

**Citation:**

Lefevre M, Champagne CM, Tulley RT, Rood JC, Most MM. 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. *Am J Clin Nutr*. 2005 Nov; 82(5): 957-693.

**PubMed ID:** [16280425](#)

**Study Design:**

Non-Randomized Crossover Trial

**Class:**

C - [Click here](#) for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

- To examine the relationship between the indexes of adiposity and insulin resistance and the magnitude of lipid response in healthy men when diets were reduced in total and saturated fat
- To examine the effects on plasma lipids of three diets that differed in total fat, 86 free-living, healthy men, aged 22 to 64 years, were fed one of three diets for six weeks each at levels designed to maintain weight. The diets included:
  - The average American diet (AAD) [(38% of energy was total fat and 14% saturated fatty acids (SFA)]
  - The Step I diet (30% fat with 9% SFA)
  - The Step II diet (25% fat with 6% SFA)

**Inclusion Criteria:**

The participants were selected to have an LDL-cholesterol concentration between the 10th and 90th percentiles, an HDL-cholesterol concentration higher than 25mg per dL and below the 95th percentile and a triacylglycerol concentration below the 95th percentile.

**Exclusion Criteria:**

- Upper BMI limit of 34kg/m<sup>2</sup>
- Evidence of cardiovascular, renal, hepatic, endocrine, gastrointestinal or other systemic disease as assessed by blood chemistry, urinalysis, medical questionnaire and physical exam
- Drug or alcohol abuse
- Extreme dietary habits
- Multiple food allergies
- Extreme levels of physical or athletic activity.

## Description of Study Protocol:

### Recruitment

- 121 men aged 22 to 64 years were recruited
- Participants were recruited in a series of sequential, partially overlapping cohorts (seven total), which varied in size from eight to 26 participants per cohort
- The length of time between the start of cohort one and the end of cohort seven was 26 months
- A total of 87 participants completed all three diet periods.

### Design

The study was a randomized, double-blinded, three-period crossover design.

### Dietary Intake/Dietary Assessment Methodology

- Each participant was fed three diets that differed in total fat and SFA, with each dietary period being six weeks in length:
  - An AAD, which was designed to contain 38% of energy as fat and 14% of energy as saturated fat
  - The Step I diet, which was designed to contain 30% of energy as fat and 9% of energy as saturated fat
  - The Step II diet, which was designed to contain 25% of energy as fat and 6% of energy as saturated fat
- A break (one to six weeks) was provided between each of the dietary periods.

### Blinding Used

Double-blind.

### Intervention

- 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
- 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 four energy levels (9.2, 10.9, 12.6 and 14.2mJ per day)
- Unit foods that were similar in macronutrient composition to the assigned diet and were 418kJ (100kcal) each were used for energy adjustments
- The participants were started on the energy level that most closely matched their estimated energy requirement.

### Statistical Analysis

- Descriptive statistics (scatterplot, mean, SD and SEM) were examined, and, if required, the data were log (ln) 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 with  $R^2$  selection was subsequently performed to determine the optimum model to predict changes in selected endpoints.

## Data Collection Summary:

### Timing of Measurements

- Blood sampling was performed at the end of weeks four, five and six of each dietary period
- Venous blood samples were collected between 6:00 a.m. and 9:00 a.m. after the subjects had fasted for 12 hours.

### Dependent Variables

Variables: Brief description of measurements include:

- Serum lipid and glucose concentrations were analyzed with a Beckman-Coulter Synchron CX7 (Brea, CA)
- Serum cholesterol concentrations were assayed with the cholesterol esteraseoxidase-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 50,000mol wt dextran sulfate (DMA, Arlington, TX)
- LDL-cholesterol concentrations were calculated with the Friedewald equation
- Glucose concentrations were measured with the glucose oxidase method
- ApoA-I and apoB were assayed by an automated immunoturbidometric assay (Wako, Inc, Richmond, VA)
- Insulin concentrations were measured with a microparticle enzyme immunoassay on an Abbott IMx analyzer (Abbott Park, IL).

### Independent Variables

Composite food samples were analyzed for protein, fat, moisture, ash, carbohydrate, fatty acid and cholesterol content.

## Description of Actual Data Sample:

- *Initial N*: 121 men; 87 men finished all three diet periods
- *Attrition (final N)*: 87
- *Age*: 22 to 64 years; average 37.5 years
- *Ethnicity*: 84% white, 11% African American
- *Other relevant demographics*: 7% of the participants were active cigarette smokers
- *Anthropometrics*:
  - 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 to 39 years and ranged between the 35th percentile (for HDL-cholesterol) and the 45th percentile (for LDL-cholesterol).
- *Location:* Louisiana US.

## Summary of Results:

### Effect of Diets on Lipid and Lipoprotein Concentrations<sup>1</sup>

	AAD	Step I Diet	Step II Diet
<b>Total cholesterol (mmol per L)</b>	4.82 ± 0.69	4.59±0.6 <sup>2</sup>	4.39±0.66 <sup>2,3</sup>
<b>Triacylglycerol (mmol per L)<sup>4</sup></b>	1.06±0.65	1.20±0.76 <sup>2</sup>	1.22±0.80 <sup>2,3</sup>
<b>LDL-cholesterol (mmol per L)</b>	3.25±0.58	3.03±0.56 <sup>2</sup>	2.87±0.52 <sup>2,3</sup>
<b>HDL-cholesterol (mmol per L)</b>	1.07±0.23	0.99±0.22 <sup>2</sup>	0.95±0.22 <sup>2,3</sup>
<b>Apolipoprotein A-1 (g per L)</b>	1.23±0.14	1.17±0.13 <sup>2</sup>	1.15±0.12 <sup>2,3</sup>
<b>Apolipoprotein B (g per L)</b>	0.97±0.19	0.93±0.20 <sup>2</sup>	0.90±0.18 <sup>2,3</sup>
<b>Total:HDL-cholesterol</b>	4.70±1.08	4.84±1.18 <sup>2</sup>	4.85±1.26 <sup>2,3</sup>

<sup>1</sup> All values are  $x \pm SD$ ; N=86; AAD, average American diet.

<sup>2</sup> Significantly different from AAD,  $P < 0.05$  (ANOVA with Bonferroni corrections).

<sup>3</sup> Significantly different from Step I diet,  $P < 0.05$  (ANOVA with Bonferroni corrections).

<sup>4</sup> Values were log transformed before statistical analyses.

- Compared with the AAD, the Step I and Step II diets lowered LDL-cholesterol, lowered HDL-cholesterol and raised triacylglycerols
- The Step II diet response showed significant positive correlations between changes in both LDL-cholesterol and the ratio of total:HDL cholesterol and baseline percentage body fat, BMI and insulin
- Sub-division 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.

### Correlation Coefficients Between Selected Screening Parameters and Changes in Lipid Endpoints

Endpoint	BMI	Waist Diameter	Percentage Body Fat	Glucose	In Insulin	In HOMA
<b>Δ TC</b>						
Step I-AAD	0.19	0.14	0.19	0.21	0.22 <sup>2</sup>	0.23 <sup>2</sup>
Step II-AAD	0.26 <sup>2</sup>	0.24 <sup>2</sup>	0.24 <sup>2</sup>	0.16	0.34 <sup>3</sup>	0.33 <sup>3</sup>
<b>Δ LDL-cholesterol</b>						

Step I-AAD	0.15	0.14	0.16	0.25 <sup>2</sup>	0.21	0.23 <sup>2</sup>
Step II-AAD	0.22 <sup>2</sup>	0.22 <sup>2</sup>	0.22 <sup>2</sup>	0.12	0.26 <sup>2</sup>	0.26 <sup>2</sup>
<b>Δ HDL-cholesterol</b>						
Step I-AAD	0.07	0.07	0.12	0.03	0.00	0.01
Step II-AAD	-0.02	0.03	0.01	0.02	0.02	0.02
<b>Δ In Triacylglycerol</b>						
Step I-AAD	0.11	-0.01	0.05	0.15	0.15	0.15
Step II-AAD	0.19	0.13	0.11	0.22 <sup>2</sup>	0.22 <sup>2</sup>	0.23 <sup>2</sup>
<b>Δ In TC:HDL-C</b>						
Step I-AAD	0.13	0.10	0.11	0.28 <sup>4</sup>	0.29 <sup>4</sup>	0.30 <sup>3</sup>
Step II-AAD	0.29 <sup>4</sup>	0.26 <sup>2</sup>	0.28 <sup>4</sup>	0.20	0.20	0.32 <sup>3</sup>

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

<sup>2</sup>P<0.05.

<sup>3</sup>P<0.005.

<sup>4</sup>P<0.01.

#### **Author Conclusion:**

Persons who are insulin resistant respond less favorably to Step II diets than do those who are insulin sensitive.

#### **Reviewer Comments:**

*None.*

#### **Research Design and Implementation Criteria Checklist: Primary Research**

#### **Relevance Questions**

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

### Validity Questions

<b>1.</b>	<b>Was the research question clearly stated?</b>	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
<b>2.</b>	<b>Was the selection of study subjects/patients free from bias?</b>	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
<b>3.</b>	<b>Were study groups comparable?</b>	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes

3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
<b>4.</b>	<b>Was method of handling withdrawals described?</b>	<b>Yes</b>
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
<b>5.</b>	<b>Was blinding used to prevent introduction of bias?</b>	<b>Yes</b>
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
<b>6.</b>	<b>Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?</b>	<b>Yes</b>
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes

6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
<b>7.</b>	<b>Were outcomes clearly defined and the measurements valid and reliable?</b>	<b>Yes</b>
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
<b>8.</b>	<b>Was the statistical analysis appropriate for the study design and type of outcome indicators?</b>	<b>Yes</b>
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	Yes
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
<b>9.</b>	<b>Are conclusions supported by results with biases and limitations taken into consideration?</b>	<b>Yes</b>
9.1.	Is there a discussion of findings?	Yes

9.2.	Are biases and study limitations identified and discussed?	???
<b>10.</b>	<b>Is bias due to study's funding or sponsorship unlikely?</b>	<b>Yes</b>
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes