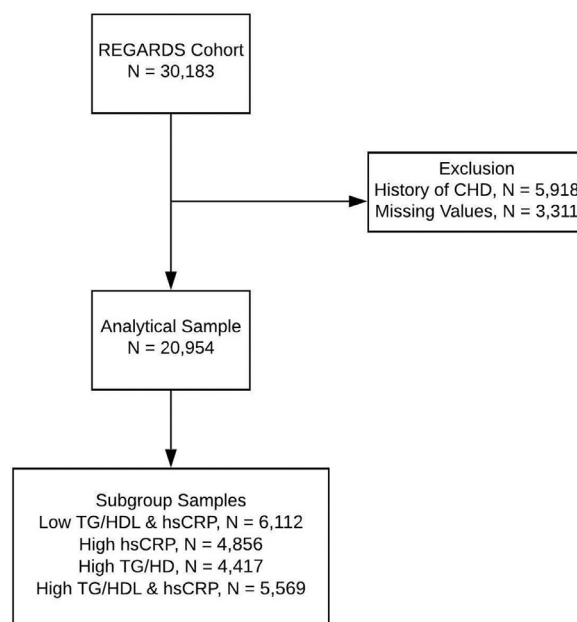


Fig. 1.

White women (respectively, 5.8 vs 4.9 events per 1000-person years; 41.8% vs 29.4%).

3.3. Lipids, inflammation and CHD risk

All baseline characteristics and covariates were significantly associated with the primary predictors even when stratified by race (Table 2). White (61.7%) and women (58.0%) participants were more likely to have high levels of both hsCRP and TG/HDL-C ratio. Similarly, individuals with lower education, lower income, higher BMI, higher blood pressure, higher blood glucose and currently smoking were more likely to have elevated levels of both biomarkers. Individuals with high hsCRP and high TG/HDL-C were 4 times more likely to be obese (Table 2).

CHD-free survival for individuals with combined high levels of hsCRP and TG/HDL-C was lower than for individuals with either isolated high hsCRP or high TG/HDL-C or with low levels of both markers (Figs. 3a & 3b), these findings were significant for both Black (log-rank test, $\chi^2 = 18.4$, $p < 0.001$) and White participants (log-rank test, $\chi^2 = 71.3$, $p < 0.001$).

In the unadjusted analysis, individuals with elevated hsCRP or TG/HDL-C ratio (when compared to individuals with low levels) had increased risk of CHD (HR 1.56; 95% CI 1.33, 1.85 vs HR 1.55; 95% CI 1.31, 1.83). Having both biomarkers elevated (compared with neither) increased the risk for CHD further (HR 2.03; 95% CI 1.74, 2.37). The association was maintained after adjusting for age, race, sex, income, education, hypertension, BMI, diabetes, and aspirin use (HR 1.69; 95% CI: 1.44, 1.99). The adjusted CHD risk was significantly increased for participants who had high hsCRP (HR 1.57 95% CI: 1.33, 1.86) or high TG/HDL-C ratio (HR: 1.28, 95% CI: 1.08, 1.52). To understand the synergistic contribution of both hsCRP and TG/HDL-C ratio to CHD risk we calculated the measures of interaction for unadjusted and adjusted models on the additive scale using the Relative Excess risk due to Interaction (RERI), the Attributable Proportion (AP), and the Synergy Index (SI). In the unadjusted and adjusted analysis there was no evidence of a synergistic interaction, thus suggesting that the two phenotypes influence CHD risk in an additive manner (Table 3).

The race stratified analysis recapitulated the patterns observed in the entire cohort for hsCRP but not for TG/HDL-C ratio (Table 4). White participants with elevated levels of both biomarkers had adjusted risk (HR 1.84; 95% CI 1.48, 2.27) greater than those with either isolated high

Table 1
Baseline Characteristics of the REGARDS Cohort by race and gender.

	Men		Women	
	Black (n = 3204)	White (n = 5677)	Black (n = 5453)	White (n = 6620)
	Mean (SD)			
Age	63.74 (9.13)	64.83 (9.14)	63.42 (9.27)	64.10 (9.49)
Cholesterol, mg/dL	186 (38.6)	187 (35.6)	198 (39.7)	202 (37.3)
LDL-C, mg/dL	115 (34.8)	114 (31.9)	120 (36.4)	117 (33.9)
HDL-C, mg/dL	48.5 (14.4)	45.3 (13.2)	57.4 (15.9)	58.3 (16.3)
Triglycerides, mg/dL	114 (58.4)	136 (68.5)	114 (48.8)	135 (65.5)
hsCRP, mg/dL	4.38 (11.9)	3.17 (6.70)	6.08 (8.28)	4.24 (7.44)
TG/HDL-C ratio	2.91 (4.27)	3.77 (3.48)	2.14 (1.97)	2.81 (2.41)
	Median (IQR)			
hsCRP, mg/dL	2.06 (3.47)	1.45 (2.56)	3.50 (6.09)	2.17 (3.90)
TG/HDL-C ratio	2.12 (1.91)	2.84 (2.79)	1.70 (1.42)	2.14 (2.09)
	Observations (Column%)			
Income				
< \$20k	568 (17.73)	360 (6.34)	1581 (28.99)	923 (13.94)
Education				
Less than HS	565 (17.63)	320 (5.64)	1000 (18.34)	434 (6.56)
Body Mass Index				
Normal	758 (23.66)	1435 (25.28)	816 (14.96)	2300 (34.74)
Smoking Status				
Current Smoker	628 (19.60)	658 (11.59)	847 (15.53)	859 (12.98)
Hypertension – Yes	2100 (65.54)	2642 (46.54)	3852 (70.54)	3014 (45.53)
Diabetes –Yes	912 (28.46)	768 (13.53)	1439 (26.39)	730 (11.03)
Aspirin Use—Yes	1140 (35.58)	2644 (46.57)	1808 (33.16)	2325 (35.12)
Lipid lowering Medication – Yes	828 (25.84)	1660 (29.24)	1509 (27.67)	1823 (27.54)
hsCRP - TG/HDL-C				
Low - Low	1001 (31.24)	1481 (26.09)	1512 (27.73)	2118 (31.99)
High - Low	709 (22.13)	596 (10.50)	2170 (39.79)	1381 (20.86)
Low - High	669 (20.88)	2086 (36.74)	461 (8.45)	1201 (18.14)
High - High	825 (25.75)	1514 (26.67)	1310 (24.02)	1920 (29.00)

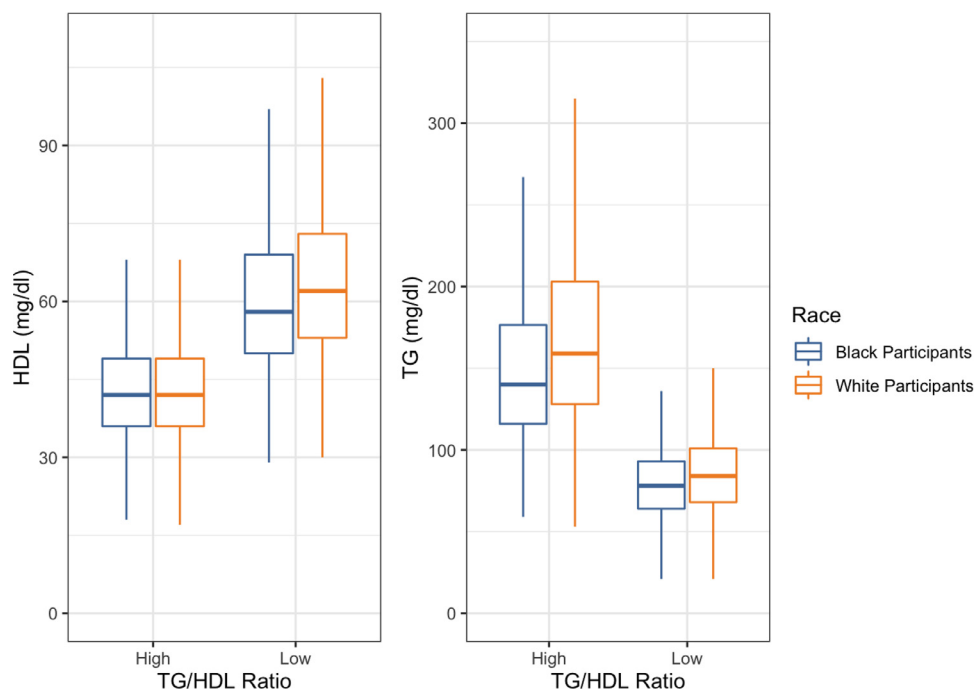


Fig. 2. The TG and HDL-C distribution in Black and White participants. The TG/HDL-C ratio high (above median_ low (below median) plasma HDL-C (left) and TG (right) levels among Black and White adults represented as boxplots.

hsCRP (HR 1.68; 95% CI 1.31, 2.15) or isolated high TG/HDL ratio (HR 1.44; 95% CI 1.15, 1.79). Black participants with high hsCRP and high TG/HDL-C ratio had an increased risk of CHD (HR 1.52; 95% CI 1.19, 1.94) relative to those with both parameters in the low range. However, while isolated elevated hsCRP was associated with increased CHD risk (HR 1.43, 95% CI 1.13, 1.81), isolated elevated TG/HDL-C ratio was not (HR 1.01; 95% CI 0.74, 1.38). The measures of interactions between hsCRP and TG/HDL-C did not reveal greater than additive interactions,

with the caveat that isolated high TG/HDL-C ratio was not associated with CHD in Black REGARDS participants (Table 4).

3.4. Sensitivity analyses

To understand if the median cutoff is a viable strategy we performed sensitivity analyses with 20,735 participants. The sensitivity model contains use of lipid lowering medication in addition to main covariates.

Table 2
Covariate Distributions for Primary Predictor Groups.

	hsCRP - TG/HDL-C									
	Low - Low		High - Low		Low - High		High - High		Total	
	Obs	%	Obs	%	Obs	%	Obs	%	Obs	%
Age -Mean	6112	64.19	4856	64.17	4417	64.15	5569	63.72	20,954	64.10
Race										
Blacks	2513	41.1	2879	59.3	1130	25.6	2135	38.3	8657	41.3
Whites	3599	58.9	1977	40.7	3287	74.4	3434	61.7	12,297	58.7
Sex										
Female	3630	59.4	3551	73.1	1662	37.6	3230	58.0	12,073	57.6
Male	2482	40.6	1305	26.9	2755	62.4	2339	42.0	8881	42.4
Income										
< \$20k	824	13.5	981	20.2	561	12.7	1066	19.1	3432	16.4
\$20k - \$34k	1308	21.4	1227	25.3	983	22.3	1447	26.0	4965	23.7
\$35k - \$74k	1901	31.1	1383	28.5	1471	33.3	1669	30.0	6424	30.6
> = \$75	1279	21.0	679	14.0	916	20.7	742	13.3	3616	17.3
Refused	807	13.1	586	12.1	486	11.0	645	11.6	2517	12.0
Education										
Less than HS	527	8.6	667	14.0	395	8.9	730	13.1	2319	11.1
HS Graduate	1366	22.4	1278	26.5	1092	24.7	1547	27.8	5283	25.2
Some College	1581	25.9	1351	28.0	1157	26.2	1590	28.6	5679	27.1
College Graduate	2638	43.1	1560	31.5	1773	40.2	1702	30.5	7673	36.6
Body Mass Index										
Normal	2609	42.6	1002	20.6	945	21.4	753	13.5	5309	25.3
Overweight	2316	38.0	1609	33.1	2052	46.4	1771	31.8	7748	37.0
Obese	1187	19.4	2245	46.3	1420	32.2	3045	54.7	7897	37.7
Smoking Status										
Current Smoker	673	11.0	696	14.3	537	12.2	1086	19.5	2992	14.3
Non-Smoker	5439	89.0	4160	85.7	3880	87.8	4483	80.5	17,962	85.8
Hypertension										
Yes	2787	45.6	2891	59.5	2329	52.7	3601	64.7	11,608	55.4
No	3325	54.4	1965	40.5	2088	47.3	1968	35.3	9346	44.6
Diabetes										
Yes	715	11.7	847	17.4	829	18.8	1458	26.2	3849	18.4
No	5397	88.3	4009	82.6	3588	81.2	4111	73.8	17,105	81.6
Aspirin Use										
Yes	2254	36.9	1645	33.9	1876	42.5	2142	38.5	7917	37.8
No	3858	63.1	3211	66.1	2541	57.5	3427	61.5	13,037	62.2
Lipid Lowering Medication										
Yes	1547	25.3	1159	23.9	1496	33.9	1618	29.1	5820	27.8
No	4512	73.8	3643	75.0	2873	65.0	3887	69.8	14,915	71.2
Missing	53	0.9	54	1.1	48	1.1	64	1.2	219	1.1

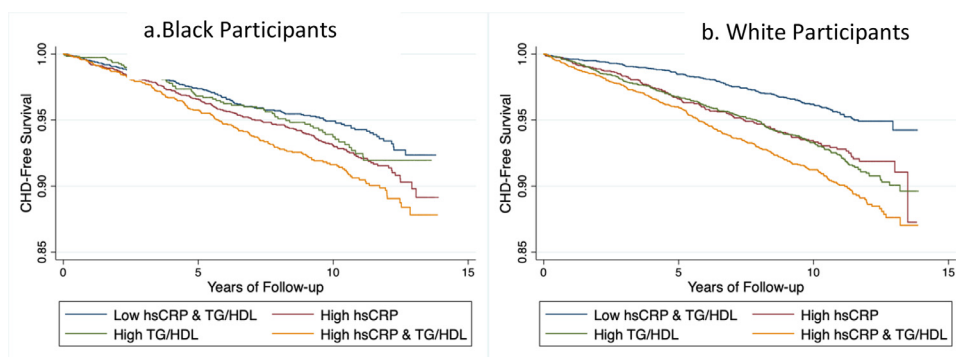


Fig. 3. Kaplan Meier curves indicating survival free of CHD or death by levels of hsCRP and TG/HDL-C ratio among Black adults (a) and White adults (b), REGARDS using baseline (2003–2007) samples. The low and high groups were determined by median thresholds for their respective phenotypes.

Coronary events were more prevalent among participants with both elevated biomarkers ($n = 471$ or 36.4%), hazard ratios and measures of interaction in the additive scale were comparable to main models (Supplementary material, Table S2). Race stratified sensitivity analysis showed that the risk of CHD is greater for Black and White adults with high levels of both biomarkers. However, high TG/HDL-C ratio associated with CHD positively in White participants only, not in Black participants (Supplementary material, Table S3).

In our stratified analysis, point estimates of the measures of interaction in the additive scale were positive for Black individuals (RERI = 0.18, AP = 0.11, SI = 1.46) suggesting biological synergism

(Supplementary material, Table S4). Because, systemic inflammation and dyslipidemia can widely differ by race and sex, we built two additional Cox models with cutoff points for hsCRP and TG/HDL-C ratio based on the median and 75th percentile of the race-sex distribution of each biomarker (Supplementary material, Table S5). These models showed comparable patterns to the main model, highlighting the double biomarker exposure as the highest risk group, followed by the high hsCRP group (Supplementary material, Table S6). Measures of interaction in the additive scale were not different between the cutoff specific models and our main model (Supplementary material, Table S6). The median cutoff point model yield point estimates with larger effect

Table 3

Fatal and nonfatal acute coronary heart disease events.

hsCRP	TG:HDL-C Ratio	Number of individuals (%)	Hazard RatioUn-adjusted	Hazard RatioAdjusted*
Low	Low	6112 (29.2%)	1.00 (Reference)	1.00 (Reference)
High	Low	4856 (23.2%)	1.56 (1.33, 1.85)	1.57 (1.33, 1.86)
Low	High	4417 (21.0%)	1.55 (1.31, 1.83)	1.28 (1.08, 1.52)
High	High	5569 (26.6%)	2.03 (1.74, 2.37)	1.69 (1.44, 1.99)
Observations		20,954	20,954	20,954
Measures of Interaction in the Additive Scale			Un-adjusted	Adjusted
Excess Risk due to Interaction (RERI)			-0.08 (-0.42, 0.26)	-0.18 (-0.50, 0.13)
Attributable Proportion (AP)			-0.04 (-0.21, 0.13)	-0.11 (-0.30, 0.08)
Synergy Index (SI)			0.93 (0.68, 1.23)	0.77 (0.53, 1.14)

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Low	Low	6112 (29.2%)	1.00 (Reference)	1.00 (Reference)
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Attributable Proportion (AP)			-0.04 (-0.21, 0.13)	-0.11 (-0.30, 0.08)
Synergy Index (SI)			0.93 (0.68, 1.23)	0.77 (0.53, 1.14)

*Model adjusted for race, sex, age, income, education, smoking status, hypertension, use of aspirin, BMI category, and diabetes status. Total events include fatal, and nonfatal Acute Coronary Heart Disease (CHD) events.

