

Citation:

Katcher HI, Legro RS, Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, Kris-Etherton PM. The effects of a whole grain-enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. *Am J Clin Nutr.* 2008; 87: 79-90.

PubMed ID: [18175740](#)

Study Design:

Randomized Controlled Trial

Class:

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

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine whether including whole-grain foods in a hypocaloric (reduced by 500kcal per day) diet enhances weight loss and improves cardiovascular disease (CVD) risk factors.

Inclusion Criteria:

Obese adults (men and women) with metabolic syndrome were eligible if they:

- Had a body mass index (BMI; in kg/m²) of 30 or more
- Met three or more of five National Cholesterol Education Program Adult Treatment Panel III criteria for metabolic syndrome. These criteria were defined as:
 - Triacylglycerol concentrations 150mg per dL or more
 - HDL-cholesterol concentrations less than 40mg per dL in men or less than 50mg per dL in women
 - Fasting glucose concentrations of 100mg per dL or more
 - Systolic blood pressure (SBP) of 130mmHg or more or diastolic blood pressure (DBP) of 85mmHg or more (or both)
 - Waist circumference of 102cm or more in men or 88cm or more in women
- Gave written informed consent.

Exclusion Criteria:

Participants were excluded if they:

- Had been diagnosed with type 1 or type 2 diabetes, CVD, cancer or any other serious medical condition
- Were using any medications known to affect glucose, insulin, cholesterol or reproductive hormones
- Smoked

- Drank more than two alcoholic beverages per day
- Consumed a diet high in whole grains (more than three servings per day)
- Were pregnant or lactating.

Description of Study Protocol:

Recruitment

The study opened to accrual in September 2005 and completed enrollment in August 2006.

Design

Randomized [stratified by sex and BMI status (BMI less than 40 or 40kg/m² or more)], parallel-arm, free-living study design.

Blinding Used

Open-label (no blinding).

Intervention

- Participants were assigned to either a whole-grain or refined-grain hypocaloric diet
- Both groups:
 - Individually met with a registered dietician at baseline to discuss the dietary intervention and were provided educational materials to facilitate understanding and adherence
 - Were given dietary advice for weight loss including calculation of energy needs (using the Mifflin equation with an activity factor of 1.3, and subtracting 500kcal to account for the calorie deficit needed to achieve weight loss)
 - Participants in both groups were asked to eat, daily, five servings of fruit and vegetables, three servings of low-fat dairy products and two servings of lean meat, fish or poultry, as recommended in the 2005 dietary guidelines for Americans [target macronutrient composition for all participants was 55% of energy as carbohydrate, 30% of energy as fat (with an emphasis on unsaturated fats) and 15% of energy as protein]
 - All participants were encouraged to engage in moderate physical activity for 30 minutes per session three or more times per week and were instructed to avoid dietary supplements throughout the study period
 - Participants in both groups were told that their aim was to lose one or more pounds per week during the study
 - During every other week of follow-up, participants visited the study site and reviewed their diet records with a dietitian on a one-on-one basis and received an educational lesson that explained the rationale for the dietary guidelines used in the study and offered nutritional guidance, encouragement and suggestions for improvement
 - On the weeks that participants did not come in for a study visit, a dietitian contacted them by telephone or e-mail to discuss their progress and address any concerns or questions
- Whole-grain group:
 - Were given a target number of daily whole-grain servings (four, five, six or seven servings per day) based on the number of grain servings recommended in the 2005 dietary guidelines for Americans for their energy needs
 - Participants were advised to consume three daily servings of whole-grain foods for the

first two weeks of the study and then to increase to their target number of daily whole-grain servings for the remaining 10 weeks

- Participants in this group were given a list and description of whole-grain foods to help them identify foods to include in their diet, and they were encouraged to select foods for which a whole grain is listed as the first ingredient
- Refined-grain group: Participants in the refined-grain group also were given a list of whole-grain foods and were asked not to consume any of these foods during the study period.

Statistical Analysis

- Two-sample T-tests were used to test for differences between the diet groups in subjects' characteristics measured at baseline
- Linear mixed-effects models were fitted to assess the effects of the two hypocaloric diet groups over the course of the 12-week study on biometric, biochemical, dietary intake and diet satisfaction values (if necessary to meet modeling assumptions such as normality, the outcome variable was logarithmically transformed)
- Data were analyzed according to the intention-to-treat principle, and all hypotheses tests were two-sided.

Data Collection Summary:

Timing of Measurements

Weight, blood pressure, and waist circumference were recorded at each visit (every other week). A fasting blood draw, two-hour oral-glucose tolerance test (OGTT), dual energy X-ray absorptiometry (DEXA) scan, and biometric measurements were done at the beginning and end of the 12-week diet period. Diet satisfaction ratings at baseline, weeks four and 12. A detailed three-day diet record at baseline and every four-weeks.

Dependent Variables

- Biometric measures (systolic and diastolic blood pressures, waist circumference, total body fat, abdominal body fat)
- Serum lipids (total, LDL and sub-fractions, HDL, triglycerides, total:HDL ratio, apolipoproteins A-I and B)
- Glycemic measures (fasting glucose, fasting insulin, two-hour glucose, two-hour insulin, area-under-the-curve glucose, insulin sensitivity index)
- Inflammatory/fibrinolysis measures (C-reactive protein, interleukin-6, plasminogen activator inhibitor-1, tumor necrosis factor-alpha)
- Dietary intake (energy, carbohydrates, protein, total fat, saturated fat, MUFA, PUFA, cholesterol, total fiber, soluble fiber, insoluble fiber, magnesium, vitamin B₆, added sugar)
- Diet satisfaction ratings (sense of healthy lifestyle, convenience, cost, family dynamics, pre-occupation with food, presence of negative feelings, ease of meal planning and preparation, overall score).

Independent Variables

- Whole-grain diet
- Refined-grain diet.

Description of Actual Data Sample:

- *Initial N*: 50 (25 male, 25 female)
- *Attrition (final N)*: 47 (two withdrew from refined-grain and one from the whole-grain group)
- *Age*: Range of 24 to 63 years
 - Mean age whole-grain was 45±8
 - Mean refined-grain was 47±10
- *Ethnicity*: 48 of 50 were white, with one African-American and one Hispanic
- *Other relevant demographics*:
 - Mean BMI in the whole-grain group was 36±4; mean refined-grain was 36±5
 - Mean weight (kg) in whole-grain group was 103±14; mean refined-grain was 106±16
- *Anthropometrics*: Similar for all covariates at baseline except SBP and LDL-III subclass, which were significantly higher in the refined-grain group (P=0.03)
- *Location*: United States.

Summary of Results:

Measurement	WG 12-week Delta	RG 12-week Delta	P-value (Group)	P-value (Time)
Weight (kg)	-3.7±3.5	-5.3±5.2	0.58	<0.001
Systolic BP (mmHg)	-2.6±7.9	-6.7±8.5	0.29	0.06
Diastolic BP (mmHg)	-2.5±7.0	-3.1±5.9	0.56	0.25
Waist circumference (cm)	-2.5±3.7	-4.7±6.4	0.85	<0.001
Total body fat (%)	-1.2±1.3	-1.0±1.6	0.94	<0.001
Abdominal body fat (%)	-2.2±2.2	-0.9±1.8	0.03 group x time	
Total cholesterol (mg per dL)	-10.8±18.0	-5.8±17.4	0.96	0.003
LDL (mg per dL)	-8.1±15.3	-3.4±15.8	0.81	0.01
HDL (mg per dL)	-1.9±3.6	-0.5±3.2	1.00	0.03
Triglycerides (mg per dL)	-3.8±37.2	-8.9±60.8	0.23	0.45
Total:HDL ratio	-0.1±0.6	-0.1±0.7	0.86	0.21
Apolipoprotein A-I (mg per dL)	-3.6±11.2	-5.7±9.1	0.60	0.003
Apolipoprotein B (mg per dL)	-2.6±9.5	-2.8±11.6	0.82	0.09
Fasting glucose (mg per dL)	-1.3±4.7	-1.5±6.6	0.79	0.10

Fasting insulin (uU per ml)	-0.7±4.7	-2.0±5.9	0.46	0.05
Two-hour glucose (mg per dL)	-4.0±32.6	-3.2±30.5	0.99	0.05
Two-hour insulin (uU per ml)	-17.3±48.8	-11.6±56.2	0.95	0.10
AUC glucose	-648±2,328	-423±2,781	0.91	0.18
AUC insulin	-1,496±3,797	-1,145±4,900	0.75	0.03
ISI	0.6±1.3	0.5±1.7	0.90	0.03
CRP (mg per L)	-2.4±5.1	0.2±2.9	0.01 group x time	
PAI-I (ng per ml)	-2.0±7.3	-7.1±8.4	0.80	<0.001
IL-6 (pg per ml)	-0.9±3.6	-0.1±0.4	0.94	0.57
TNF-alpha (pg per ml)	-0.04±0.3	0.1±0.2	0.04	0.80

Other Findings

- Participants in the whole-grain group increased their intake of whole-grain foods to approximately five servings per day, whereas participants in the refined-grain group decreased their intake to less than 0.2 servings per day
- CRP decreased in 18 (75%) of 24 participants who completed the study in the whole-grain group but in only 12 (52%) of 23 who completed the study in the refined-grain group. In a comparison of only the participants who had a reduction in CRP, the average percentage decrease in CRP was 45% in the whole-grain group and 26% in the refined-grain group ($P<0.01$). Although CRP was significantly correlated with BMI at baseline ($R=0.46$, $P<0.001$), the change in CRP did not correlate significantly with weight loss ($R=-0.07$, $P=0.66$)
- Energy intake decreased significantly ($P<0.001$) from baseline in both diet groups. However, on average, participants in the refined-grain group had a non-significantly (NS) greater decrease in energy intake
- The percentage of energy from carbohydrate and protein increased significantly ($P<0.01$) and that from fat decreased significantly ($P<0.001$) in both diet groups compared with baseline
- Participants in the whole-grain group increased their intake of total, insoluble and soluble fiber by 50%, 52% and 47%, respectively, and those in the refined-grain group increased their intakes by 7%, 5% and 14%, respectively. Magnesium intake also was significantly ($P<0.001$) higher throughout the study period in the whole-grain group than in the refined-grain group
- At week 12, participants in both groups had a significantly greater overall satisfaction with their diet, rated a significantly greater sense of having a healthy lifestyle, had a significantly lower pre-occupation with food ($P<0.001$ for all), and considered their families to be significantly ($P<0.001$) more approving of their diet than at baseline
- Participants in only the whole-grain group rated their meal planning and preparation as more difficult than at baseline ($P=0.04$ for group-times-time interaction).

Author Conclusion:

- Both hypocaloric diets were effective means of improving CVD risk factors with moderate weight loss
- There were significantly ($P < 0.05$) greater decreases in CRP and percentage body fat in the abdominal region in participants consuming whole grains than in those consuming refined grains.

Reviewer Comments:

- *This study had a high completion and compliance rate, which suggests that both diets were well tolerated. May also be due to diligent monitoring and calling patients in between follow-up visits*
- *A strength of the present study is that it was conducted in a free-living population with metabolic syndrome, so that the results easily translate to persons at risk of CVD who want to include whole grains in their diet with the goal of losing weight*
- *A limitation, however, is that other behavioral changes in exercise and diet may account for the effects that we observed*
- *The present study had a small sample size and duration, which gave little power to detect differences between groups in secondary outcomes*
- *Funding: Supported by the General Mills Bell Institute of Health and Human Nutrition, grants no. K24 HD01476 and M01 RR10732 from the National Institutes of Health, and construction grant no. C06 RR016499 (to the General Clinical Research Center of The Pennsylvania State University).*

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

- | | | |
|----|---|-----|
| 1. | Was the research question clearly stated? | 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
2.	Was the selection of study subjects/patients free from bias?	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
3.	Were study groups comparable?	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?	N/A
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
4.	Was method of handling withdrawals described?	Yes
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%.)	N/A

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
5.	Was blinding used to prevent introduction of bias?	No
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	No
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?	N/A
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
6.	Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	Yes
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?	No
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
7.	Were outcomes clearly defined and the measurements valid and reliable?	Yes
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?	???
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes
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?	No
8.7.	If negative findings, was a power calculation reported to address type 2 error?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration?	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	Is bias due to study's funding or sponsorship unlikely?	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes