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Healthy diet reduces markers of cardiac injury and inflammation regardless of macronutrients: results from the OmniHeart trial

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest associated with this manuscript.

Data sharing: Data described in the manuscript, code book, and analytic code is publicly available upon request through the NHLBI BioLincc repository.

Trial Registration: This trial is registered at clinicaltrials.gov, number: NCT00051350; URL: <https://clinicaltrials.gov/ct2/show/NCT00051350>

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Abstract

Background: Despite diet being a first-line strategy for preventing cardiovascular disease, the optimal macronutrient profile remains unclear. We studied the effects of macronutrient profile on subclinical cardiovascular injury and inflammation.

Methods: OmniHeart was a randomized 3-period, crossover feeding study in 164 adults with high blood pressure or hypertension (SBP 120-159 or DBP 80-99 mm Hg). Participants were fed each of 3 diets (emphasizing carbohydrate (CARB), protein (PROT), or unsaturated fat (UNSAT)) for 6-weeks, with feeding periods separated by a washout period. Weight was held constant. Fasting serum was collected at baseline while participants ate their own diets and after each feeding period. High-sensitivity troponin I (hs-cTnI) and high-sensitivity C-reactive protein (hs-CRP) were measured in stored specimens.

Results: The average age was 53.6 years, 55% were African American, and 45% were women. At baseline, the median (25th-percentile, 75th-percentile) hs-cTnI was 3.3 ng/L (1.9, 5.6) and hs-CRP was 2.2 mg/L (1.1, 5.2). Compared to baseline, all 3 diets reduced hs-cTnI: CARB -8.6% (95%CI: -16.1, -0.4), PROT -10.8% (-18.4, -2.5), and UNSAT -9.4% (-17.4, -0.5). Hs-CRP was similarly changed by -13.9 to -17.0%. Hs-cTnI and hs-CRP reductions were of similar magnitudes as SBP and low-density lipoprotein cholesterol (LDLc) but were not associated with these risk-factor reductions (*P-values*=0.09). There were no between-diet differences in hs-cTnI and hs-CRP reductions.

Conclusions: Healthy diet, regardless of macronutrient emphasis, directly mitigated subclinical cardiac injury and inflammation in a population at risk for cardiovascular disease. These findings support dietary recommendations emphasizing healthy foods rather than any one macronutrient.

Keywords

diet; randomized trial; high-sensitivity troponin I; high-sensitivity C-reactive protein; cardiovascular risk factors; hypertension

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States.⁽¹⁾ Dietary interventions play a critical role in recommendations to prevent CVD in adults^(2,3) based on reported improvements in CVD risk factors.⁽⁴⁻⁷⁾ However, there has been minimal improvement in diet quality among US adults over the past several decades.^(8,9) One of the challenges facing promotion of healthy diet in the US has been conflicting recommendations for what macronutrients should be emphasized as part of a healthy diet. Some experts have emphasized high fat/low carbohydrate pattern as optimal, while others focus on low fat/high

carbohydrate diets.(10) However, it is possible that the macronutrients matter less than simply eating healthy foods. In spite of this, there is limited evidence for whether a healthy diet might directly improve causal intermediaries of CVD, e.g. subclinical myocyte injury and inflammation(11,12) not to mention the effects of specific macronutrients on direct measures of subclinical CVD.

The Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) trial was designed to examine the effects of 3 healthy diets that emphasize different macronutrients (carbohydrates, protein, or unsaturated fat) on CVD risk factors.(6) Participants were included with baseline elevated blood pressure (BP) or hypertension, but not yet on medications for BP or cholesterol.(6) All 3 OmniHeart diets showed large reductions in systolic BP (SBP) and low-density lipoprotein cholesterol (LDLc) after six-weeks, which were predicted to reduce 10-year coronary heart disease risk by 16-21%.(6) However, whether these diets had a direct impact on myocyte injury or inflammation was not reported. With the advent of assays for high-sensitivity troponin, a highly specific marker of myocardial cell injury detectable even in the ambulatory population, it is now possible to directly measure subclinical cardiac damage.(13-15) Furthermore, recent studies have re-established the importance of inflammation, reflected by high-sensitivity CRP (hs-CRP), as an independent factor associated with the development of atherosclerosis and CVD.(16-18)

Using stored specimens from OmniHeart, we measured high-sensitivity troponin I (hs-cTnI) and hs-CRP to: (1) determine the effects of 3 healthy diets on hs-cTnI and hs-CRP, (2) examine whether macronutrient profile would further affect hs-cTnI and hs-CRP, and (3) study the relationship between change in hs-cTnI and hs-CRP with changes in important CVD risk factors, i.e. SBP and LDLc. We hypothesized that both hs-cTnI and hs-CRP would be reduced from baseline with little difference between diets, reflecting the magnitude of changes in SBP and LDLc observed from baseline in the original OmniHeart trial.

SUBJECTS AND METHODS

The rationale, design, and main outcomes of the OmniHeart Trial have been reported.(6,19) In brief, OmniHeart was a two-center, investigator-initiated, feeding study with a randomized, 3-period crossover design sponsored by the NHLBI. This trial tested the effects of 3 healthful diets, differing in macronutrient composition, on traditional CVD risk factors (BP and LDLc) in the setting of stable weight. Specimens from the original trial were maintained and curated by the NHLBI and made available by request via the BioLincc repository.

Institutional Review Boards at Johns Hopkins University, Brigham & Women's Hospital, and the Harvard School of Public Health approved the original study protocol.

Participant Recruitment

Adult men and women, residing in and around Boston, MA, and Baltimore, MD, participated in OmniHeart between April 2003 and June 2005. Participants were required to be aged ≥ 30 years with SBP 120-159 or DBP 80-99 mmHg. Adults with a diagnosis of diabetes, kidney disease (eGFR <60 ml/min per 1.73m²), a prior history of CVD, >2

alcoholic drinks per day for men or >1 alcoholic drink per day for women, or use of medications for the treatment of hypertension or hyperlipidemia were excluded. (6) Of the initial 191 participants randomly assigned to 6 diet sequences, 164 completed at least 2 feeding periods. Of these, 162 had stored specimens at the time of hs-cTnI measurement, and 155 had stored specimens at the time of hs-CRP measurement (Supplemental Figure 1).

Dietary Intervention

OmniHeart included 3 healthful diets: a carbohydrate-rich diet (CARB) with 58% kilocalories from carbohydrates (similar to the DASH diet), a protein-rich diet (PROT) with 10% of kilocalories from carbohydrates replaced by protein, and an unsaturated fat-rich diet (UNSAT) with 10% of kilocalories from carbohydrate replaced by unsaturated fats (Supplemental Table 1). All 3 diets were low in saturated fat, cholesterol, and sodium (2,300 mg/day), while providing other nutrients at recommended dietary levels. In the PROT diet, the food sources for protein replacement were two-thirds vegetable-based. Diets were designed using commonly available foods.

Participants were randomized to 1 of 6 dietary sequences with a 2 to 4-week wash-out period between each diet, during which participants ate their own food (Supplemental Figure 1).(6) Each feeding period lasted 6-weeks. Calorie targets were determined for each participant based on body size, sex, and physical activity; calorie targets were then adjusted throughout the study to keep weight within 2% of baseline. Participants were encouraged to maintain usual physical activity levels and alcohol consumption for the duration of the study. Ultimately, participants were compliant with the feeding protocol for >95% of trial person-days, i.e. complete consumption of all study foods without any non-study foods.(6)

Measurement of Main Outcomes: High-sensitivity Troponin I (hs-cTnI) and High-sensitivity C-reactive Protein (hs-CRP)

Fasting serum was collected from each participant at baseline and at the completion of each 6-week feeding period. Blood samples were allowed to clot at room temperature for 15 minutes, centrifuged at 2°C, and stored at -70°C. In 2018, hs-cTnI was measured in serum specimens at University of Maryland (Baltimore), using donated investigational Advia Centaur High-Sensitivity Troponin I assays (Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA) with a range of 0.10-25,000 ng/L. Values below 0.1 ng/L were imputed as 0.05. This affected only 2 people: one participant was < 0.1 ng/L at baseline and another was undetectable at baseline and each of the 3 follow-up visits. Details of assay performance have been published previously.(20) Hs-CRP was measured by nephelometric assay in 2008 (Vista Intelligent Lab System, Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA).

Other Measurements and Variables

Age, sex, race (white, black, or other), ethnicity (Hispanic or non-Hispanic), current smoking status, and education were self-reported via questionnaires. Body mass index (BMI) was derived via baseline height and weight measurements. Baseline SBP and DBP were measured using the average of 3 BP assessments obtained during separate screening visits at least one week apart. Participants were considered to have stage 1 or 2 hypertension

at baseline if they had an average baseline SBP ≥ 130 mmHg or DBP ≥ 80 mmHg. Traditional assays were used to measure total triglycerides and HDL cholesterol. LDLc levels were estimated by the Friedewald equation.(21)

Statistical Analysis

Baseline characteristics and marker distributions

Study population characteristics were described using means (SD) and proportions. Both hs-cTnI and hs-CRP were log-transformed to account for data skew. Means of log-transformed hs-cTnI and hs-CRP were examined at baseline and the end of each of the 3 feeding periods. Kernel density plots were used to compare the distributions of log-transformed hs-cTnI and hs-CRP at baseline and at the end of the 3 feeding periods.

Change from baseline and between diet comparisons

The primary outcomes were log-transformed hs-cTnI and log-transformed hs-CRP. The primary comparisons were % baseline change in hs-cTnI and hs-CRP, which were determined for each feeding period with linear regression, using generalized estimated equations (GEE) with robust standard errors and exchangeable covariance structure to account for correlated measures.

End of period, log-transformed hs-cTnI and hs-CRP were also compared across diets (PROT versus CARB, UNSAT versus CARB, PROT versus UNSAT), using the GEE models above.

Comparison with cardiovascular disease risk factors

We examined the relationship between SBP and LDLc with hs-cTnI and hs-CRP at baseline using linear regression. Furthermore, we compared baseline and between-diet changes in hs-cTnI and hs-CRP with changes in SBP and LDLc reported in the original OmniHeart trial. (6) Linear regression, Lowess curves, and scatter plots were used to compare baseline changes in hs-cTnI or hs-CRP with baseline change in SBP or LDLc.

To understand whether there were disproportionate dietary effects among at-risk subgroups, we performed stratified analyses, based on age (≥ 60 years), sex, black race, hypertension (baseline SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg), obesity (≥ 30 kg/m²), or current smoking status. Interaction terms were used to compare effects across strata.

All analyses were performed using STATA version 14.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Baseline Characteristics

Demographic characteristics are provided in Table 1. Overall, the mean age was 53.5 (SD, 10.9) years, 55% were African American, and 45% were female. The mean BMI was 30.2 (SD, 6.1) kg/m², and 55% had stage 1 or 2 hypertension (SBP ≥ 130 or DBP ≥ 80 mm Hg).

Changes from Baseline and End-Period Comparisons

At baseline, median (25th percentile, 75th percentile) hs-cTnI was 3.3 (1.9, 5.6) ng/L and median hs-CRP was 2.2 (1.1, 5.2) mg/L (Table 1). Compared to baseline, all 3 diets significantly reduced hs-cTnI and hs-CRP (Figure 1). This was reflected by a leftward shift in the distribution of hs-cTnI and hs-CRP values (Supplemental Figure 2). The CARB diet changed hs-cTnI by -8.6% (95% CI $-16.1, -0.4$; $P = 0.04$) and hs-CRP by -17.0% ($-26.6, -6.1$; $P < 0.003$). Similarly, the PROT diet changed hs-cTnI by -10.8% ($-18.4, -2.5$; $P = 0.01$) and hs-CRP by -13.9% ($-24.9, -1.3$; $P = 0.03$), and the UNSAT diet changed hs-cTnI by -9.4% ($-17.4, -0.5$; $P = 0.04$) and hs-CRP by -16.0% ($-26.5, -4.1$; $P = 0.01$). None of the diets differed in terms of the magnitude of hs-cTnI or hs-CRP reductions, i.e. all pairwise contrasts were non-significant (Table 2).

Comparison with Risk Factors

We examined the association between SBP and LDLc with hs-cTnI and hs-CRP measured at baseline (Supplemental Table 2). There was a positive association between baseline SBP and baseline hs-cTnI ($P = 0.005$), but not baseline hs-CRP ($P = 0.09$). LDLc was not significantly associated with either outcome (Supplemental Table 3). We then compared changes in hs-cTnI and hs-CRP (end of intervention minus baseline) with changes in CVD risk factors reported in the original OmniHeart trial (Table 2). The largest differences in SBP and LDLc were observed compared to baseline with reductions of 8-9 mm Hg for SBP and 11-14 mg/dL for LDLc. Differences between diets in the original study were modest (< 2 mm Hg in SBP and < 4 mg/dL for LDLc). In linear regression models, changes from baseline in SBP or LDLc were not associated with hs-cTnI and hs-CRP (Supplemental Figure 3).

Stratified analysis

We examined baseline change in hs-cTnI and hs-CRP by diet in strata of age, sex, race, hypertension, obesity, and smoking status (Table 3). In black participants, the 3 healthy diets had a greater impact on hs-cTnI (-10.2 to -17.3%) compared to non-black participants (-4% to 1.3% , $P = 0.04$); although, no significant difference was seen for hs-CRP. Among participants without hypertension, hs-CRP was more affected by healthy diet (-26.7 to -31.4%) than among participants with hypertension (-2.7 to -8.6% , $P = 0.04$).

DISCUSSION

In the OmniHeart study, 3 healthy DASH-pattern diets lowered both hs-cTnI and hs-CRP over 6-weeks in participants with elevated BP or hypertension. Effects did not differ by macronutrient. While changes in hs-cTnI and hs-CRP mirrored the magnitude of the diets' effects on SBP and LDLc, these changes were not associated with changes in SBP and LDLc. Together, these findings suggest that a healthy diet, regardless of macronutrient profile, can directly mitigate subclinical cardiac damage and inflammation beyond traditional risk factors. While stratified analyses indicated that certain subgroups may benefit more in terms of hs-cTnI and hs-CRP reduction, our results were largely consistent across groups.

Troponin is the gold-standard marker for diagnosing acute myocardial infarction (MI), as a highly specific marker of myocardial cell injury.(13) Improvements in the assay led to the development of high-sensitivity troponin, detectable even in healthy, ambulatory populations and potentially representing the impact of structural heart disease or reversible cell damage. (13-15) Both isoforms of troponin I and T are expressed selectively in cardiac muscle, but can be released in many situations including MI, direct cardiotoxic trauma, increased wall tension, and excess catecholamines.(13) Observational studies have shown that detectable levels of high-sensitivity cardiac troponin T (hs-cTnT) are highly predictive of CVD events, and hs-cTnT increases at different rates over time depending on baseline CVD risk factors. (22,23) Among adults without baseline CVD, progression or development of diabetes, hypertension, and obesity are strongly associated with increases in hs-cTnT.(14) Moreover, treatment of LDLc with pravastatin in the West of Scotland Coronary Prevention Study reduced hs-cTnI by 13% (10-15%, $P < 0.001$) compared to placebo over 5-years of follow-up.(24) However, whether a healthy diet could also reduce hs-cTnI has not been previously shown.

Evidence for a causal relationship between healthy diet and the reversal of subclinical cardiac injury is scarce, and observational data has been contradictory. While some studies have shown that healthy diet in combination with other healthy lifestyle choices is associated with reductions in subclinical myocardial injury based on hs-cTnT over a 6-year period(25), others have not found an association between hs-cTnT and healthy diet.(26) Furthermore, two trials, both a dietary intervention with fatty acids(27) and a comparison study of low glycemic index versus high fiber diets(28), did not show an effect on subclinical cardiac injury by hs-cTnI or hs-cTnT. Contrary to these studies, OmniHeart demonstrated that 3 healthful diets, modeled after the DASH diet, reduced cardiac injury over 6-weeks.

Another important causal mediator for CVD is high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation that is independently associated with the development of atherosclerosis and coronary heart disease events.(16,17) Exposure to hs-CRP ≥ 3 mg/L over time is associated with higher risk of CVD.(29) Furthermore, one large trial (CANTOS) recently demonstrated that CVD events were reduced by targeting inflammatory pathways. (30) In fact, CANTOS participants who achieved on-treatment hs-CRP < 2 mg/L had a 31% reduction in both cardiovascular and all-cause mortality compared to those with hs-CRP ≥ 2 mg/L.(18)

There are few studies examining the relationship between diet and hs-CRP. Observational studies have demonstrated an inverse relationship between healthy diet and hs-CRP.(31-33) Interventional studies and meta-analyses have been mixed with some showing that diet and physical activity lower hs-CRP,(34,35) while others show no effect.(12,36) In a sub-study of the DASH-Sodium trial, baseline hs-CRP strongly modified the effect of the DASH diet on LDLc levels, but the study (N=100) was underpowered to see an effect from DASH on hs-CRP.(11) With similar diets but greater power in OmniHeart, our findings provide support for the role of diet in reducing cardiac inflammation.

This study meaningfully informs ongoing debates about the importance of macronutrient intake for cardiovascular health.(10) Recent evidence suggests that macronutrient pattern

does not influence CVD risk factors.(37) In OmniHeart, the CARB diet was similar to the DASH diet, which is high in carbohydrate, while UNSAT is a version of the DASH diet that emphasizes unsaturated fat, i.e. similar to a Mediterranean-style diet.(38) However, in the primary study, the between-diet differences in SBP and LDLc were small and did not translate into significantly different effects on hs-cTnI and hs-CRP. While the long-term consequences of these small differences in CVD risk factors are unknown, in the short-term adopting any of the 3 healthy diets appeared to be more important than the macronutrient composition of any one single diet. This finding supports flexibility in food selection for individuals attempting to consume a healthful diet and should improve adherence. With only 1 in 10 US adults meeting the daily recommended fruits and vegetable intake, and the average American eating 1 serving of fruit and < 2 servings of vegetables,(39) the typical American diet is quite different from the Omniheart diets, which each included 4-6 servings each of fruits and vegetables per day.

Our study has limitations. First, feeding periods were 6-weeks long, and outcomes represent causal mediators of CVD rather than clinical events. While hs-cTnI and hs-CRP are strongly associated with CVD events over time, the trial was neither designed nor powered to study clinical outcomes. Second, there was no control diet in OmniHeart. As a result, it is possible that the observed effects partially reflect trial participation (Hawthorne effect) and potentially regression to the mean. However, it should be noted that the trial did not select participants based on high levels of hs-cTnI and hs-CRP, thereby minimizing the potential for regression to the mean. The stratified analysis showed some possible sub-group effects, though the differences seen between groups are more likely related to this study being underpowered to see true subgroup disparities.

Our study has several notable strengths. OmniHeart's crossover design in a population at risk for CVD afforded a unique opportunity to evaluate the effects of a dietary intervention on biomarkers of subclinical CVD. Assessments were rigorously performed following a standardized protocol and within the same people allowing us to determine change in hs-cTnI and hs-CRP. Furthermore, OmniHeart was conducted in a diverse population, thereby enhancing generalizability. As a feeding trial, with all foods provided to participants, Omniheart tested the biological effects of the diets without biases related to non-adherence and measurement error, typical of observational studies. Finally, assessments of hs-cTnI and hs-CRP afforded us an opportunity to examine the effects of healthy diet on pathways of CVD injury. Given the high adherence and follow-up during each of the dietary periods without weight change, our study provides strong justification and a feasible way to lower CVD risk with diet alone.

This study has important public health implications. We documented that changes in diet can reduce subclinical cardiac injury and inflammation concurrent with reductions in other CVD risk factors. These results add substantial support to the hypothesis that diet influences causal pathways of CVD - findings meaningful for population strategies for primary prevention of CVD. Clinical CVD is the culmination of years of subclinical cardiovascular injury. While the incremental impact of short-term unhealthy lifestyle may be small, its accumulated effects becomes clinically evident in adults often after irreversible ischemic events.(40) A healthy diet continues to be a critical strategy, not only by shifting the

distribution of cardiovascular risk factors in the population,(41) but also by reductions in both cardiac injury and inflammation. We believe our findings should serve to further motivate physicians to recommend and patients to adopt a healthy diet, given the benefits seen in our study.

In conclusion, consumption of a healthy diet directly lowered subclinical hs-cTnI and hs-CRP, beyond reductions in SBP and LDLc, regardless of whether they were high in carbohydrates, protein, or fat. This study provides strong support for simplified dietary recommendations that emphasize healthy foods rather than any one macronutrient as a means to reverse subclinical cardiac injury and inflammation in populations at risk for CVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CARB	the OmniHeart carbohydrate feeding period
CI	confidence interval
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
DBP	diastolic blood pressure
BMI	body mass index
LDLc	low-density lipoprotein cholesterol
DASH	Dietary Approaches to Stop Hypertension
GEE	generalized estimating equation
hs-cTnI	high-sensitivity troponin I
hs-CRP	high-sensitivity C-reactive protein
MI	myocardial infarction
Omniheart	Optimal Macronutrient Intake Trial to Prevent Heart Disease
PROT	the OmniHeart protein feeding period

SBP	systolic blood pressure
SD	standard deviation
UNSAT	the OmniHeart unsaturated fat feeding period

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Highlights

- Three healthy diets led to reduction in high-sensitivity troponin, a marker of subclinical cardiac injury
- Inflammation, measured by high-sensitivity CRP, was also reduced by all three healthy diets
- These changes were not explained alone by improvement in hypertension or hyperlipidemia
- All three healthy diets can be recommended to help reduce cardiovascular risk

Figure 1.

The mean log-transformed high-sensitivity troponin I (hs-cTnI) (**A**) and the mean log-transformed high-sensitivity CRP (hs-CRP) (**B**) with 95% confidence intervals. Y-axes are on a log-scale. Baseline and 6-week mean log-transformed hs-cTnI and hs-CRP are shown along with P -values for each comparison. Mean hs-cTnI values vary slightly from the median baseline values reported in Table 1

Table 1.**Baseline Characteristics of OmniHeart Trial Participants**

	Overall (n=164)[*]
Age, mean (SD), years	53.5 (10.8)
Women, No. (%)	74 (45)
Race, No. (%)	
African American	90 (55)
Non-Hispanic white	66 (40)
Other	8 (5)
Education, No. (%)	
High School Diploma	33 (20)
Some College Education	131 (80)
Body mass index, mean (SD) kg/m ²	30.2 (6.1)
Baseline hypertension [†] No. (%)	90 (55)
Smoking Status, No (%)	
Current	18 (11)
Former & Never	146 (89)
Triglycerides, mean (SD), mg/dL [‡]	109.1 (1.8)
HDL, mean (SD), mg/dL	50.0 (16.1)
LDLc, mean (SD), mg/dL	129.2 (32.4)
Hs-cTnI, (median [25 th percentile, 75 th percentile]), ng/L	3.3 [1.9, 5.6]
Hs-CRP, (median [25 th percentile, 75 th percentile]), mg/L	2.2 [1.1, 5.2]

DBP: diastolic blood pressure; HDL: high-density lipoprotein cholesterol; Hs-CRP: high-sensitivity C-reactive protein; Hs-cTnI: high-sensitivity troponin I; LDLc: low-density lipoprotein cholesterol; SBP: systolic blood pressure

^{*} In some cases, fewer than 164 participants had all the covariates of interest

[†] Hypertension defined by SBP ≥ 130 or DBP ≥ 80 mmHg

[‡] Geometric mean given data skew

Effects of 3 Healthy Diets on High-sensitivity Troponin, High-sensitivity C-reactive protein, Cardiovascular Disease Risk Factors, and Coronary Heart Disease Risk^{*}

Table 2.

	Systolic Blood Pressure, mm Hg		LDL Cholesterol, mg/dL		High-sensitivity Troponin I (%)		High-sensitivity C-reactive Protein (%)		Estimated 10-yr CHD risk reduction (%)
	Mean Change	P	Mean Change	P	Mean % Difference	P	Mean % Difference	P	
CARB vs BL	-8.2	<0.01	-11.6	<0.01	-8.6	0.04	-17.0	0.003	-16.1
PROT vs BL	-9.5	<0.01	-14.2	<0.01	-10.8	0.01	-13.9	0.03	-21.0
UNSAT vs BL	-9.3	<0.01	-13.1	<0.01	-9.4	0.04	-16.0	0.01	-19.6
PROT vs CARB	-1.4	<0.01	-3.3	0.01	-2.4	0.49	3.7	0.52	-5.8
UNSAT vs CARB	-1.3	<0.01	-1.5	0.22	-0.8	0.85	1.1	0.86	-4.2

BL: Baseline; CARB: Carbohydrate diet; CHD: coronary heart disease; PROT: Protein diet; UNSAT: Unsaturated-fat diet

^{*} Note magnitudes for systolic blood pressure, LDL cholesterol, and estimated 10-year risk reduction in coronary heart disease were quoted from the original trial(6)

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Table 3.

Baseline change in high-sensitivity troponin I and high-sensitivity C-reactive protein according to strata

	Baseline N ^a	Carbohydrate		Protein		Unsaturated Fat	
		% Difference (95% CI)	P - interaction	% Difference (95% CI)	P - interaction	% Difference (95% CI)	P - interaction
High-sensitivity Troponin I							
Age ≥60 years							
No	118	-9.7 (-17.8,-0.8)	0.82	-12.4 (-21.2,-2.7)	0.99	-10.4 (-20.1, 0.5)	0.78
Yes	44	-5.9 (-20.3,11.1)		-6.5 (-17.5, 5.8)		-6.8 (-17.9, 5.8)	
Women							
No	89	-2.8 (-12.6, 8.2)	0.71	-8.0 (-16.5, 1.4)	0.71	1.0 (-10.1,13.5)	0.15
Yes	73	-11.5 (-22.1, 0.6)		-10.2 (-22.5, 4.1)		-17.3 (-28.2,-4.8)	
Black							
No	72	-1.6 (-12.2,10.2)	0.12	-4.0 (-16.1, 9.8)	0.15	1.3 (-12.5,17.2)	0.04
Yes	90	-13.6 (-22.7,-3.5)		-15.6 (-23.4,-7.0)		-16.7 (-25.3,-7.1)	
Hypertension [†]							
No	71	-12.0 (-24.3, 2.3)	0.31	-17.0 (-27.0,-5.8)	0.74	-14.7 (-28.4, 1.7)	0.62
Yes	91	-11.8 (-19.8,-3.0)		-11.3 (-21.9, 0.7)		-10.9 (-19.7,-1.1)	
Obesity (BMI ≥ 30 kg/m ²)							
No	87	-10.9 (-20.6, 0.1)	0.73	-12.1 (-21.4,-1.6)	0.52	-9.8 (-19.6, 1.1)	0.44
Yes	75	-9.8 (-20.6, 2.4)		-13.2 (-24.4,-0.2)		-12.8 (-25.1, 1.5)	
Current smoker							
No	144	-7.7 (-15.6, 0.9)	0.68	-10.6 (-18.5,-1.9)	0.95	-9.4 (-17.6,-0.3)	0.87
Yes	18	-14.3 (-29.1, 3.6)		-11.1 (-26.7, 7.8)		-8.1 (-24.0,11.1)	
High-sensitivity C-reactive protein							
Age ≥60 years							
No	114	-19.3 (-29.0,-8.4)	0.81	-15.9 (-27.5,-2.4)	0.90	-16.3 (-28.2,-2.5)	0.74
Yes	41	-6.7 (-27.5,20.1)		-4.4 (-26.8,25.0)		-11.6 (-31.5,14.1)	
Women							
No	82	-25.8 (-37.6,-11.7)	0.79	-12.1 (-27.9, 7.3)	0.052	-20.1 (-35.0,-1.8)	0.41
Yes	72	-12.4 (-25.5, 3.0)		-22.8 (-34.7,-8.9)		-18.1 (-29.8,-4.4)	
Black							
No	68	-21.8 (-35.7,-4.9)	0.51	-19.4 (-35.6, 0.8)	0.50	-27.7 (-41.4,-10.7)	0.08
Yes	87	-13.6 (-25.2,-0.2)		-9.8 (-22.8, 5.4)		-6.4 (-20.4,10.0)	
Hypertension [†]							
No	69	-27.7 (-40.3,-12.5)	0.19	-26.7 (-40.5,-9.7)	0.14	-31.4 (-44.2,-15.7)	0.04
Yes	86	-8.6 (-20.4, 5.0)		-3.6 (-18.0,13.3)		-2.7 (-16.9,14.0)	
Obesity (BMI ≥ 30 kg/m ²)							
No	85	-25.1 (-37.6,-10.1)	0.58	-21.4 (-34.8,-5.1)	0.77	-26.6 (-39.1,-11.6)	0.29
Yes	70	-6.4 (-18.4, 7.4)		-4.3 (-20.2,14.7)		-1.4 (-17.3,17.5)	
Current smoker							
No	138	-18.3 (-27.6,-7.7)	0.39	-14.3 (-25.8,-0.9)	0.40	-16.5 (-27.3,-4.2)	0.43
Yes	15	-5.8 (-41.8,52.4)		-6.9 (-35.4,34.1)		-8.0 (-44.8,53.1)	

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Limited to number with either high-sensitivity troponin **I** or high-sensitivity C-reactive protein measurements
*
† Baseline systolic blood pressure >130 or baseline diastolic blood pressure >80 mm Hg