Dietary interventions that lower lipoproteins containing apolipoprotein C-III are more effective in whites than in blacks: results of the OmniHeart trial[1-3]

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ABSTRACT

Background: Blacks have lower average triglyceride and LDL cholesterol concentrations than do whites but higher rates of coronary heart disease. Apolipoprotein (apo) C-III in VLDL and LDL stimulates atherogenic processes in vascular cells. In blacks, the concentration of lipoproteins with apo C-III is unknown, and the response to dietary strategies that lower triglyceride and apo C-III has not been investigated

Objective: We compared the concentration of and dietary effects on apo C-III–containing lipoproteins in blacks and whites.

Design: In a randomized, 3-period feeding study [OmniHeart (Optimal Macronutrient Intake Trial to Prevent Heart Disease)], we measured lipoprotein concentrations in 89 blacks and 73 whites who consumed self-selected diets (baseline) and after 3 healthful diets emphasizing carbohydrate, unsaturated fat, or protein. Participants had prehypertension or hypertension, and 79% were overweight or obese.

Results: While consuming self-selected diets, blacks had lower apo C-III in total plasma, VLDL, and LDL than did whites. Unsaturated fat and protein diets lowered plasma apo C-III (16% and 18%, respectively) and triglyceride (12% and 21%, respectively) in whites but not in blacks, reducing racial differences. Most important, blacks had a lower concentration of atherogenic LDL with apo C-III at baseline and after study diets (34–41% lower, $P < 0.02$). The molar ratio of apo E to apo B was higher in blacks than in whites in total plasma and LDL at baseline and after the study diets.

Conclusions: Blacks have lower concentrations of atherogenic lipoproteins that contain apo C-III than do whites when consuming diverse diets and an attenuated dietary response of triglyceride and apo C-III. Dietary efforts to lower triglyceride and apo C-III may be more effective in whites than in blacks. The OmniHeart Trial was registered at www.clinicaltrials.gov as NCT00051350. *Am J Clin Nutr* 2010;92:714–22.

INTRODUCTION

Black Americans suffer a higher morbidity and mortality from coronary heart disease (CHD) than do white Americans (1–3) and are nearly twice as likely to die prematurely (1). In 2005, the age-adjusted rate for deaths from heart disease was 30% higher in black Americans than in white Americans (2). Blacks tend to have higher incidence of obesity, hypertension, and diabetes (1), diseases that are intimately tied to cardiovascular disease (CVD), diet, and plasma lipids, and elevated concentrations of inflammation markers (4, 5). Yet, many studies have reported that blacks on average have lower LDL cholesterol and plasma triglyceride than do whites (6–10), which are well-established risk factors for CHD (11–13).

Although blood lipids are associated with CHD, recent studies have found even stronger associations between CHD and plasma apolipoprotein (apo) B (14–20) and apo C-III (21–23). Apo C-III blocks the clearance of VLDL by the liver (24–26), channeling it to formation of LDL (26, 27). Recent data also show direct proinflammatory, atherogenic activity of apo C-III through activation of human endothelial cells and monocytes (28, 29). LDL particles with apo C-III, a remnant particle produced by lipolysis in plasma of VLDL with apo C-III (30), is the apo B lipoprotein type that predicts CHD most strongly in patients with type 2 diabetes (21). In contrast, plasma apo E increases the clearance rate of apo B particles through recognition and uptake by liver receptors (25, 31), reducing the concentration of atherogenic lipoprotein remnants and LDL (30). Whites have higher concentrations of triglyceride and LDL cholesterol than do blacks, but racially stratified data are scarce on apolipoprotein concentrations.

Diet has a direct effect on plasma lipids and lipoproteins. Compared with a typical high-saturated-fat diet, healthy diets that emphasize carbohydrate, protein, or unsaturated fat reduce plasma total and LDL apo B (32). Substituting protein for carbohydrate in the context of a healthy dietary pattern reduces atherogenic apo C-III–containing LDL and its precursor, apo C-III–containing VLDL (32).

For the first time, to our knowledge, we examine racial differences in lipoprotein subtypes and their response to dietary

intervention, information lacking in the literature yet crucial to the understanding of the racial disparity in CHD. We hypothesize that the higher burden of CHD in blacks than in whites may be explained in part by higher concentrations in blacks of atherogenic apo B lipoproteins containing apo C-III, despite their lower overall concentration of apo C-III. The majority of apo C-III resides in non–apo B lipoproteins. As such, blacks could have lower plasma apo C-III and triglyceride but a greater concentration of apo B particles that contain apo C-III, explaining the higher burden of CHD. This hypothesis took into account the greater insulin resistance and obesity in blacks than in whites (9, 10), both of which are associated with elevated apo C-III. In addition, we compare the effects of controlled study diets in blacks and whites on these lipoprotein risk factors to assess their effectiveness in reducing CHD risk.

METHODS

The rationale and design of the Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) (33), the main lipid results (34), and the results on lipoprotein subtypes (32) have been published previously. Briefly, the OmniHeart trial is an investigator-initiated National Heart, Lung, and Blood Institute–sponsored study that used a randomized, 3-period crossover design to compare the effects of macronutrients on blood pressure and plasma lipids. Study diets were modeled on the successful Dietary Approaches to Stop Hypertension (DASH) diet and emphasized either carbohydrate (CARB), unsaturated fats (UNSAT), or protein, with emphasis on plant sources such as soy, legumes, nuts, and seeds (PROT). The DASH diet was chosen as the model for the study diets because it is effective at lowering blood pressure and LDL cholesterol. Although DASH lowered LDL cholesterol, it also lowered HDL cholesterol and did not affect triglycerides, findings attributable to its high carbohydrate content (35). In OmniHeart, we examined the effect of replacing some of the carbohydrate with unsaturated fat or protein. The study protocol was approved by the Institutional Review Boards at all affiliated institutions (Johns Hopkins University, Brigham and Women's Hospital, and the Harvard School of Public Health).

Participant recruitment and controlled feeding

Details of participant recruitment and controlled feeding have been described previously (34, 36). Briefly, participants were recruited from the population of the greater Baltimore, MD, and Boston, MA, areas. They were ≥30 y of age with blood pressure (BP) at enrollment that was above normal but less than stage 2 hypertension (systolic BP of 120–159 mm Hg or diastolic BP of 80–99 mm Hg). Participants' fasting LDL cholesterol could not exceed 220 mg/dL, and triglycerides could not exceed 750 mg/dL. One of the primary recruitment goals was to ensure that ≈50% of enrolled participants were black due to blacks' disproportionately high burden of CVD. This was achieved by self-identification of race on the screening questionnaire.

To assess eligibility, each participant was required to complete 3 clinical visits, which were all conducted a minimum of 7 d after the previous visit. Blood samples were drawn and processed at each of the visits, and participants completed a food-frequency questionnaire (FFQ) at screening visit 3 (Walter Willett FFQ, version 88GP; Channing Laboratory, Boston, MA). After completing the 3 visits, eligible participants then participated in a 6-d run-in period to determine ability to adhere to the diet sequences. Those who completed the run-in period successfully were randomly assigned to 1 of 6 possible sequences of the 3 diets (CARB, UNSAT, PROT). During the run-in period and all study diet periods, subjects were provided with all of their food for each day, and no nonstudy food was to be consumed. A detailed description of these 3 diets has been published previously (36, 37). Briefly, the composition of the study diets was 58:27:15 (carbohydrate:protein:fat) for CARB, 48:37:15 for PROT, and 48:27:25 for UNSAT. Adherence was monitored through daily diet diaries and at participants' weekday visits to the study center. Participants were instructed to maintain usual levels of physical activity, and changes in weight were prevented by weight checks at food distribution and alteration of caloric intake as necessary. Blood was drawn at the end of the fourth and sixth weeks of each diet period. The 6-wk samples were used in this substudy. Participants then ate their usual diet of their own choice for a minimum of 2 wk before beginning the next diet period. Controlled feeding took place from April 2003 to June 2005. To quantify insulin resistance, the homeostasis model assessment (HOMA) index was calculated from fasting glucose and insulin concentrations as HOMA = [(fasting plasma insulin concentration in μU/mL) × (fasting plasma glucose concentration in mmol/L)]/22.5. This was calculated at baseline and after all 3 diet periods.

Laboratory measurements

The details of laboratory measurements have been published previously (32). Briefly, samples were thawed, filtered, and incubated overnight in anti––apo C-III immunoaffinity columns (polyclonal goat anti-human apo C-III antibody bound to Sepharose 4B Resin; Academy Biomedical Company Inc, Houston, TX) to separate apo C-III–containing and apo C-III–deficient lipoproteins. These fractions were then ultracentrifuged at 15°C and 25,000 rpm in the outermost row of a Beckman 25-Ti rotor with a Beckman L8-70M ultracentrifuge (Beckman Coulter Inc,Fullerton, CA) to produce 6 fractions for analysis: VLDL (d < 1.006 g/mL) without apo C-III, VLDL (d < 1.006 g/mL) with apo C-III, LDL (1.006 g/mL < d < 1.063 g/mL) without apo C-III, LDL (1.006 g/mL < d < 1.063 g/mL) with apo C-III, and remaining plasma proteins with and without apo C-III (d > 1.063 g/mL). Each participant's 4 samples (baseline and after each of the three 6-wk diet periods) were analyzed in the same batch in random order to reduce analytic variation. Batches consisted of samples of 5 or 9 participants, and analyses were completed within 5 d. All laboratory staff were blinded to the diet sequences of the participants.

Concentrations of apo B, apo C-III, and apo E in whole plasma and lipoprotein fractions were determined by sandwich ELISA procedures by using affinity purified antibodies (Academy Biomedical Company Inc). Triglyceride and cholesterol were determined by enzymatic assay (Thermo Scientific, Waltham, MA). Liquid transfer for 96-well plate loading and ELISA dilutions were handled robotically with a Multiprobe II (Perkin Elmer, Waltham, MA) to minimize error. Both ELISA and lipids

plates were read with a BioTek ELx808iu 96-well plate reader controlled by KCJunior software (BioTek, Winooski, VT). All assays were completed in triplicate, and any sample with an intraassay CV >15% was repeated.

Statistics

The primary outcomes for this analysis were triglyceride, apo C-III, apo E, apo B, and cholesterol concentrations in whole plasma and in the lipoprotein subfractions. We also calculated the molecular ratios of apoE to apoB and apoC-III to apoB. The main comparisons in this study were between blacks and whites in the outcome variables at baseline and after each of the 3 study diets. The effect of race was calculated by using regression models that simultaneously adjusted for study site, sex, and age. Analyses were performed by using SAS version 9.1 (SAS Institute Inc, Cary, NC). In cases in which the distributions of outcome measures were at risk of violating the normality assumptions of our statistical models, testing was also performed on log-transformed outcomes. Secondarily, we examined racial differences in the changes elicited by the study diets by using similar regression models. Statistical significance was defined as $P < 0.05$, and we did not adjust P values for multiple comparisons because the hypotheses tested were prespecified. Many of the outcome variables under analysis are correlated and produce patterns of significance that corroborate one another.

For a study such as this with many subsamples per participant, there were randomly occurring missing values stemming from limitations in laboratory technology (eg, problems with sample aliquots, lack of sufficient sample, or liquid transfer failures). Because it is reasonable to assume that sample loss was statistically independent of participant characteristics and the value of the missing sample, no missing data were imputed for the primary analysis. Instead, the tests for each outcome were performed by using subsets of the data that exclude any subject who is missing data for that particular analyte. To ensure that bias was not introduced by the exclusion of participants without complete data sets, we performed several sensitivity analyses. First, we compared the means of the outcome variables in the subsets with those in the whole population and observed that they were not statistically different. We then performed the analyses on all available data points, allowing the n to vary for each outcome. This produced patterns of significance and results in line with the primary subset analyses with no significant discrepancies in the data. Finally, we used for secondary analysis the SAS "proc MI" (multiple imputation) procedure, which uses available observations in the data set to impute probable values for the missing data points and to estimate SEs and P values on the basis of analysis of within-imputation and between-imputation variances. Once again, this produced results highly consistent with the basic primary analysis.