Table 4

Cox regression models stratified by race.

hsCRP	TG:HDLRatio	Models for Blacks		Models for Whites	
		Hazard RatioUn-adjusted	Hazard RatioAdjusted*	Hazard RatioUn-adjusted	Hazard RatioAdjusted*
Low	Low	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
High	Low	1.34 (1.07, 1.68)	1.43 (1.13, 1.81)	1.72 (1.35, 2.20)	1.68 (1.31, 2.15)
Low	High	1.16 (0.86, 1.57)	1.01 (0.74, 1.38)	1.84 (1.49, 2.27)	1.44 (1.15, 1.79)
High	High	1.64 (1.29, 2.07)	1.52 (1.19, 1.94)	2.38 (1.94, 2.91)	1.84 (1.48, 2.29)
Observations		8657	8657	12,297	12,297
Measures of Interaction in the Additive Scale					
RERI		0.14 (-0.32, 0.59)	0.06 (-0.37, 0.48)	-0.19 (-0.70, 0.33)	-0.30 (-0.76, 0.17)
AP		0.08 (-0.19, 0.36)	0.04 (-0.25, 0.33)	-0.08 (-0.29, 0.14)	-0.16 (-0.42, 0.91)
SI		1.28 (0.51, 3.16)	1.14 (0.40, 3.29)	0.88 (0.63, 1.23)	0.73 (0.48, 1.12)

Total including fatal, and nonfatal CHD events.

+ Stratified model by race adjusted for sex, age, income, education, smoking status, hypertension, use of aspirin, BMI category, and diabetes status. 95% CI in parenthesis.

size than the 75th cutoff point model suggesting that dichotomizing our biomarkers at the median has more predictive value than at a higher percentile point.

To evaluate the effect of LDL-C, we further adjusted the Cox model in Table 4 and found that adjustment by LDL-C did not change the point estimates and the overall results (Supplementary material, Table S7). We also further explored the role of using lipid lowering medication in our main association of interest by fitting the Cox regression model among those who used lowering lipid medications and stratifying by race (Supplementary material, Table S8 and S9)

4. Discussion

We evaluated the associations of the TG/HDL-C ratio and hsCRP with incident CHD over a mean follow-up of 8.91 years in 20,954 participants from the biracial REGARDS cohort. Independent of race, participants with high hsCRP had increased CHD risk only in White adults, no association was seen in Black adults. Overall, the combined effect of both risk factors (e.g., TG/HDL-C ratio and hsCRP) is no more than what is expected when adding the effect of each risk factor alone.

The TG/HDL-C ratio has been shown to be a viable surrogate of the atherogenic lipid phenotype characterized by elevated levels of remnant lipoproteins (included in non-HDL-C), low HDL-C, and reduced LDL

particle size [39]. In many cohorts the biologically linked pair of high triglycerides and low HDL-C was found strongly associated with cardiovascular risk [40–43]. Although one might argue that creating a ratio of dichotomized risk factors at their median could result in the loss of statistical power and loss of efficiency relative to an ungroup analysis [44], in our REGARDS cohort the median TG/HDL-C ratio cutoff only missed 10.7% of participants with either isolated low HDL-C (<40 mg/dL for males and <50 mg/dL for females), isolated high TG (>150 mg/dL), or combination of both.

Currently, there is no agreement on the normal cut-off threshold for the TG/HDL-C ratio. For example, the dyslipidemia of metabolic syndrome as defined by ATP-III criteria uses thresholds of TG <150 mg/dL and HDL-C >40 mg/dL (men) and >50 mg/dL (women) [2] corresponding to TG/HDL-C ratios of 3.75 and 3.0, respectively. Studies by Sumner et al. using the threshold of 3.0 showed that TG/HDL-C ratio may be useful to predict insulin resistance among Whites but not Blacks [45]. Lower and race specific thresholds of 2.5 for men and 2.0 for women have also been recommended [41,46]. Studies by McLaughlin et al. indicated that a level of 3.5 may be useful in identifying individuals at increased risk of developing CVD [15,47].

In REGARDS the median TG/HDL-C ratio was 2.45 for White adults, 1.85 for Black adults, and 2.17 for the full cohort. The lower TG/HDL-C ratio for Black participants is contributed by lower TG (in men and

women) and higher HDL (in men only). A TG/HDL-C ratio above the median was associated with 1.44 higher risk of CHD in White but not in Black participants. The lack of association among Black individuals suggests that the TG/HDL-C ratio alone may not be a marker of CHD risk in this group, or that the predictive value is triggered after a specific threshold rather than showing linear association with risk.

A recent study has surprisingly shown that very low HDL-C levels (<30 mg/dL) are associated with reduced risk of incident CHD in Black adults [48]. In our analysis these cases are captured with the high TG/HDL-C ratio group which showed no association with CHD risk. It is possible that the strength of the association between high TG/HDL-C ratio and CHD risk is tempered by an unusual association between very low HDL-C and CHD risk in Black adults.

In REGARDS, high hsCRP levels were not only independently associated with CHD risk in both Black and White adults, but also were the driving variable in the joint association of elevated TG/HDL-C ratio and elevated hsCRP with CHD risk. For example, the difference in risk between participants with elevation of both biomarkers vs. participants with only high levels of hsCRP was estimated to be 1.08 (95% CI: 0.87, 1.34) and 1.03 (95%CI: 0.83, 1.27) among White and Black individuals, respectively. However, the difference in risk between participants with elevation of both biomarkers vs. participants with only high levels of TG/HDL-C was estimated to be 1.26 (95%CI: 1.06, 1.51) and 1.49 (95%CI: 1.11, 2.00) among White and Black individuals, respectively. Our findings are consistent with results from the CANTOS trial [49]. Canakinumab significantly reduced hsCRP levels from baseline, without reducing the LDL cholesterol level, and the 150-mg dose decreased the incidence of recurrent cardiovascular events. While this trial was not designed to look at race-specific effects (only around 3% of participants were Black), these findings and ours support the idea that strategies targeting inflammation may reduce ASCVD risk irrespective of race.

The point estimates for the measures of additive interaction seemed to differ by race. Calculated measures of interaction between inflammation and dyslipidemia for White participants showed an additive rather than synergistic interaction. However, these measures were weaker in Black individuals, probably due to the lack of association between high TG/HDL-C ratio and CHD risk. Due to the wide confidence intervals for the additive measures of interaction, we do not interpret these apparent differences as effect modification by race. Rather, our results show that, for both racial groups the effect of increased levels of inflammation on CHD risk is greater than the effect of an adverse lipid profile.

Due to the triglyceride-lowering effect of statins, statins use may have had an impact on our findings. In REGARDS, the medication use is self-reported and statin use is categorized as lipid lowering medication which likely includes other medications. The analysis of the subcohort with only participants that use a lipid lowering medication revealed significant disparities among White and Black adults: Among 5728 adults on medication, 2315 (~40%) were Black participants. In addition, the CHD event was 410 (169 for Black adults and 241 for White adults) – much lower than the entire cohort, 1306 (530 for Black adults and 776 for White adults) (Supplemental Table S8). Despite the lower power, the associations between higher inflammation, adverse lipid profiles and greater CHD risk were maintained for White adults. However, since the sample size for Black adults was smaller than for White adults –in particular with regard to CHD events, the model for Black adults should be interpreted with caution.

Hypertension was defined according to blood pressure guidelines that were in effect for the majority of the study period —2002–2016— as above 140 and 90 mmHg for diastolic and systolic blood pressure (ACC/AHA 2003).

The time between inflammation and cholesterol measures and the CHD event, the self-reporting of some risk factors and co-morbidities, and the use of BMI as an obesity measure are limitations of our study. Smoking status was self-reported at the telephone interview and classified as dichotomous variable (smoker or non-smoker) which misses information on former smokers. The risk models in clinical practice use

10-year predicted risk to determine interventions to reduce CHD risk, so while a limitation our approach reflects clinical practice [50]. The observational design limits the ascertained CHD incidence, which might result in spuriously lower rates.

Collectively, our data suggest that dyslipidemia expressed as elevated ratio of TG/HDL-C and inflammation assessed as elevated hsCRP have additive power in predicting CHD risk in White adults but not in Black adults. While hsCRP was comparably associated with CHD risk in both races, the TG/HDL ratio did not predict CHD risk in Black individuals. Further studies are needed to elucidate the mechanisms responsible for the lack of association between the ratio of TG/HDL-C in Black adults and to determine if incorporating inflammation in CHD risk prediction especially in Black patients improves clinical outcomes. In the meantime, providers should be aware that the TG/HDL-C ratio is not an informative proxy for increased atherogenicity in Black patients.

Author contributions

CH: Data analysis, initial draft

JM: Study design, Supervising the data analysis, data interpretation SF, MMS, LDC, MRI, VH: Critical review and editing

NAZ: Data interpretation, study design, critical review and editing

NP: Study design, data interpretation, manuscript writing

Declaration of Competing Interest

There are no conflicts to disclose for all authors.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2021.100198.

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