Individual variability in cardiovascular disease risk factor responses to low-fat and low-saturated-fat diets in men: body mass index, adiposity, and insulin resistance predict changes in LDL cholesterol

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ABSTRACT

Background: Although reductions in total and saturated fat consumption are recommended to reduce the risk of cardiovascular disease, individual variability in plasma lipid responses exists.

Objective: Our aim was to determine the effect of adiposity and insulin resistance on the lipoprotein response to diets lower in total and saturated fat than the average American diet (AAD).

Design: A randomized, double-blind, 3-period crossover controlled feeding design was used to examine the effects on plasma lipids of 3 diets that differed in total fat: the AAD (designed to contain 38% fat and 14% saturated fatty acids (SFAs)), the Step I diet (30% fat with 9% SFAs), and the Step II diet (25% fat with 6% SFAs). The diets were fed for 6 wk each to 86 free-living, healthy men aged 22–64 y at levels designed to maintain weight.

Results: Compared with the AAD, the Step I and Step II diets lowered LDL cholesterol by 6.8% and 11.7%, lowered HDL cholesterol by 7.5% and 11.2%, and raised triacylglycerols by 14.3% and 16.2%, respectively. The Step II diet response showed significant positive correlations between changes in both LDL cholesterol and the ratio of total to HDL cholesterol and baseline percentage body fat, body mass index, and insulin. These associations were largely due to smaller reductions in LDL cholesterol with increasing percentage body fat, body mass index, or insulin concentrations. Subdivision of the study population showed that the participants in the upper one-half of fasting insulin concentrations averaged only 57% of the reduction in LDL cholesterol with the Step II diet of the participants in the lower half.

Conclusion: Persons who are insulin resistant respond less favorably to Step II diets than do those who are insulin sensitive. Am J Clin Nutr 2005;82:957–63.

KEY WORDS Dietary fat, saturated fat, obesity, adiposity, insulin resistance, metabolic syndrome, blood lipids, diet response

INTRODUCTION

The prevalence of persons who are classified as overweight [body mass index (BMI; in kg/m²) ≥ 25] or obese (BMI ≥ 30) has increased at a dramatic rate over the past 2 decades (1). The associated health consequences of increased adiposity are well established and include the development of insulin resistance that leads to type 2 diabetes and the development of an atherogenic lipoprotein phenotype that is characterized by high triacylglycerols, low HDL cholesterol, and the presence of small, dense LDL (2). Although elevated LDL cholesterol is not regarded as a key feature of obesity and insulin resistance, the presence of insulin resistance is associated with a substantially increased risk of cardiovascular disease (CVD), even at moderate LDL-cholesterol concentrations (3). Therefore, aggressive attempts should be made to reduce both the degree of adiposity and LDL-cholesterol concentrations to reduce CVD risk.

Although dietary approaches to reduce adiposity have met with mixed results, diet therapy is an effective approach to lower LDL-cholesterol concentrations in many persons with elevated LDL cholesterol (4). Although obesity has been shown to affect the lipid risk factor response to diets (5–10), it is unknown to what extent this is due to adiposity per se or to an underlying insulin resistance. As part of an ongoing series of analyses that are aimed at identifying predictors of the CVD risk factor response to diet therapy, we examined the relation between the indexes of adiposity and insulin resistance and the magnitude of lipid response in healthy men to diets that were reduced in total and saturated fat.

SUBJECTS AND METHODS

Subjects

One hundred twenty-one men aged 22–64 y were recruited. The participants were selected to have an LDL-cholesterol concentration between the 10th and 90th percentiles, an HDL cholesterol concentration > 25 mg/dL and below the 95th percentile, and a triacylglycerol concentration below the 95th percentile; the percentiles were based on age and sex specific values from the National Health and Nutrition Examination Survey II (11). An
upper BMI limit of 34 was set to exclude persons with very high caloric intakes. Additionally, participants were excluded if they had evidence of cardiovascular, renal, hepatic, endocrine, gastrointestinal, or other systemic disease as assessed by blood chemistry, urinalysis, medical questionnaire, and physical exam. Participants were also excluded for drug or alcohol abuse, extreme dietary habits, multiple food allergies, or extreme levels of physical or athletic activity.

At screening, dual-energy X-ray absorptiometry (Hologic QDR2000, Waltham, MA) was performed to measure the body composition (lean and fat mass) of each participant with the use of Hologic enhanced whole-body version 6.0 software. All participants indicated their willingness to participate in the present study by signing a consent form, which was approved by the Pennington Biomedical Research Center Institutional Review Board.