RESULTS

Participants

A total of 191 participants, 104 black and 87 white, successfully completed the run-in period and were randomly assigned to 1 of the 6 diet sequences. Of these, 89 blacks and 73 whites finished ≥2 of the 3 diet periods and were eligible for inclusion in the analysis. Dropout occurrence was low, similar for both races, and distributed evenly across the 3 diets with no one diet proving more difficult to adhere to than the others. Adherence to the feeding protocol was high, with individuals reporting that on >95% of person-days all study foods were consumed and no nonstudy foods were added. On average, mean body weight decreased from baseline by 1 kg, and this change occurred equally across all 3 diets in both blacks and whites.

A summary of population characteristics is presented in **Table 1**. Baseline characteristics of participants did not differ according to the 6 diet sequences, but there were differences by race. A higher percentage of blacks were female, and fewer black than white women were postmenopausal. Approximately two-thirds of the black participants were from Baltimore. Lipoprotein differences between blacks and whites tended to be greater in women than in men. There was no difference detected

TABLE 1
Characteristics of study population[1]

	All			Female			Male		
	Black	White	P	Black	White	P	Black	White	P
n	89	73	—	50	22	—	39	51	—
Percentage in study	55	45	—	31	14	—	24	31	—
Postmenopausal (%)	66	90	—	66	90	—	—	—	—
Age (y)	52 ± 11[2]	55 ± 11	0.13	53 ± 10	60 ± 7	<0.01	51 ± 11	52 ± 11	0.5
BMI (kg/m^2)	31.5 ± 6.3	29.0 ± 5.6	<0.01	31.5 ± 6.5	32.1 ± 6.9	0.7	31.6 ± 6.1	27.6 ± 4.3	<0.01
HOMA index	2.58 ± 1.98	2.27 ± 2.72	0.4	2.51 ± 1.87	2.76 ± 4.11	0.7	2.67 ± 2.13	2.05 ± 1.85	0.1
Triglycerides (mg/dL)	88 ± 65	116 ± 66	<0.01	79 ± 61	109 ± 64	0.06	100 ± 69	119 ± 67	0.2
LDL-C (mg/dL)	125 ± 33	138 ± 41	0.03	128 ± 36	163 ± 43	<0.01	121 ± 30	127 ± 35	0.1
HDL-C (mg/dL)	51.3 ± 18.0	48.5 ± 13.6	0.27	56.4 ± 17.1	56.2 ± 15.5	0.9	44.7 ± 17.2	45.1 ± 11.3	0.9
Apo B (mg/dL)	80 ± 22	88 ± 30	0.06	82 ± 21	96 ± 35	0.05	77 ± 22	84 ± 28	0.2
Apo C-III (mg/dL)	10.7 ± 5.8	15 ± 9.4	<0.01	11.0 ± 6.4	16.7 ± 12.1	0.01	10.4 ± 4.8	14.3 ± 8.0	<0.01
Apo E (mg/dL)	7.65 ± 2.86	7.03 ± 2.61	0.2	8.0 ± 3.3	8.1 ± 3.6	0.9	7.2 ± 2.2	6.6 ± 1.9	0.2

[1] HOMA, homeostasis model assessment; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; Apo, apolipoprotein. P values were derived from Student's t test comparing blacks and whites; the race-by-sex interaction was significant for BMI only.

[2] Unadjusted mean ± SD (all such values).

TABLE 2
Concentrations of plasma lipids and lipoproteins with consumption of free-living and controlled study diets in blacks and whites, adjusted for age, sex, and site of recruitment[1]

	Baseline					CARB			UNSAT			PROT		
	Black		White											
	n	Values	n	Values	P	Black	White	P	Black	White	P	Black	White	P
Whole plasma (mg/dL)														
Triglycerides	57	88 (7.3)	50	115 (8.1)	0.02	93 (7.2)	105 (7.9)	0.3	90 (7.9)	101 (8.8)[2]	0.4	84 (7.4)	96 (8.2)[2]	0.3
Apo C-III	59	12 (1.1)	56	16 (1.1)	0.02	13 (1.0)	14 (1.0)[2]	0.4	12 (1.0)	13 (1.0)[2]	0.4	12 (0.8)	13 (0.9)[2]	0.7
Total cholesterol	59	202 (5.9)	52	225 (6.3)	0.01	185 (5.3)[2]	208 (5.7)[2]	<0.01	182 (5.2)[2]	201 (5.6)[2]	0.02	174 (5.0)[2]	203 (5.3)[2]	<0.01
LDL-C	59	123 (5.0)	52	141 (5.4)	0.02	110 (4.4)[2]	131 (4.8)[2]	<0.01	109 (4.4)[2]	124 (4.7)[2]	0.03	105 (4.0)[2]	124 (4.3)[2]	<0.01
Apo B	43	78 (4.5)	45	87 (4.4)	0.2	76 (3.5)	80 (3.5)[2]	0.5	73 (3.6)	80 (3.5)[2]	0.2	71 (3.6)[2]	78 (3.5)[2]	0.2
Apo E	75	7.7 (0.3)	65	7.2 (0.4)	0.3	7.2 (0.3)[2]	6.3 (0.3)[2]	0.05	7.1 (0.3)[2]	6.0 (0.3)[2]	0.01	7.1 (0.3)[2]	6.0 (0.3)[2]	0.03
Lipoproteins without apo C-III														
VLDL (mg/dL)														
Triglycerides	57	30 (5.5)	50	37 (5.9)	0.4	30 (4.8)	36 (5.1)	0.4	28 (5.3)	32 (5.7)	0.6	26 (5.5)[2]	28 (5.9)	0.8
Cholesterol	59	9.3 (1.2)	52	13 (1.3)	0.09	9.2 (1.2)	11.4 (1.3)	0.2	8.5 (1.2)	11 (1.3)	0.1	7.4 (1.4)	11 (1.5)	0.2
Apo B	43	2.5 (0.5)	45	2.9 (0.4)	0.5	2.5 (0.4)	3.3 (0.4)	0.2	2.3 (0.3)	2.9 (0.3)	0.2	2.2 (0.3)	2.6 (0.3)	0.5
Apo E	75	0.20 (0.03)	65	0.22 (0.03)	0.5	0.22 (0.03)	0.21 (0.03)	0.8	0.19 (0.02)	0.20 (0.03)	0.8	0.21 (0.03)	0.20 (0.03)	0.9
LDL														
Triglycerides	57	25 (2.0)	50	33 (2.1)	0.02	25 (1.9)	26 (2.0)[2]	0.8	25 (2.3)	24 (2.5)[2]	0.6	25 (1.8)	23 (2.0)[2]	0.5
Cholesterol	59	113 (4.8)	52	126 (5.1)	0.07	101 (4.1)[2]	116 (4.4)[2]	0.02	100 (4.0)[2]	110 (4.3)[2]	0.1	97 (3.7)[2]	110 (4.0)[2]	0.02
Apo B	43	69 (3.7)	45	74 (3.6)	0.4	66 (2.9)	65 (2.9)[2]	0.8	64 (2.9)	67 (2.9)[2]	0.5	63 (2.9)	66 (2.9)[2]	0.5
Apo E	75	0.41 (0.03)	65	0.38 (0.03)	0.4	0.41 (0.03)	0.34 (0.03)	0.2	0.37 (0.02)	0.33 (0.02)	0.2	0.39 (0.03)	0.33 (0.03)	0.2
Apo E:apo B (mol/mol)	42	0.11 (0.01)	43	0.09 (0.01)	0.1	0.11 (0.01)	0.09 (0.01)	0.2	0.10 (0.01)	0.09 (0.01)	0.1	0.11 (0.01)	0.09 (0.01)	0.1
Lipoproteins with apo C-III														
VLDL (mg/dL)														
Triglycerides	57	13 (1.9)	50	16 (2.0)	0.2	16 (2.3)	22 (2.5)	0.08	17 (2.9)	23 (3.1)	0.1	15 (2.4)	20 (2.5)	0.2
Apo C-III	59	1.04 (0.13)	56	1.50 (0.13)	0.02	1.4 (0.16)	1.7 (0.16)	0.2	1.2 (0.15)	1.8 (0.15)	<0.01	1.3 (0.15)	1.6 (0.15)	0.2
Cholesterol	59	4.0 (0.6)	52	5.0 (0.6)	0.1	4.5 (0.6)	6.1 (0.7)	0.1	4.8 (0.7)	5.9 (0.8)	0.4	4.3 (0.7)	6.0 (0.7)	0.1
Apo B	43	0.80 (0.13)	45	1.08 (0.13)	0.2	1.0 (0.17)	1.5 (0.17)[2]	0.08	0.89 (0.15)	1.5 (0.14)[2]	0.01	0.93 (0.15)	1.2 (0.14)	0.2
Apo E	75	0.31 (0.03)	65	0.31 (0.03)	0.9	0.42 (0.04)	0.46 (0.05)	0.5	0.38 (0.04)	0.46 (0.05)	0.3	0.40 (0.05)	0.41 (0.05)	0.8
LDL														
Triglycerides	57	7.8 (0.8)	50	9.6 (0.8)	0.1	8.6 (0.8)	11.5 (0.9)	0.03	8.5 (0.8)	11 (0.8)[2]	0.04	8.7 (0.7)	10 (0.8)[2]	0.2
Apo C-III	59	1.50 (0.14)	56	1.96 (0.15)	0.03	1.5 (0.14)	2.0 (0.15)	0.02	1.4 (0.13)	2.0 (0.14)	<0.01	1.5 (0.13)	1.8 (0.14)	0.1
Cholesterol	59	10 (1.3)	52	15 (1.4)	0.02	9.2 (1.4)	15 (1.5)	<0.01	8.9 (1.2)	14 (1.3)	<0.01	8.2 (1.2)[2]	14 (1.3)	<0.01
Apo B	43	6.0 (1.0)	45	9.2 (1.0)	0.02	6.1 (1.0)	9.8 (0.9)	<0.01	6.0 (0.8)	8.8 (0.8)	0.01	5.5 (0.7)	8.1 (0.7)	0.01
Apo E	75	0.42 (0.03)	65	0.36 (0.04)	0.3	0.41 (0.03)	0.37 (0.03)	0.5	0.41 (0.03)	0.37 (0.04)	0.4	0.41 (0.03)	0.37 (0.04)	0.4
Apo E:apo B (mol/mol)	42	1.62 (0.17)	43	0.97 (0.17)	0.01	1.44 (0.15)	0.96 (0.15)	0.03	1.58 (0.18)	0.92 (0.18)	0.01	1.78 (0.22)	1.04 (0.22)	0.02
HDL (mg/dL)														
Apo C-III	59	9.4 (0.9)	56	12 (1.0)	0.04	9.5 (0.09)	10 (0.9)	0.7	9.2 (0.9)	9.3 (0.9)	0.9	9.7 (0.8)	9.5 (0.8)	0.8

[1] Values are presented as least-squares means; SEs in parentheses. CARB, carbohydrate diet; UNSAT, unsaturated fats diet; PROT, protein diet; Apo/apo, apolipoprotein; LDL-C, LDL cholesterol. P values for comparison of blacks and whites were derived from a generalized linear model adjusted for age, sex, and site of recruitment.

[2] Significant change from baseline, $P < 0.05$ (generalized linear model adjusted for age, sex, and site of recruitment).

TABLE 3
Free-living diet composition for select nutrients in blacks (n = 87) compared with whites (n = 71)[1]

	Univariate analysis			Multivariate analysis[2]		
	Black	White	P value	Black	White	P value
Calories (kcal)	2267 (126)	2355 (140)	0.6	2298 (131)	2317 (147)	0.9
Alcohol						
(% kcal)	1.2 (0.3)	2.0 (0.3)	0.05	1.6 (0.3)	1.5 (0.3)	0.9
(g/d)	3.2 (0.9)	7.0 (1.0)	<0.01	4.4 (0.8)	5.6 (0.9)	0.4
Carbohydrate (% kcal)	51.5 (0.9)	47.9 (1.0)	<0.01	51.1 (0.9)	48.3 (1.0)	0.05
Protein (% kcal)	17.5 (0.4)	17.3 (0.5)	0.8	17.2 (0.5)	17.6 (0.5)	0.6
Animal (% kcal)	12.7 (0.5)	11.5 (0.5)	0.08	12.5 (0.5)	11.7 (0.5)	0.3
Other (% kcal)	4.8 (0.2)	5.9 (0.2)	<0.01	4.7 (0.2)	5.9 (0.3)	<0.01
Fat (% kcal)	29.9 (0.7)	32.8 (0.7)	<0.01	30.1 (0.7)	32.5 (0.8)	0.02
Saturated fat (% kcal)	10.7 (0.3)	12.0 (0.3)	<0.01	10.8 (0.3)	11.9 (0.4)	0.05
Monounsaturated fat (% kcal)	12.6 (0.3)	13.6 (0.4)	0.02	12.7 (0.3)	13.5 (0.4)	0.1
Polyunsaturated fat (% kcal)	6.6 (0.2)	7.2 (0.2)	0.02	6.6 (0.2)	7.2 (0.2)	0.05
Omega-3 fatty acids (% kcal)	0.68 (0.02)	0.67 (0.02)	0.7	0.68 (0.02)	0.68 (0.03)	0.9
Long-chain omega-3 fatty acids (% kcal)	0.22 (0.02)	0.17 (0.02)	0.02	0.21 (0.02)	0.18 (0.02)	0.1
Omega-6 fatty acids (% kcal)	5.1 (0.2)	5.7 (0.2)	0.01	5.1 (0.2)	5.6 (0.2)	0.05
Saturated fat (% of total fat)	35.9 (0.5)	26.3 (0.6)	0.6	35.9 (0.6)	36.3 (0.6)	0.7
Monounsaturated fat (% of total fat)	41.9 (0.3)	41.2 (0.3)	0.1	41.9 (0.3)	41.1 (0.3)	0.07
Polyunsaturated fat (% of total fat)	22.2 (0.6)	22.5 (0.6)	0.8	22.1 (0.6)	22.6 (0.6)	0.6
Fiber (g/1000 kcal)	10.1 (0.5)	11.2 (0.5)	0.1	10.0 (0.5)	11.4 (0.5)	0.06
Total folate (μg/1000 kcal)	266 (19)	317 (21)	0.07	254 (19)	331 (21)	0.01
Cholesterol (mg/d)	353 (22)	327 (25)	0.4	356 (23)	324 (26)	0.4
Vitamin E (mg/d)	59.6 (10.0)	59.5 (11.1)	0.9	57.2 (10.4)	62.5 (11.6)	0.8
Sodium (mg/d)	2222 (151)	2468 (167)	0.3	2242 (158)	2443 (177)	0.4

[1] Values are means; SEs in parentheses.
[2] Multivariate linear regression model adjusted for site of enrollment, sex, BMI, and age. Assessed by the Walter Willett food-frequency questionnaire (version 88GP; Channing Laboratory, Boston, MA). Four of the 162 eligible participants did not have food-frequency questionnaire data available.

between races in HOMA index. Body mass index (BMI) and menopausal status were not observed to be significant confounders of race-biomarker associations.

Lipid and lipoprotein differences between blacks and whites when consuming their usual self-selected diets

When consuming their usual self-selected diets, blacks had lower total plasma triglycerides, apo C-III, and LDL cholesterol in crude analysis (P < 0.03; Table 1) and after adjustment for age, sex, and site of recruitment (all P = 0.02; **Table 2**). Blacks trended toward having lower apo B (P = 0.06) (Table 1). Blacks had lower apo C-III in VLDL and in LDL (31% and 24%, respectively; P < 0.03), lower concentrations of LDL with apo C-III (presented in Table 2 as apo B in LDL with apo C-III) (35%, P = 0.02), and lower cholesterol in LDL with apo C-III (33%, P = 0.02) (Table 2). Plasma total apo E concentrations were not different between the 2 races, but the average amount of apo E on LDL lipoproteins containing apo C-III as determined by the ratio of molecules of apo E to apo B was significantly higher in blacks than in whites (P = 0.01). All together, these differences signify a less atherogenic lipoprotein profile in blacks than in whites while consuming their usual, self-selected diets.

Because diet affects lipoprotein profile and diet was not controlled in the free-living state, we compared the self-selected diets in blacks and whites to see if this might explain the lipid and lipoprotein differences. On average, blacks reported that they consumed about half the amount of alcohol per day than was reported by whites (P < 0.01) (**Table 3**). The difference in these reports was confounded by site of recruitment and sex, with participants from Boston reporting consuming nearly 3 times as much as those reported in Baltimore and men consuming 6 times as much as women. The significant difference in reported alcohol intake between blacks and whites was eliminated in the model that adjusted for site of recruitment and sex.

Blacks obtained a smaller percentage of calories from saturated and unsaturated fats than did whites and a greater percentage of their calories from carbohydrate. Percentage of calories from carbohydrate was significantly related to apo C-III and triglyceride concentrations in VLDL with apo C-III in a univariate model, but these associations lost significance when race was added to the model, suggesting that carbohydrate intake was acting as a marker of race in the model. A diet richer in carbohydrate would be expected to result in a higher plasma triglyceride and apo C-III concentration, although in our population as in others plasma triglyceride and apo C-III was lower in blacks than in whites. Blacks also obtained less of their protein from nonanimal sources than did whites. The percentage of calories from long-chain omega-3 (n–3) fatty acids was slightly higher in blacks than in whites, whereas the percentage from omega-6 fatty acids was lower. After adjustment for site of recruitment and sex, blacks consumed 12% less fiber (P = 0.06) and 23% less folate (P = 0.01) than did whites (Table 3). These differences in self-selected diets between blacks and whites do not explain the differences in lipoprotein profiles that we observed.

Lipid and lipoprotein differences comparing blacks and whites while consuming study diets

LDL with apo C-III

On each of the 3 diets, blacks maintained a 32–38% lower concentration of LDL with apo C-III (presented in Table 2 as apo B in LDL with apo C-III) as compared with whites ($P < 0.02$) and 36–41% lower concentrations of cholesterol in LDL with apo C-III (Table 2). Concentrations of apo C-III in LDL with apo C-III were lower in blacks compared with whites after the CARB and UNSAT diets but not after the PROT diet.

Triglycerides and apo C-III

Mean plasma total triglycerides and apo C-III, although lower in blacks than in whites at baseline, were no longer significantly different after the study diets (Table 2) because the diets reduced plasma triglycerides and apoC-III in whites more than in blacks (**Figure 1**), bringing the means for the 2 groups closer together. Apo C-III in VLDL was significantly lower in blacks than in whites after the UNSAT diet but not after the CARB and PROT diets (Table 2).

It could be argued that these differential effects of diet were due to the lower mean triglyceride and apo C-III concentrations in blacks at baseline—a "floor effect" that defines a lower limit to dietary responses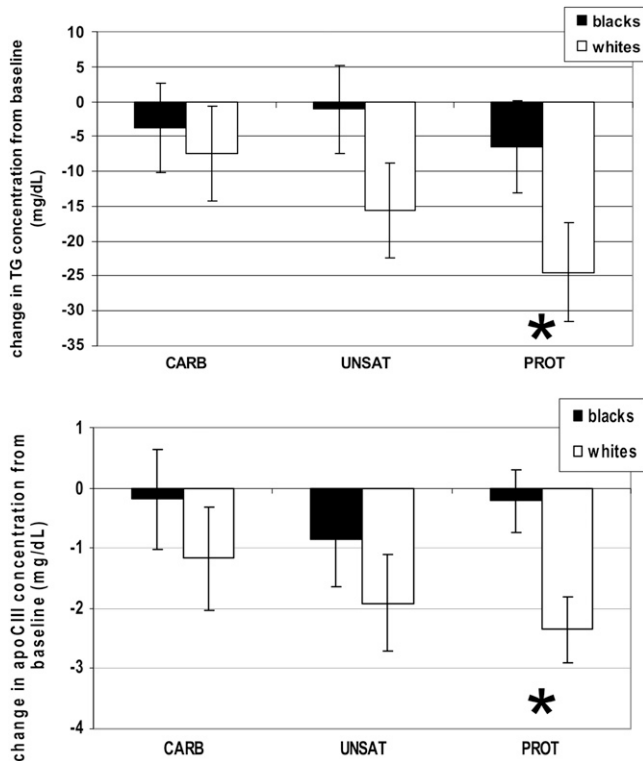. To test this, we fit 2 regression models relating change from baseline in plasma triglycerides or apo C-III to baseline plasma triglyceride or apo C-III concentration (to match the dependent variable) with control for dichotomous race, sex, age, BMI, and site of recruitment. All 3 diets showed trends toward a smaller reduction in triglycerides by the diets from baseline in blacks compared with whites, with the largest apparent difference in diet effect occurring after the PROT diet. There was a 15-mg/dL and 23-mg/dL decrease in triglycerides after the UNSAT and PROT diets in whites, respectively ($P < 0.02$), with no significant change in blacks. We then added an interaction term between race and baseline plasma triglycerides to the model. The interaction term was significant in all 3 diets ($P < 0.02$), indicating that there is a difference in how blacks' and whites' triglyceride concentrations respond to the diets. Race is also a significant predictor of the change from baseline in plasma apo C-III ($P < 0.01$ comparing races), with the largest difference between races after the PROT diet where blacks showed a nonsignificant decrease of 0.2 mg/dL compared with a significant decrease of 2.3 mg/dL in whites (**Figure 2**). Whites also showed a significant decrease of 1.9 mg/dL after the UN-SAT diet whereas blacks showed none. The interaction term between baseline apo C-III and race was only significant after the PROT diet ($P < 0.01$), where the effect of diet was greatest in whites. As with triglycerides, the higher the baseline concentration of plasma apo C-III, the more the diets lowered plasma apo C-III from baseline concentrations in whites. This effect was greatly attenuated almost to the point of nonexistence in blacks. This difference was especially evident in the PROT diet, which resulted in the greatest apo C-III changes from baseline.

Apo B and LDL cholesterol

The study diet lowered plasma total apo B and LDL cholesterol similarly in blacks and whites (**Figure 3**). Plasma total apo B concentrations remained similar between the races after the 3 study diets (Table 2), with the UNSAT and PROT diets reducing concentrations by 6–10% in both races. LDL cholesterol was reduced by 7–15% ($P < 0.03$) in both blacks and whites after all 3 study diets, and LDL cholesterol in blacks remained 12–16%
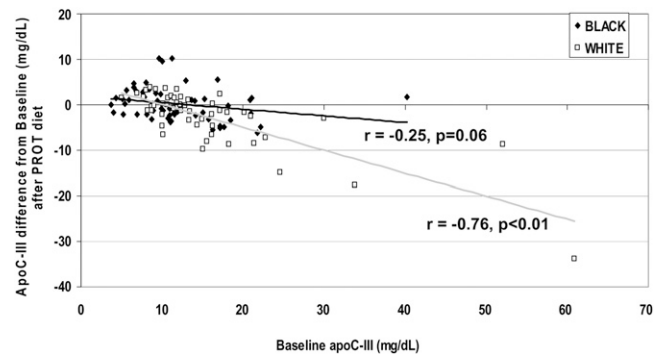

FIGURE 1. Mean (±SEM) changes from baseline in plasma TG and apo C-III by diet in blacks and whites. The study diets reduced plasma triglyceride (TG) (top) and apolipoprotein (apo) C-III (bottom) in whites more than in blacks, after adjustment for baseline concentrations. Plasma TG: blacks, $n = 57$; whites, $n = 50$; plasma apo C-III: blacks, $n = 59$; whites, $n = 56$. *P for race < 0.05 in the linear regression model, adjusted for baseline plasma TG, sex, age, and site of recruitment, indicating that the differences from baseline differ significantly by race. CARB, carbohydrate diet; UNSAT, unsaturated fats diet; PROT, protein diet.

FIGURE 2. Higher baseline apolipoprotin (apo) C-III concentrations were associated with greater reductions in plasma apo C-III from baseline in whites than in blacks ($n = 115$, 57 blacks and 58 whites). This effect remained with the top 5 outliers removed from both groups (not shown). r = correlation coefficient comparing baseline apo C-III and change from baseline in apo C-III after the protein (PROT) diet. $P = P$ value for correlation coefficient; P value for race = 0.03 in the linear regression model comparing change from baseline apo C-III after the PROT diet to baseline apo C-III, adjusted for race, sex, age, and site of recruitment.
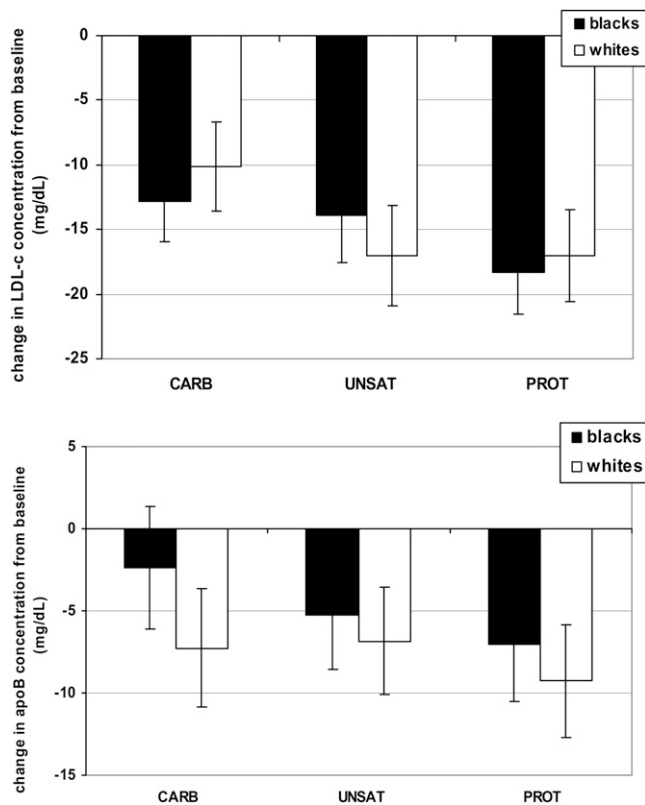
FIGURE 3. Mean (±SEM) changes from baseline in plasma LDL cholesterol and apolipoprotein (apo) B by diet in blacks and whites. The study diets reduced LDL cholesterol (LDL-c) (top) and apo B (bottom) equally in whites and blacks. LDL-c: blacks, $n = 59$; whites, $n = 52$; plasma apo B: blacks, $n = 43$; whites, $n = 45$. All P values for race >0.05 in the linear regression models, adjusted for race, sex, age, and site of recruitment. CARB, carbohydrate diet; UNSAT, unsaturated fats diet; PROT, protein diet.

lower than in whites (Table 2). Cholesterol in LDL without apo C-III (the major apo B lipoprotein type) was 9–13% lower in blacks than in whites in the multivariate model after the study diets, significantly so for the PROT and CARB diets but not for the UNSAT diet. These postdiet racial differences are similar to those while consuming the baseline self-selected diets. The diet changes from baseline in LDL without apo C-III did not differ between the races.

Apo E

Blacks had 14–18% higher plasma total apo E after all 3 diets compared with whites (Table 2) and a higher apo E:apo B ratio in LDL with apo C-III (**Figure 4**). All 3 diets reduced plasma apo E compared with the baseline diet in both blacks (6–9%) and whites (11–16%).

DISCUSSION

Apo C-III can be present on apo B–containing or apo A-I–containing (ie, HDL) lipoproteins but is not integral to the basic lipoprotein particle structure; thus, particles exist both with and without apo C-III. Apo B–containing lipoproteins with apo C-III are enriched in triglycerides and cholesterol and have reduced clearance from plasma. The concentration of apo C-III in VLDL and LDL is highly and independently predictive of CHD, more so than triglycerides alone (23). Above all, LDL particles

with apo C-III, remnant particles produced by partial lipolysis in plasma of VLDL with apo C-III (26), are the lipoprotein particle type most predictive for CHD in patients with type 2 diabetes (21). apo C-III inhibits direct clearance of VLDL particles from plasma, causing them to be metabolized to LDL (30). New research strengthens the association between CHD and apo C-III by showing that apo C-III increases adhesion of human monocytes to endothelial cells and activates proinflammatory molecules such as nuclear transcription factor κB in these cells (28, 29, 38).

When consuming their usual diets, blacks had a much lower concentration of atherogenic LDL lipoproteins containing apo C-III that could not be explained by differences in diet. For example, blacks reported consuming 4% more calories from carbohydrate and less fat than did whites. Increases in dietary carbohydrate increase plasma triglyceride and apo C-III. After the controlled study diets, blacks continued to have lower LDL with apo C-III, and these racial differences remained consistent even after adjustment for insulin sensitivity (HOMA index) and obesity (BMI). Blacks had a higher BMI and similar HOMA index to whites, yet had lower triglyceride and apo C-III concentrations. Given all of this, we suggest that there is some inherent racial difference in the metabolism of apo C-III–containing apo B lipoproteins that produces this more favorable lipoprotein profile in blacks. One plausible mechanism for these racial differences lies with apo E. Animal studies report that plasma apo E increases the clearance rate of apo B particles through recognition and uptake by liver receptors (31, 39). A study of the kinetics of apo B metabolism in humans showed that apo E when present with apo C-III directs flux from lipolysis toward clearance, limiting LDL formation (26). The ratio of molecules of apo E to apo B in LDL with and without apo C-III was higher in blacks than in whites, suggesting a better likelihood for clearance of these atherogenic particles. In the aforementioned kinetics study, the ratio of apo E to apo B in VLDL correlated with its fractional catabolic rate [Figure 7 in reference (26)].

In a global test across all diets, blacks had significantly lower concentrations of apo C-III than did whites in total plasma and in their VLDL and LDL lipoproteins. Triglyceride correlates with apo C-III, and we observed that blacks also had significantly lower triglyceride in total plasma, VLDL with and without apo C-III, and LDL with apo-C-III in the global test. From a public health perspective, the differences in triglyceride are striking. In this population, 10% of blacks exhibited plasma triglyceride concentrations above the generally recognized cutoff for elevated plasma triglyceride of 150 mg/dL, whereas 23% of whites fell above the cutoff. Over half of the blacks had plasma triglycerides <70 mg/dL, whereas less than 20% of whites fit that category.

In our previous publication we noted that we were surprised to find that the UNSAT diet did not significantly lower triglycerides when it replaced carbohydrate (32), as has been observed in other studies (40). We now find that the UNSAT diet does reduce plasma triglycerides in whites but not in blacks. Thus, the lack of a significant effect in the total cohort resulted from the combination of highly responsive whites and nonresponsive blacks. Most previous studies had entirely or predominantly white populations, and our findings in the white participants agree with this literature (40).
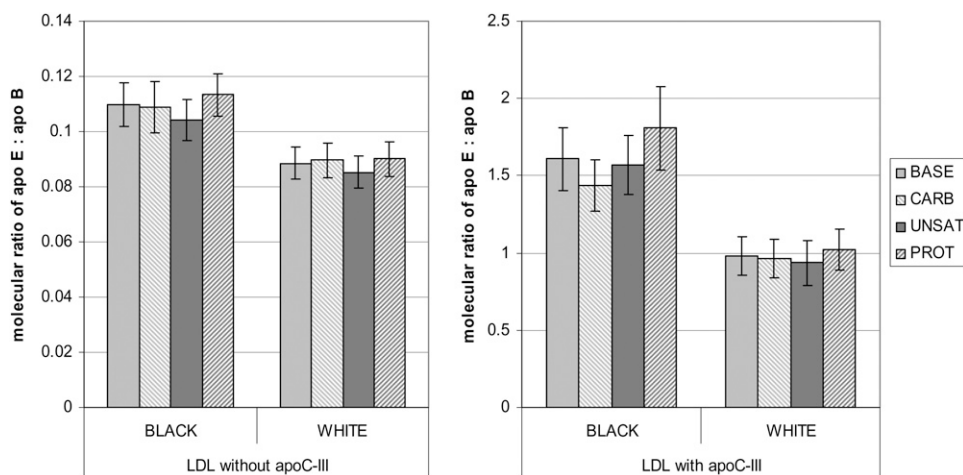
FIGURE 4. Molecular ratio of apolipoprotein (apo) E to apo B in LDL lipoproteins with and without apo C-III at baseline (BASE) and after the study diets in blacks and whites. Data are presented as mean ($\pm$SEM) ratios of molecules of apo E to molecules of apo B. Blacks, $n = 42$; whites, $n = 43$. All P values for race <0.05 in the univariate regression models with race. P value for race in LDL with apo C-III remained significant after adjustment for sex, age, and site of recruitment (all $P \leq 0.03$), whereas $P = 0.08$–0.2 for LDL without apo C-III. CARB, carbohydrate diet; UNSAT, unsaturated fats diet; PROT, protein diet.

The controlled study diets lowered plasma apo C-III and triglycerides from concentrations on the participants' usual diets in whites but not in blacks, bringing whites closer to the low means of blacks and eliminating the large differences between the races in these atherogenic lipoprotein components. We observed that the lack of diet effects on triglycerides and apo C-III in blacks is independent of their lower baseline concentrations. The specific reasons for this cannot be ascertained from this study. Whatever the mechanism, dietary therapies to reduce atherogenic apo C-III and triglyceride that are useful in whites may not prove to be as successful in blacks. However, these diets may still be effective in reducing CHD risk in blacks through reductions in blood pressure, cholesterol, and apo B.

Strengths and limitations

The sample size was large, and the participants were demographically heterogeneous, which strengthens the application of the results to the general US population. Statistical power was high due to recruitment of nearly equal numbers of blacks and whites and the crossover design. Risk of bias was low due to similarly high rates of adherence to and completeness of follow-up in both races after all 3 of the diets. Changes in lipids and lipoproteins can be attributed to dietary factors because other important factors that might elicit these changes were successfully controlled for (ie, weight, calorie intake, and alcohol consumption patterns).

The relatively brief duration of each diet period does not allow for assessment of permanence of lipoprotein changes. However, for the conventional lipid risk factors—plasma total cholesterol and triglycerides, HDL cholesterol, and LDL cholesterol—the 4-wk results were similar to the 6-wk results, suggesting that a new baseline was reached. The controlled diet design makes it difficult to gauge the success of long-term adherence to each diet when the diet is adopted by people in a free-living, uncontrolled environment, which is essential to continued CHD risk reduction. Because the free-living diet was not controlled, examination of changes from baseline elicited by study diets, where we have

observed the largest diet effects, are not as robust as comparison between study diets.

Conclusions

Based solely on lipoprotein profile, blacks would be expected to have lower risk of CHD than whites, independent of dietary intake. However, epidemiologic studies report otherwise. Thus, blacks are susceptible to CHD at lower concentrations of these lipid and lipoprotein risk factors compared with whites, possibly due to their higher rates of hypertension, diabetes, and obesity, eclipsing their atheroprotective lipoprotein profile. It will be important to determine risk curves in blacks for apo C-III and triglyceride-related lipoproteins to know if current recommendations should be race-specific for healthy concentrations for these lipids and lipoproteins. If the risk curves are similar for blacks and whites, then there must be other, very strong adverse risk factors in blacks to overcome the protective influence of their favorable lipoprotein profile. Although the study diets are useful for reduction of CHD risk by reducing apo B, LDL cholesterol, and blood pressure in both races, they did not lower plasma triglycerides and apo C-III in blacks.

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