Study design

The study was a randomized, double-blinded, 3-period crossover design. Each participant was fed 3 diets that differed in total fat, with each dietary period being 6 wk in length. A 6-wk diet period was chosen to stabilize the lipoprotein endpoints (4). A break (1–6 wk) was provided between each of the dietary periods. The participants were recruited in a series of sequential, partially overlapping cohorts (7 total), which varied in size from 8 to 26 participants per cohort. The length of time between the start of cohort 1 and the end of cohort 7 was 26 mo. A total of 87 participants completed all 3 diet periods.

Diets

The participants were fed 3 diets that differed in total fat and saturated fat content: 1) an average American diet (AAD), which was designed to contain 38% of energy as fat and 14% of energy as saturated fat; 2) the Step I diet, which was designed to contain 30% of energy as fat and 9% of energy as saturated fat; and 3) the Step II diet, which was designed to contain 25% of energy as fat and 6% of energy as saturated fat. Because one focus of our overall project was on the health effects of milkfat, we achieved the dietary goals of the experimental diets through specific reductions in milkfat from 18% of energy derived from milkfat in the AAD to 10% and 5% of energy on the Step I and Step II diets, respectively. This was accomplished by substituting low fat or nonfat dairy products for their higher fat equivalents. The different diets were outwardly identical; most of the changes in fat were visibly hidden. The only difference the participants could have perceived would have been changes in the volume and proportion of the food items.

Each day, one complete meal was prepared for chemical analysis; the experimental diet and energy level selected for analysis was systematically changed after each 5-d menu cycle. These prepared meals for each menu cycle were combined, composited, and analyzed for proximates, fatty acids, and cholesterol by the Pennington Biomedical Research Center Food Analysis Laboratory.

Free-living participants were provided with all food during the study except for Saturday night dinners. This meal was self-selected by the participants, and they were counseled to choose a meal similar to the Step I diet or a meal was provided by the resident chef. On weekdays, the participants consumed breakfast and dinner at the Pennington Biomedical Research Center dining facility. Meal trays were inspected after each meal to ensure that all food items were consumed. Weekday packaged lunches were distributed at breakfast; evening snacks were distributed at dinner. A daily compliance questionnaire was administered to determine whether the subjects had eaten all their supplied food items and whether they had consumed food items other than those that were provided. Weekend meals were packaged and distributed on Friday. Meals were prepared at 4 energy levels (9.2, 10.9, 12.6, and 14.2 MJ/d). Unit foods that were similar in macronutrient composition to the assigned diet and were 418 kJ (100 kcal) each were used for energy adjustments. The participants were started on the energy level that most closely matched their estimated energy requirement. Body weight was measured twice weekly. If a participant’s weight differed from his initial weight by >1 kg, the energy level was adjusted until his weight returned to within 1 kg of the initial value.

Endpoint sample collection

Blood sampling was performed at the end of weeks 4, 5, and 6 of each dietary period. Venous blood samples were collected between 0600 and 0900 after the subjects had fasted for 12 h. Blood was collected with a 20-gauge needle butterfly set to minimize hemostasis. Red top evacuated tubes (with no additive) were used for lipid analyses. The samples were stored at room temperature immediately after their collection and during transport to the laboratory. The blood samples were centrifuged at 3000 × g for 15 min at room temperature. Processing of the samples was completed within 1 h of collection. Serum was aliquoted into plastic cryovials and frozen at −80 °C until analysis. All analyses were performed as a batch at the end of each cohort to minimize interassay variations on the outcome of the results.

Food analysis

Composite food samples were analyzed for protein, fat, moisture, ash, carbohydrate, fatty acid, and cholesterol content. Protein content was analyzed with a Perkin Elmer nitrogen analyzer. This method is an enhanced version of the classical Dumas method and is an approved method (992.15) of the Association of Official Analytic Chemists. Moisture content was measured on a LabWave 900 microwave solid analyzer (CEM, Matthews, NC). Ash content was measured on a CEM MAS 7000 microwave furnace. Total fat content was extracted with chloroform and methanol. Fatty acid content was measured by gas chromatography of fatty acid methyl esters according to a modified Association of Official Analytic Chemists Ce 1b-89 method (12). Cholesterol content was analyzed with Association of Official Analytic Chemists method 976.26 with some modifications (13).

Laboratory analyses

Serum lipid and glucose concentrations were analyzed with a Beckman-Coulter Synchroin CX7 (Brea, CA). Serum cholesterol concentrations were assayed with the cholesterol esterase-oxidase-peroxidase method. Triacylglycerol concentrations were measured with the GPO-Trinder method. HDL-cholesterol concentrations were measured after precipitation of apolipoprotein (apo) B-containing lipoproteins with 50 000 mol wt dextran sulfate (DMA, Arlington, TX). LDL-cholesterol concentrations were calculated with the Friedewald equation (14). Glucose concentrations were measured with the glucose oxidase method.
the greatest ranges in the difference between any pairs of diets were saturated fat, and 43 mg/MJ for cholesterol. Across the cohorts, AAD was 2.8% of energy for total fat, 1.9% of energy for saturated fat, 1.4% of energy for total fat, 1.3% of energy for saturated fat, and 36 mg/MJ for cholesterol.

Across the cohorts, AAD and was 2.8% of energy for total fat, 1.9% of energy for saturated fat; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

**Statistical analysis**

Descriptive statistics (scatterplots, means, SDs, and SEMs) were examined, and, if required, the data were log (In) transformed to achieve a normal distribution. A repeated-measures analysis of variance was used to identify significant (P < 0.05) effects of diet. Statistical differences between diet pairs were assessed with Bonferroni adjustments of the P values. Univariate correlation analysis between variables was performed with Pearson’s product moment correlations. A multiple regression analysis of variance was used to identify significant (P < 0.05) changes in selected endpoints. All analyses were performed with CRUNCH software ver 4.04 (CRUNCH Software Corp, Oakland, CA).

### RESULTS

#### Diets

Because of the length of the study, we continuously monitored the composition of the prepared diets to examine possible variation across cohorts. Ninety-one 5-d menu cycles were collected and analyzed across 13 individual 6-wk diet-periods. The composition of our diets closely met our targets for key nutrients (ie, total fat and saturated fat; **Table 1**). The relatively small SDs for the nutrients suggest that the meals were prepared in a consistent manner with little compositional deviation. The range in the average analyzed values across the cohorts was greatest for the AAD and was 2.8% of energy for total fat, 1.9% of energy for saturated fat, and 43 mg/MJ for cholesterol. Across the cohorts, the greatest ranges in the difference between any pairs of diets were 2.6% of energy for total fat, 1.3% of energy for saturated fat, and 36 mg/MJ for cholesterol.

#### Participant characteristics

Eighty-seven men finished all 3 diet periods. Data for one participant were not included in the final analysis because of medication use during the study, which interfered with lipid values. The characteristics of the remaining 86 participants are shown in **Table 2**. Of the participants, 84% were white and 11% were African Americans. Seven percent of the participants were active cigarette smokers. The participants’ mean BMI slightly exceeded the age-adjusted 50th percentile for men. Mean concentrations for all screening lipid values were slightly below the population median for men aged 30–39 y and ranged between the 35th percentile (for HDL cholesterol) and the 45th percentile (for LDL cholesterol).

**Effect of diets on endpoints**

Reductions in dietary total fat, saturated fat, and cholesterol lowered the serum concentrations of total cholesterol (TC), LDL cholesterol, and HDL cholesterol (**Table 3**). Compared with the AAD, TC decreased 4.8% and 8.9%, LDL cholesterol decreased 6.8% and 11.7%, and HDL cholesterol decreased 7.5% and 11.2% on the Step I and Step II diets, respectively. Although triacylglycerol concentrations were significantly higher on the Step I diet than on the AAD, they did not increase significantly more on the Step II diet. Compared with the AAD, the ratio of total to HDL cholesterol (total:HDL cholesterol) increased significantly on both the Step I and Step II diets. The percentage...
TABLE 4

Correlation coefficients between selected screening parameters and changes (Δ) in lipid endpoints.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>BMI</th>
<th>Waist diameter</th>
<th>Percentage body fat</th>
<th>Glucose</th>
<th>ln Insulin</th>
<th>ln HOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔTC Step I-AAD</td>
<td>0.19</td>
<td>0.14</td>
<td>0.19</td>
<td>0.21</td>
<td>0.22</td>
<td>0.23</td>
</tr>
<tr>
<td>ΔTC Step II-AAD</td>
<td>0.26</td>
<td>0.24</td>
<td>0.24</td>
<td>0.16</td>
<td>0.34</td>
<td>0.33</td>
</tr>
<tr>
<td>ΔLDL cholesterol Step I-AAD</td>
<td>0.15</td>
<td>0.14</td>
<td>0.16</td>
<td>0.25</td>
<td>0.21</td>
<td>0.23</td>
</tr>
<tr>
<td>ΔLDL cholesterol Step II-AAD</td>
<td>0.22</td>
<td>0.22</td>
<td>0.22</td>
<td>0.12</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>ΔHDL cholesterol Step I-AAD</td>
<td>0.07</td>
<td>0.07</td>
<td>0.12</td>
<td>0.03</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>ΔHDL cholesterol Step II-AAD</td>
<td>−0.02</td>
<td>0.03</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Δln Triacylglycerol Step I-AAD</td>
<td>0.11</td>
<td>−0.01</td>
<td>0.05</td>
<td>0.15</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>Δln Triacylglycerol Step II-AAD</td>
<td>0.19</td>
<td>0.13</td>
<td>0.11</td>
<td>0.22</td>
<td>0.22</td>
<td>0.23</td>
</tr>
<tr>
<td>Δln TC:HDL-C Step I-AAD</td>
<td>0.13</td>
<td>0.10</td>
<td>0.11</td>
<td>0.28</td>
<td>0.29</td>
<td>0.30</td>
</tr>
<tr>
<td>Δln TC:HDL-C Step II-AAD</td>
<td>0.29</td>
<td>0.26</td>
<td>0.28</td>
<td>0.20</td>
<td>0.32</td>
<td>0.32</td>
</tr>
</tbody>
</table>

1 n = 86 participants. HOMA, homeostasis model assessment; TC, total cholesterol; AAD, average American diet; HDL-C, HDL cholesterol.

2 P < 0.05.

3 P < 0.005.

4 P < 0.01.

Decreases in apoB on the Step I and Step II diets (4.1% and 7.2%, respectively) were less than those observed for LDL cholesterol. Similarly, the percentage decreases in apoA-I on the Step I and Step II diets (4.9% and 6.5%, respectively) were less than those observed for HDL cholesterol.

Effect of adiposity and markers of insulin resistance on lipid responses

Changes in TC, LDL cholesterol, and ln total:HDL cholesterol between the AAD and Step II diet were significantly and positively correlated (eg, smaller reductions) with BMI, waist diameter, percentage body fat, ln insulin, and ln HOMA values that were measured at screening (Table 4, Figure 1, and Figure 2). Similarly, changes in ln TC were significantly and positively correlated (eg, greater increases) with fasting glucose concentrations, ln insulin, and ln HOMA. Changes in TC, LDL cholesterol, and ln total:HDL cholesterol between the AAD and the Step I diet were also positively correlated with the indexes of adiposity and insulin resistance, but reached statistical significance with fewer indexes. However, changes in HDL cholesterol, apoB, and apoA-I were not correlated with these indexes in either of the dietary changes.

Measures of insulin resistance were highly correlated with measures of adiposity. We therefore simultaneously considered BMI, waist diameter, percentage body fat, glucose, ln insulin, and ln HOMA as potential predictor variables for changes in both LDL cholesterol and total:HDL cholesterol in a stepwise multiple regression model. Only ln insulin was entered into a model as a predictor for changes in both LDL cholesterol and total:HDL cholesterol (data not shown).

Finally, to assess the effect of these correlations on defined populations, we divided the study population in half based on BMI values that were measured at screening. The participants in the upper half of BMI (ie, BMI ≥ 25.3) averaged only 70% of the reduction in LDL cholesterol and had a significantly greater increase in total:HDL cholesterol with the Step II diet than did the participants in the lower half of BMI (Figure 3). The differences were even greater when we compared the upper and lower half of study population after dividing it by insulin concentrations that were measured at screening. The participants in the upper half of insulin concentrations (ie, insulin ≥ 6.8 μU/mL) averaged only 58% of the reduction in LDL cholesterol with the Step II diet.
compared with the participants in lower half of insulin concentrations (Figure 4). Furthermore, the participants in the upper half experienced an average increase in total:HDL cholesterol whereas this ratio was not significantly changed, on average, in the participants in the lower half.

**DISCUSSION**

The strength of this study lies in the high degree of control in providing the diets, in the multiple endpoint sampling, and in the power of the crossover design. The composition of all menus was verified by chemical analysis before their use. All meals, except for one weekend dinner, were prepared and provided to the participants. A continuous menu sampling protocol allowed us to examine changes in diet composition over time, which were relatively small (within 3%). Endpoint sampling each week during the final 3 wk of each diet period reduced the influence of within-subject variability. Finally, the crossover design maximized the statistical power of the study by allowing each participant to serve as his own control.

In these regards, this study is similar to the multicenter Dietary Effects on Lipoproteins and Thrombogenic Activities (DELTA) study (4), which also examined Step I and Step II diets against an AAD. However, in the DELTA study the cohorts were studied at the same time at 4 research centers, whereas in the present study the cohorts were studied at a single center but were spread out over time. Additionally, in contrast with the DELTA study, the present study examined men only and achieved reductions in saturated fat primarily through reductions in milkfat. Despite these differences, the changes in LDL cholesterol were almost identical in the 2 studies (DELTA: −0.24 mmol and −0.37 mmol; present study, −0.22 mmol and −0.38 mmol for Step I and Step II diets, respectively). Changes in HDL cholesterol were also similar between the studies.

On a percentage basis, the changes in apoB and apoA-I were less than those observed for LDL and HDL cholesterol. These observations are consistent with the generation of a greater proportion of small, dense LDL cholesterol and a greater proportion of HDL3 cholesterol relative to HDL2 cholesterol, as was previously reported with lower fat diets (16, 17). A direct measurement of HDL cholesterol particle size distribution confirmed these changes (18).

An analysis of potential anthropometric predictors of the risk factor response to diet showed significant correlations between the indexes of adiposity and changes in LDL cholesterol concentrations, but not with changes in HDL cholesterol or triacylglycerol concentrations. In our study, the men with a BMI ≥ 25.3 had 30% smaller reductions in LDL-cholesterol concentrations than did the men with a BMI < 25.3. We also observed the typical decrease in HDL-cholesterol concentrations that is associated with lower-fat diets. When combined with the smaller reduction in LDL-cholesterol concentrations, this translated into a significant increase in total:HDL cholesterol. Similar correlations were also observed with the percentage body fat and the waist-to-hip ratio, which is a measure of abdominal obesity.

An effect of BMI on the LDL-cholesterol response is consistent with data from dietary intervention and epidemiologic studies. Katan and Beynen (5) first reported that total cholesterol response to increases in dietary cholesterol was negatively correlated with BMI in women but not in men. In studies conducted in premenopausal women, Cole et al (6) found that women with a BMI between 24 and 30 had smaller reductions in LDL-cholesterol concentrations than did women with BMI < 24 when switched from a typical American diet to one lower in total fat, saturated fat, and cholesterol. Additionally, triacylglycerols increased the most in women with a BMI > 30. Additional studies conducted in both men and women and with diets of varying fatty acid composition have shown a positive correlation between BMI and LDL cholesterol (higher BMI, lower LDL cholesterol reduction) in response to reductions in dietary saturated fat (7–10).

In the Chicago Western Electric Study, the change in serum cholesterol concentrations in men who spontaneously changed their dietary cholesterol intake over a 1-y period was greater in leaner men (BMI < 24.1) than in fatter men (BMI > 26.7). In a linear regression analysis, the interaction between the change in dietary cholesterol and mean BMI was a significant predictor of serum cholesterol, with the absolute change in serum cholesterol decreasing with increasing BMI (19). Furthermore, the relation between dietary cholesterol intake and CVD mortality was only significant in lean subjects, when the subjects’ fat content was defined by skinfold thickness. Although the CVD relative risk was greater in the subjects who were fatter, no apparent relation was evident across tertiles of cholesterol intake in those persons (20).

Increased adiposity is associated with a worsening insulin sensitivity and is a major risk factor for the development of type 2 diabetes. In our study, indexes of insulin resistance were more strongly correlated with the LDL cholesterol response than were indexes of adiposity. Furthermore, indexes of insulin resistance also predicted greater increases in triacylglycerols that, when combined with smaller reductions in LDL cholesterol, resulted in
a significant difference in total:HDL cholesterol. A multivariate analysis confirmed that insulin resistance per se, rather than the associated increased adiposity, was the best predictor of the LDL-cholesterol response.

Many mechanisms have been proposed to account for the relation between both BMI and adiposity and the reduced LDL-cholesterol response to therapeutic diets. With a focus on the role of adipocytes in fatty acid metabolism, Denke (21) proposed that the high very-low-density lipoprotein concentrations seen with obesity lead to increased conversion of very-low-density lipoprotein to LDL cholesterol and thereby result in hypercholesterolemia. In obese patients, reducing saturated fat intake may not correct the overproduction of LDL cholesterol and therefore may reduce the responsiveness to dietary interventions. Additionally, dietary fatty acids may be diluted by a larger pool of endogenous fatty acids within the adipose tissue and thus buffer the effects of dietary fatty acids on the liver (18). With focus on the role of adipocytes in cholesterol metabolism, Hannah et al (8) proposed that the production and storage of cholesterol by adipocytes may help maintain high plasma cholesterol concentrations despite dietary changes. However, if differences in body fat were the key factor in determining the LDL-cholesterol responses to dietary changes, then, because of their generally higher bodyfat content, women would be expected to have consistently smaller reductions in LDL-cholesterol concentrations relative to men given the same dietary contrasts. However, significant sex differences in the LDL-cholesterol response have not been typically found in controlled dietary interventions (4).

Our data offer an alternative mechanism—that either insulin resistance or elevated insulin concentrations directly lead to metabolic changes in the hepatocyte that result in diminished responsiveness of the hepatic LDL-cholesterol receptor to changes in dietary fatty acids. We speculate that this occurs through a mechanism whereby elevated insulin concentrations directly increase hepatic cholesterol synthesis through activation of the liver X receptor (22). Secondary to the elevated endogenous production of cholesterol, hepatic LDL-cholesterol receptors would be expected to be down-regulated and therefore refractory to additional reductions in LDL cholesterol that are typically associated with dietary changes.

In support of this, it has long been known that cholesterol synthesis is increased with obesity (23, 24). In a recent study, insulin resistance, which was measured by hyperinsulinemic eu- and hyperglycemic clamp, was associated with increased cholesterol synthesis, as measured by plasma metabolites. The correlation with cholesterol synthesis was weakest for BMI, intermediate for whole body glucose uptake, and strongest for fasting insulin concentrations, which is supportive of a direct role for insulin in the regulation of cholesterol synthesis (25). A link between diet responsiveness and cholesterol synthesis was established by Katan (5), who showed that persons with low absolute cholesterol synthetic rates were the most responsive to dietary cholesterol changes and, conversely, persons with high absolute cholesterol synthetic rates were the least responsive to dietary cholesterol changes.

Being overweight and the associated insulin resistance that can lead to the metabolic syndrome is a growing health problem. Only 7% of our study population met the criteria for having metabolic syndrome as defined by National Cholesterol Education Program (26). Nonetheless, the participants who were overweight or who had higher insulin concentrations had altered metabolic responses to lower fat diets. Thus, the effects of elevated insulin concentrations on the LDL-cholesterol and triacylglycerol responses preceded the development of overt metabolic syndrome. It is not known if weight loss alone is sufficient to reverse the observed diminished LDL-cholesterol response to a dietary intervention. Reduced dietary responsiveness may be an integral metabolic feature for persons who are predisposed to weight gain and to the development of insulin resistance. If it can be experimentally established that weight reduction can restore diet responsiveness, this would provide a strong rationale for dietary recommendations that include both weight reduction and changes in dietary composition (ie, reduced saturated fat, trans fatty acids, and cholesterol) to maximally reduce CVD risk.

In conclusion, insulin resistance and elevated insulin concentrations are associated with a diminished LDL-cholesterol reduction and an increased triacylglycerol elevation, which culminate in an increase in total:HDL cholesterol in response to reductions in dietary total fat, saturated fat, and cholesterol. Thus, persons who may already be at increased risk of CVD because of their underlying insulin resistance, and thus who are prime candidates for dietary intervention, may be less likely to benefit from dietary changes. The data suggest that even in the absence of overt metabolic syndrome, weight reduction may be required to fully derive the benefit of dietary changes on CVD risk.

We acknowledge Beth Foust and the staff of the Pennington Metabolic Kitchen for their ability to reliably prepare and deliver diets over the 2-y course of this study and Susan Mancuso for providing the day-to-day oversight of the study.

ML was responsible for the conception and design of the study, providing oversight of the conduct of the overall study, interpreting the data, and drafting the manuscript. CMC participated in developing the study menus and providing estimates of nutrient composition. RTT and ICR were responsible for acquisition of the data, including clinical laboratory assays and food chemistry analysis. MMM participated in the design of the study as it pertained to dietary preparation and provision, participated in the development of the study menus, and was responsible for implementing the dietary protocol. Additionally, all the coauthors participated in critically important ways to the interpretation of the data and to the development of the manuscript. None of the authors had any conflicts of interest.

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