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A low-fat dietary pattern and risk of metabolic syndrome in postmenopausal women: The Women's Health Initiative

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Abstract

Objective—Nutrition plays an important role in metabolic syndrome etiology. We examined whether the Women's Health Initiative (WHI) Dietary Modification Trial influenced metabolic syndrome risk.

Materials/Methods—48,835 postmenopausal women aged 50–79 years were randomized to a low-fat (20% energy from fat) diet (intervention) or usual diet (comparison) for a mean of 8.1 years. Blood pressure, waist circumference and fasting blood measures of glucose, HDL-cholesterol and triglycerides were measured on a subsample (n= 2816) at baseline and years 1, 3 and 6 post-randomization. Logistic regression estimated associations of the intervention with metabolic syndrome risk and use of cholesterol-lowering and hypertension medications. Multivariate linear regression tested associations between the intervention and metabolic syndrome components.

Results—At year 3, but not years 1 or 6, women in the intervention group (vs. comparison) had a non-statistically significant lower risk of metabolic syndrome (OR=0.83, 95% CI 0.59–1.18). Linear regression models simultaneously modeling the five metabolic syndrome components

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revealed significant associations of the intervention with metabolic syndrome at year 1 ($p<0.0001$), but not years 3 ($p=0.19$) and 6 ($p=0.17$). Analyses restricted to intervention-adherent participants strengthened associations at years 3 ($p=0.05$) and 6 ($p=0.06$). Cholesterol-lowering and hypertension medication use was 19% lower at year 1 for intervention vs. comparison group women (OR=0.81, 95% CI 0.60–1.09). Over the entire trial, fewer intervention vs. comparison participants used these medications (26.0% vs. 29.9%), although results were not statistically significant ($p=0.89$).

Conclusions—The WHI low-fat diet may influence metabolic syndrome risk and decrease use of hypertension and cholesterol-lowering medications. Findings have potential for meaningful clinical translation.

Keywords

clinical trials; aging; dietary fat; metabolic syndrome

INTRODUCTION

Metabolic syndrome is a distinct clinical entity (ICD-9 code 277.7) that is associated with insulin resistance, obesity, poor diet and physical inactivity. Data from NHANES (National Health and Nutrition Examination Survey) suggest that 34% of all US adults meet the criteria for metabolic syndrome and the prevalence is six times greater in women over the age of 60 compared to younger women. Metabolic syndrome components include dyslipidemia, elevated glucose, central (abdominal) obesity and elevated blood pressure. This syndrome, thought to be in large part a consequence of obesity and insulin resistance, reflects an underlying pathology that increases the risk of cardiovascular disease, diabetes, cancer and other chronic diseases. As such, metabolic syndrome is an intermediate phenotype on the pathway to the clinical detection of these age and obesity-related chronic diseases. Thus, prevention or early intervention for reversal of metabolic syndrome would likely reduce the incidence of these common diseases.

Lifestyle behaviors, including diet and physical activity, may play an important role in the etiology and prevention of metabolic syndrome. Observational studies have consistently shown inverse associations of whole grains and fruit and vegetable intake as well as Mediterranean type diets with risk of metabolic syndrome and positive associations of Western-type (high-fat, high-refined carbohydrate) dietary patterns and risk of high serum triglycerides, low HDL and frank metabolic syndrome. There are no data on the effects of long-term controlled dietary intervention trials on the risk of metabolic syndrome. The Women's Health Initiative Dietary Modification Trial (WHI-DM) was a randomized, controlled trial testing whether a low-fat dietary pattern (20% of energy from fat/day, ≥ five servings of fruit and vegetables/day and ≥ six servings of grains/day) would reduce the incidence of breast and colon cancer (primary outcomes) and coronary heart disease (secondary outcome). This report from the WHI-DM examines whether the low-fat dietary pattern influenced the risk of metabolic syndrome.

METHODS

Overview of the Women's Health Initiative Dietary Modification Trial

Details of the WHI-DM design, recruitment methods and primary outcomes have been published elsewhere. Briefly, 48,835 women between the ages of 50 and 79 years, were enrolled between 1993 and 1998 at 40 clinical centers across the United States and were randomly assigned to a low-fat dietary pattern (intervention group) (40%, n = 19,541) or a usual diet (comparison group) (60%, n = 29,294). Eligibility criteria included being

postmenopausal, and consuming a diet at baseline with fat intake ≥ 32% of total energy as fat, as evaluated by a food frequency questionnaire (FFQ) designed and validated specifically for use in WHI. Major exclusions for the dietary intervention included any prior breast cancer or colorectal cancer, or other cancers except non-melanoma skin cancer in the last 10 years, mental illness that would preclude participation, medical conditions with predicted survival less than 3 years, history of alcoholism, or a baseline dietary fat intake < 32.0% energy from fat. The protocol and consent forms were approved by the Institutional Review Boards at the Fred Hutchinson Cancer Research Center (Clinical Coordinating Center) and all 40 clinical centers. All women provided written, informed consent. The trial is registered at clinicaltrials.gov as NCT00000611.

The WHI Dietary Intervention

The goals of the WHI-DM trial were to reduce total fat to ≤ 20% of daily energy intake, and increase intake of vegetables and fruit to five or more servings daily and grains to six or more servings daily. This intervention goal of <20% energy from fat was based on data from the WHI feasibility study as well as published observational and small-scale intervention studies demonstrating that a fat intake of this level reduces intermediate endpoints (i.e., serum estradiol) and lowers breast cancer risk. The intervention targeted total fat as a % of energy goal, but there were no specific recommendations given to participants regarding percent of energy from saturated fat or unsaturated fat. The WHI feasibility research showed that by instructing participants to lower fat intake, saturated fat intake was also reduced (18, 31, 29, 30). Women were encouraged to maintain their current weight and physical activity levels in the following manner. During screening, women were advised that the low-fat dietary intervention was not designed to be a weight loss program and if their motivation to join the study was for weight loss that they may not be appropriate candidates and they may be ineligible. This concept was reviewed and discussed periodically with intervention-arm participants throughout the intervention and maintenance sessions, although women (in either intervention or usual diet comparison) were not prevented from following a weight loss program.

The WHI-DM dietary intervention group received intensive nutritional and behavioral modification training consisting of 18 group sessions (8–15 participants per group) and one individual session in the first year followed by quarterly refresher sessions throughout the trial. The program was standardized across WHI and delivered by Registered Dietitians. During group sessions, food and behavioral skills, which were based on the principles of self-efficacy, social support and cognitive behavioral change, were presented and accompanied by discussion, practice and home assignments. Participants self-monitored their food intake throughout the intervention. If a participant missed a group or individual session, make-ups were offered by allowing attendance at another group or by giving the instruction by phone by a Registered Dietitian. Each intervention arm participant received an individualized total fat gram goal (20% of the individual's estimated energy requirement) along with the fruit and vegetable goals. Self-monitoring techniques and group session attendance were emphasized to promote achievement and maintenance of these intervention goals. Group activities were supplemented during the intervention by an intensive intervention protocol consisting of three individual interviews that used validated reflective listening techniques, targeted message campaigns and personalized feedback. Individual contacts were completed by telephone or mail for women who could not attend the sessions. DM intervention and maintenance activities continued throughout the average 8.1 year follow-up period, which concluded as planned on March 31, 2005.

Participants in the usual diet group received a copy of the Dietary Guidelines for Americans as well as other health-related materials, but had no contact with the nutrition interventionists and were not asked to self-monitor or make specific dietary changes. Over

the course of the follow-up period, 4.7% of women in the intervention group and 3.9% in the control group withdrew, were considered lost to follow-up, or had stopped providing outcome information for more than 18 months. This report is restricted to the WHI-DM blood draw subsample cohort (5.8% of total). This subsample had repeated measures of the relevant blood analytes, blood pressure and waist circumference.

Dietary Monitoring and Study Adherence

Dietary intake for both the intervention and comparison groups was monitored primarily by the WHI FFQ. This FFQ was administered at baseline and 1 year post-randomization to all WHI-DM participants and thereafter to one-third of participants annually in a rotating sample. Intervention vs. comparison group nutrient intake was monitored and compared throughout the trial using this FFQ. To monitor attendance at intervention sessions, study staff collected data on the number of sessions attended and the number of self-monitoring records submitted by participants as markers of program participation. Participants could make up missed intervention sessions by completing in-person, phone, or written contacts.

Other Data Collection/Clinic Visits

WHI-DM participants completed three pre-randomization screening visits during which baseline information was obtained; annual clinic visits were completed thereafter until the end of the trial. All WHI-DM participants completed baseline height and baseline and annual weight assessments and an annual current medications inventory while the participants in the blood draw subsample cohort also completed blood pressure and waist circumference measures at baseline and years 1, 3, 6 and 9. Height was measured while the participant was without shoes using a wall-mounted stadiometer to the nearest one-tenth cm using a standardized protocol. Following removal of heavy clothing and pocket contents, weight was measured to the nearest one-tenth kg with a calibrated balance beam or digital scale. Blood pressure was measured using a standard stethoscope and mercury manometer. After a five-minute rest, two blood pressure measurements were taken and recorded in mm Hg to the nearest even digit; the mean of the two measures was used in analysis. After removing all but non-binding garments, a fiberglass, retractable tape was used to measure the natural waist (narrowest part of the torso) to the nearest one-half cm at end-breath expiration.

Blood Collection, Processing and Analysis

Fasting (≥ 12 hours) blood specimens were collected on all WHI-DM participants at baseline and on the 5.8% subsample of participants, which was enriched for minority participants, at years 1, 3, 6 and 9. This report does not include data from the year 9 blood draw due to few available data points. All blood was processed within one hour of collection and stored at −70°C at a central biorepository (Fisher BioServices) until analysis. Glucose, triglycerides and HDL cholesterol were among the 20 core blood analytes measured in all blood cohort members at each time point (baseline, years 3, 6 and 9). Serum glucose was measured using the hexokinase method on the Hitachi 747 (Boehringer Mannheim Diagnostics). Triglycerides were measured by enzymatic methods on the Hitachi 747 analyser using EDTA plasma. HDL cholesterol was measured in EDTA plasma by manganese sulfate precipitation. The laboratory coefficients of variation were 1.7%, 2.1% and 1.4% for glucose, HDL-cholesterol and triglycerides, respectively.

Metabolic Syndrome

We used the definition of metabolic syndrome established by the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III); however, other slight variations for the definition also exist with the biggest difference being the waist

circumference cutpoints. Metabolic syndrome includes any three or more of the following: (1) waist circumference > 88.0 cm; (2) serum triglycerides ≥ 1.7 mmol/L; (3) blood pressure ≥ 130/85 mm Hg; (4) HDL cholesterol < 1.3 mmol/L; (5) serum glucose ≥ 5.5 mmol/L. For this report, metabolic syndrome was assessed at baseline and each follow-up time point that included a blood draw, blood pressure measurement and waist circumference measurement.

Statistical Analysis

Participants were included in this analysis if they were enrolled in the WHI-DM and were part of the blood sample cohort at baseline and years 1, 3 and 6. Descriptive statistics were used to characterize the study sample, including the five individual components of the metabolic syndrome. Participants with metabolic syndrome at baseline were excluded from further analyses. The t-test was used to compare continuous variables and the chi-square test was used for categorical variables. We used two approaches to examine associations of the WHI-DM and risk of metabolic syndrome. We first used unconditional logistic regression to estimate the odds ratios and 95% confidence intervals for risk of metabolic syndrome (as a binary outcome). We next constructed a multivariate linear regression model using general estimating equations (GEE) where the outcome was the five components of the metabolic syndrome modeled simultaneously in continuous scales. The advantage of this approach is that the continuous scale maximizes power in this relatively small sub-cohort while modeling the metabolic syndrome components as a single dependent variable. We modeled the 1, 3 and 6 year follow-up time points plus a time dependent approach that modeled years 1–6 incorporating data from all time points. Since this sub-sample of the WHI-DM was not a random sample of the entire trial population these models were adjusted for age, race/ethnicity, history of diabetes, recreational physical activity and use of hypertension or cholesterol-lowering medications at baseline. We examined the intervention effect with and without inclusion of women with self-reported diabetes (n=66); since there were no apparent differences in the associations, diabetics remained in the model. The p-values for the models represent the test for the overall intervention effect on metabolic syndrome. These models were repeated, restricting to those women who were adherent to the protocol based on number of number of attended sessions, as described above. Finally, we were interested in whether the low-fat dietary pattern reduced use of medications that are often used to treat metabolic syndrome components. To test this question, we used multivariate-adjusted unconditional logistic regression to evaluate the relative odds of using medication to treat hypertension or elevated cholesterol (key components of the metabolic syndrome) as a function of intervention arm assignment. All tests were two-sided with statistical significance set at $p<0.05$. All analyses were conducted using SAS (version 9.2, SAS Institute, Cary, NC).

RESULTS

Baseline demographic and lifestyle characteristics for WHI-DM participants were very similar across the two study arms, as would be expected from a randomized controlled trial (Table 1). Mean ages were 61.6 years and 61.8 years for intervention and comparison arm women, respectively. For the blood cohort sampling, efforts were made to explicitly include a large number of non-whites and this sampling scheme is reflected in the race/ethnicity distributions (over 50% are non-white). Participants were relatively well-educated (35% of both the intervention and comparison arms had a college degree). Less than one-quarter of participants had a BMI < 25.0 kg/m^2; nearly 80% of both the intervention and comparison arm women in the blood cohort were either overweight (BMI = 25.0–29.9 kg/m^2) or obese (BMI ≥ 30.0 kg/m^2). Other baseline characteristics, such as use of postmenopausal hormones, history of metabolic-related diseases, such as diabetes, hypertension and cardiovascular disease, smoking and alcohol habits did not differ between women in the

intervention and comparison arms in this subcohort. For the metabolic syndrome and its five components, the baseline prevalence was similar in the intervention and comparison groups (Table 2).

Table 3 provides results for risk of metabolic syndrome at three time points post-randomization. In the multivariate-adjusted logistic regression models, we found a modest, but statistically non-significant 17% reduced risk (OR=0.83, 95% CI 0.59–1.18) of metabolic syndrome at year 3, but not at years 1 or 6. We next show the linear regression models and mean (SD) change and percent change for each of the metabolic syndrome components by randomization arm. These values are derived from the β-coefficients from the GEE models. While the five component values are presented, their interpretation should be viewed as a group without undue emphasis on any one value in much the same way that one would interpret collectively all the β-coefficients from a linear regression model. However, we present these means and percent changes for reader interest. The p-value for each model represents the overall intervention effect for the combination of metabolic syndrome components modeled simultaneously. We observed the strongest associations at year 1, where the intervention effect was statistically significant ($p<0.0001$) with only suggestive associations at years 3 ($p=0.19$) and 6 ($p=0.16$). These analyses were repeated, restricted to women who were adherent to the trial protocol, where non-adherence was defined as the earliest missed annual visit, failure to participate in ≥ 9 intervention sessions in year 1 or ≥ 2 sessions in subsequent years (Table 4) (29,30). Again, while undue emphasis should not be placed on individual values, the overall intervention effect remained highly statistically significant at year 1 ($p<0.001$) and borderline significant at years 3 ($p=0.05$) and 6 ($p=0.06$).

We next examined whether women randomized to the low-fat dietary pattern experienced improved metabolic health such that they no longer needed to use cholesterol-lowering or hypertension medications (Table 5). At year 1 women in the intervention group were 19% less likely to use these medications compared to those in the comparison arm. Over the entire follow-up period, a lower proportion of women in the intervention arm used medications at follow-up (26.0% vs. 29.2% for intervention and comparison arms, respectively), but the overall differences were not statistically significant.

DISCUSSION

The Women's Health Initiative Dietary Modification Trial tested whether a low-fat dietary pattern would reduce the risk of invasive breast cancer and colorectal cancer as primary outcomes and coronary heart disease as a secondary outcome. Since the goals of the WHI DM trial were very similar to other low-fat dietary recommendations for general health and disease prevention, we hypothesized that the low-fat intervention may have beneficial effects on the metabolic syndrome, which is an independent risk factor for many adverse health events including diabetes, cardiovascular disease and cancer. In the 5.8% subsample of WHI participants who had blood measures and other relevant clinical data at baseline and three follow-up time points, randomization to the low-fat dietary intervention was significantly associated with metabolic syndrome components at year 1 of the follow-up period. Randomization to the low-fat dietary pattern was associated with clinically meaningful, but non-statistically significant, 17% decreased risk of metabolic syndrome for those in the low-fat intervention, compared to those in the usual diet group at year 3. Our findings further suggested a lower use of cholesterol-lowering and hypertension medications for women in the DM intervention vs. the comparison arms during the follow-up period. Our results are consistent with findings of Seligman et al who reported that a variety of lifestyle interventions (including increased physical activity, no sugar or low-fat diets) can significantly improve metabolic syndrome. The results presented in this report are also

consistent with previous WHI-DM trial reports showing that the low-fat dietary intervention had beneficial effects on weight and body composition, particularly at year 1 when adherence was at its highest point in the trial. If adherence had been consistently stronger throughout the trial, the findings may have been stronger and sustained for the entire years of follow-up. However, it is not possible to determine to what extent the changes were due to the dietary intervention alone or due to changes in participant weight. Exploratory analyses to test whether weight change mediated the observed associations did not further inform the results (data not shown).

The optimal diet for the prevention and treatment of the metabolic syndrome remains unspecified. However, weight reduction diets, dietary patterns such as the Mediterranean diet, and diets plentiful in fruit and vegetables are consistently associated with reduced risk of the metabolic syndrome, particularly among individuals with existing risk factors, and improved clinical symptoms in those with a confirmed diagnosis of the metabolic syndrome. Many lower fat, high complex/carbohydrate also improve measures of inflammatory factors and other metabolic molecules, such as the insulin-like growth factors and C-reactive protein, further underscoring healthful benefits. Other potentially useful dietary treatments may be found in AbouRjaili et al.. Questions remain regarding the ideal macronutrient composition and whether diets should be lower-carbohydrate/higher-fat or higher-carbohydrate/lower-fat. Supporters of the latter maintain that decreasing total fat in the diet is associated with reduced energy intake since fat contributes more than twice the number of calories per gram compared to carbohydrate. Dietary fat may also have a direct effect on adipose tissue biology since dietary fat influences synthesis and distribution of sex steroid hormones and inflammatory cytokines. Adipose tissue, once thought inert, is an active endocrine organ that synthesizes estrogens and several peptides including leptin, TNF-α, MCP-1, IL-6 and resistin. Conversely, proponents of low carbohydrate diets suggest that a high carbohydrate intake increases triglycerides, decreases glycemic control, reduces satiety (thereby leading to increased food intake) and reduces beneficial HDL while having minimal to no effect on reducing LDL. In addition, some healthful fats, such as monounsaturated fat in the Mediterranean diet, have been found to promote health. However, many of these studies have not differentiated between complex vs. refined carbohydrate sources nor have the potential benefits of naturally occurring sources of dietary fiber commonly associated with complex carbohydrate foods been evaluated. The results from this report indicate that the low-fat dietary pattern was associated with some improvements in MS components, although the effects were small and thus the overall odds ratio for metabolic syndrome risk reduction did not reach statistical significance. The WHI has previously reported no increase in self-reported incident diabetes and no adverse effects on fasting glucose, triglycerides, HDL-cholesterol, insulin or insulin sensitivity for women in the low-fat intervention.

Our finding that use of hypertension or cholesterol-lowering medications was suggestively different between treatment arms is novel. While the differences were not statistically significant, after adjusting for baseline medication use, women in the intervention arm had a 19% lower odds of using these medications after one year compared to those in the comparison arm. While the associations were attenuated as the trial progressed, the odds of medication use remained lower in the intervention arm throughout the trial. These noteworthy findings lend support to the benefits of lifestyle modification for treatment of elevated cholesterol and blood pressure as recommended by leading clinical advisory groups. While the overall WHI-DM trial results did not demonstrate a reduced incidence of coronary heart disease, subgroup analysis indicated reduced cardiovascular risk among women who adhered to nationally recommended cardioprotective approaches, including reduced intake of saturated fatty acids. The lessened use of risk factor-treating medications

suggests that the intervention may have a positive effect on some of the metabolic syndrome-associated precursor risk factors for cardiovascular disease.

The strengths of this study include use of data from a large and very well characterized clinical trial. The length of the trial (mean of 8.1 years) is longer than most short term interventions evaluating dietary effects on metabolic syndrome. The data collection was conducted at 40 clinical centers throughout the United States using a standardized protocol and quality control measures were incorporated into all phases of data collection, data management and laboratory assays. All laboratory measures were conducted at a single laboratory with good CVs for all analytes. Limitations include the fact that the blood draw subsample was not a random sample of all WHI-DM participants and thus the results from this report may not be generalizable to all WHI participants or to all postmenopausal women. Another limitation is that while adherence and retention were excellent in WHI, it is nonetheless challenging to adhere to a prescribed dietary pattern for a lengthy period of time. In addition, while diet in both arms was carefully monitored throughout the trial, it is possible that some women in the comparison arm changed their diets, which would have weakened the ability to detect differences between the intervention and comparison arms. Finally, WHI did not collect data on omega-3 fatty acid supplements, which may influence metabolic syndrome.

In summary, WHI Dietary Modification Trial was significantly associated with change in the components of the metabolic syndrome after one year of participation in the trial. There was also evidence suggesting that the DM intervention may be associated with reduced need for cholesterol-lowering or hypertension medications, which are often used by people at risk for metabolic syndrome or those with a frank diagnosis. The WHI-DM dietary pattern did not increase risk of metabolic syndrome and, on the contrary, may be beneficial in reducing not only metabolic syndrome, but its associated cardiovascular risk factors and use of hypertension and cholesterol-lowering medications. The next steps in this research will be to examine long-term maintenance of the low-fat dietary pattern after the intervention was completed and whether long-term adherence influences risk of metabolic syndrome and its associated diseases. If confirmed using long-term data then the findings, together with those previously reported by Seligman et al will have important and relevant translational potential.

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Abbreviations used

WHI	Women's Health Initiative
WHI-DM	Women's Health Initiative Dietary Modification Trial
FFQ	Food Frequency Questionnaire
MS	Metabolic Syndrome
BMI	Body Mass Index
LDL	Low Density Lipoprotein
HDL	High Density Lipoprotein

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Table 1

Baseline Demographic and Lifestyle Characteristics in a sub-cohort of WHI DM participants (n = 5.8% subsample, n = 2818)

Characteristic	Intervention arm[1] (n= 1111)	Comparison arm[1] (n=1707)
Age, years [mean, (SD)]	61.6 (6.9)	61.8 (6.9)
50–59 [n (%)]	453 (40.8)	665 (39.0)
60–69 [n (%)]	497 (44.7)	791 (46.3)
70–79 [n (%)]	161 (14.5)	251 (14.7)
Race/Ethnicity [n (%)]		
Non-Hispanic white	543 (48.9)	830 (48.6)
African-American	306 (27.5)	499 (29.2)
Hispanic	129 (11.6)	184 (10.7)
Asian/Pacific Islander	82 (7.4)	115 (6.7)
Other, mixed race[2]	51 (4.6)	79 (4.6)
Education [n (%)]		
< High school	80 (7.2)	129 (7.4)
High school diploma/GED	176 (15.9)	297 (17.5)
Some College	453 (40.9)	679 (40.1)
College Degree or higher	399 (36.0)	593 (35.0)
Body weight (kg), mean (SD)	77.5 (16.0)	78.6 (17.9)
Body Mass Index [kg/(m)^2]		
Mean (SD)	29.7 (5.8)	30.1 (6.2)
Normal - < 25.0 [n (%)]	239 (21.6)	363 (21.4)
Overweight - 25.0–29.9	394 (35.6)	571 (33.6)
Obese - ≥ 30.0	473 (42.8)	764 (45.0)
Postmenopausal hormone use [n (%)]		
Never used	549 (49.5)	846 (49.7)
Past user	186 (16.8)	295 (17.3)
Current user	375 (33.8)	561 (32.9)
Physical Activity (met hrs/wk)		
Mean (SD)	9.5 (11.6)	9.4 (11.8)
Medical History [n (%)]		
Diabetes	93 (8.4)	141 (8.3)
Hypertension	402 (36.5)	669 (39.5)
Cardiovascular Disease	161 (16.3)	259 (17.2)
Smoking history [n (%)]		
Never	576 (52.5)	898 (53.3)
Past	437 (39.8)	667 (39.6)
Current	85 (7.7)	121 (7.2)
Alcohol Use		
Servings/week [mean (SD)]	1.60 (3.5)	1.45 (3.4)

[1]Participants were randomized to either a low-fat dietary pattern (% energy from fat ≤ 20%/day, ≥5 servings fruits & vegetables and 6 servings grains/day) or comparison (no dietary change). 40% of participants were randomized to the intervention and 60% to the comparison.

[2]Includes Native American, Mixed Race (not further specified) and unknown race/ethnicity.

Table 2

Baseline Prevalence of Metabolic Syndrome in a sub-cohort of the Women's Health Initiative Dietary Modification Trial

Metabolic Syndrome Criteria[1]	Intervention Arm (n = 1111)	Comparison Arm (n = 1707)
Waist circumference (cm)		
Mean (SD)	90.1 (13.7)	90.5 (14.3)
n (%) > 88 cm	572 (51.6)	877 (51.5)
HDL cholesterol (mmol/L)		
Mean (SD)	1.5 (0.4)	1.5 (0.4)
n (%) < 1.3 mmol/L	363 (34.1)	572 (34.5)
Serum triglycerides (mmol/L)		
Mean (SD)	1.7 (0.9)	1.7 (0.9)
n (%) ≥ 1.7 mmol/L	404 (37.8)	646 (38.8)
Blood pressure (mm Hg)		
Mean (SD)		
Systolic	127.3 (17.4)	129.2 (17.8) *
Diastolic	76.3 (9.4)	76.7 (9.1)
n (%) ≥ 130/85 mmHg	507 (45.6)	844 (49.4)
Blood glucose (mmol/L)		
Mean (SD)	5.7 (1.7)	5.6 (1.6)
n (%)≥ 5.5 mmol/L	380 (35.5)	543 (32.2)
Presence of Metabolic Syndrome		
n (%)	394 (37.2)	612 (37.1)

[1] Metabolic syndrome criteria are defined by the Expert Panel on Detection, Evaluation and Treatment of High Blood Pressure and Cholesterol in Adults (Adult Treatment Panel III).

* $p < 0.01$

Table 3

Low-fat dietary pattern and risk of metabolic syndrome components at years 1, 3 and 6 post-randomization in the Women's Health Initiative Dietary Modification Trial

Follow-up	Odds ratios (95% Confidence Intervals) for Metabolic Syndrome		
	Intervention	Comparison	OR (95% CI)[1]
	no. cases (%)	no. cases (%)	
Year 1	71 (10.9)	114 (11.9)	0.98 (0.70, 1.37)
Year 3	70 (12.3)	132 (15.4)	0.83 (0.59, 1.18)
Year 6	91 (17.0)	141 (17.3)	1.01 (0.73, 1.40)

Changes in post-randomization metabolic syndrome components									
	Intervention (n=1111)				Comparison (n=1707)				
	N	Mean change	SD	% Change[2]	N	Mean change	SD	% Change	*P*[3]
Year 1									<.0001
Diastolic BP (mm Hg)	716	−1.1	8.3	−1.4%	1060	−1.2	8.9	−1.6%	
Systolic BP (mm Hg)	717	−0.1	14.5	−0.10%	1060	−2.0	15.4	−1.6%	
Glucose (mmol/L)	658	−0.1	0.7	−1.9%	996	0.03	0.9	0.6%	
HDL-C (mmol/L)	656	−0.04	0.2	−2.7%	990	0.01	0.2	0.8%	
Triglyceride (mmol/L)	657	0.1	0.5	6.6%	992	0.05	0.5	3.6%	
Waist (cm)	708	−1.6	5.7	−1.9%	1046	0.05	6.2	0.1%	
Year 3									0.19
Diastolic BP (mm Hg)	663	−1.6	8.9	−2.2%	1003	−1.8	8.9	−2.4%	
Systolic BP (mm Hg)	662	0.5	15.6	0.4%	1003	−1.2	15.5	−1.0%	
	N	**Mean change**	**SD**	**% Change**	**N**	**Mean change**	**SD**	**% Change**	***P***
Glucose (mmol/L)	573	−0.1	0.8	−1.7%	881	0.1	0.7	0.90%	
HDL-C (mmol/L)	569	−0.03	0.3	−2.0%	878	−0.02	0.3	−0.9%	
Triglyceride (mmol/L)	572	0.1	0.5	5.9%	880	0.08	0.6	5.8%	
Waist (cm)	564	0.06	6.6	0.07%	844	1.2	8.1	1.4%	
Year 6									0.17
Diastolic BP (mm Hg)	606	−2.9	9.9	−3.9%	940	−3.4	9.9	−4.5%	

	N	Mean change	SD	% Change	N	Mean change	SD	% Change	*P*
Systolic BP (mm Hg)	606	1.4	16.8	1.2%	941	−1.1	17.7	−0.9%	
Glucose (mmol/L))	534	0.1	41.2	2.3%	834	0.3	1.3	4.7%	
HDL-C (mmol/L)	533	−0.07	0.3	−4.0%	832	−0.1	0.3	−2.9%	
Triglyceride (mmol/L)	534	0.1	0.6	4.5%	835	0.1	0.7	3.8%	
Waist (cm)	465	1.9	7.4	2.3%	709	2.5	8.7	2.9%	

[1] Logistic regression models are adjusted for age, race/ethnicity, history of diabetes, physical activity, baseline use of cholesterol lowering or hypertension medications (see text for details)

[2] % change from baseline was calculated as mean change from baseline divided by the mean value at baseline

[3] *P*-value was calculated based on multivariate regression model using the five components of Metabolic Syndrome simultaneously in continuous scales as outcomes, adjusted for age, race/ethnicity, history of diabetes, physical activity, use of hypertension or cholesterol medications at baseline. The multivariate regression model provides an overall test for the intervention impact on all five components as a whole.

Table 4

Low-fat dietary pattern and risk of metabolic syndrome components at years 1, 3 and 6 post-randomization among adherent participants in the Women's Health Initiative Dietary Modification Trial

Follow-up	Odds ratios (95% Confidence Intervals) for Metabolic Syndrome		
	Intervention	Comparison	OR (95% CI)[1]
	no. cases (%)	no. cases (%)	
Year 1	37 (7.8)	114 (12.0)	0.68 (0.45, 1.03)
Year 3	41 (10.6)	131 (15.4)	0.76 (0.51, 1.12)
Year 6	50 (16.2)	141 (17.4)	0.94 (0.64, 1.38)

Changes in post-randomization metabolic syndrome components									
	Intervention (n=491)				Comparison (n=993)				
	N	Mean change	SD	% Change[2]	N	Mean change	SD	% Change	*P*[3]
Year 1									<.0001
Diastolic BP (mm Hg)	490	−1.4	7.8	−1.9%	989	−1.3	8.9	−1.7%	
Systolic BP (mm Hg)	491	−1.3	14.0	−1.0%	989	−2.0	15.5	−1.6%	
Glucose (mmol/L)	446	−0.1	0.7	−1.8%	919	0.03	0.9	0.6%	
HDL-C (mmol/L)	446	−0.05	0.2	−3.1%	913	0.01	0.2	0.6%	
Triglyceride (mmol/L)	447	0.1	0.5	4.9%	915	0.06	0.5	4.2%	
Waist (cm)	487	−1.8	5.8	−2.1%	974	0.08	642	0.1%	
Year 3									0.05
Diastolic BP (mm Hg)	422	−1.6	8.9	−2.1%	938	−1.7	8.9	−2.3%	
Systolic BP (mm Hg)	421	1.0	15.2	0.8%	938	−1.1	15.4	−0.86%	
	N	**Mean change**	**SD**	**% Change**	**N**	**Mean change**	**SD**	**% Change**	***P***
Glucose (mmol/L)	363	−0.1	0.9	−2.3%	813	0.03	0.7	0.62%	
HDL-C (mmol/L)	363	−0.04	0.3	−2.6%	810	−0.02	0.3	−1.16%	
Triglyceride (mmol/L)	364	−0.07	0.5	4.7%	812	0.09	0.6	6.4%	
Waist (cm)	355	−0.4	6.1	−0.4%	787	1.2	8.3	1.5%	
Year 6									0.06
Diastolic BP (mm Hg)	338	−2.9	9.7	−3.9%	881	−3.3	9.7	−4.3%	

	N	Mean change	SD	% Change	N	Mean change	SD	% Change	*P*
Systolic BP (mm Hg)	338	1.7	16.9	1.4%	882	−1.1	17.4	−0.8%	
Glucose (mmol/L))	287	0.03	1.0	0.5%	777	0.2	1.3	4.4%	
HDL-C (mmol/L)	288	−0.1	0.3	−4.8%	775	−0.1	0.3	−3.2%	
Triglyceride (mmol/L)	288	0.1	0.6	5.2%	778	0.1	0.7	3.7%	
Waist (cm)	253	1.3	6.6	1.5%	666	2.7	8.4	3.2%	

[1] Logistic regression models are adjusted for age, race/ethnicity, history of diabetes, physical activity, baseline use of cholesterol lowering or hypertension medications (see text for details)

[2] % change from baseline was calculated as mean change from baseline divided by the mean value at baseline.

[3] *P*-value was calculated based on multivariate regression model using the five components of Metabolic Syndrome simultaneously in continuous scales as outcomes, adjusted for age, race/ethnicity, history of diabetes, physical activity, use of hypertension or cholesterol medications at baseline. The multivariate regression model provides an overall test for the intervention impact on all five components as a whole. Adherence was defined based in participation in intervention activities (see text for details).

Table 5

Relative odds of use of hypertension of cholesterol-lowering medications as a function of participation in the WHI low-fat dietary intervention

Year	Intervention n (%)	Comparison n (%)	Odds ratio (95% CI)	*P*
Baseline	162/1111 (14.6)	318/1707 (18.6)	0.75 (0.61–0.92)	0.005[1]
Year 1	165/1037 (15.9)	318/1557 (20.4)	0.81 (0.60–1.09)	0.16[2]
Year 3	248/982 (25.3)	415/1492 (27.8)	1.03 (0.82–1.29)	0.80[2]
Year 6	358/942 (38.0)	579/1448 (40.0)	1.01 (0.84–1.22)	0.91[2]
Years 1–6	771/2961 (26.0)	1312/4497 (29.2)	0.99 (0.84–1.16)	0.89[3]

[1] *P*-value was calculated from logistic model with use of hypertension of cholesterol medications (yes/no) as outcome and DM treatment as the independent variable.

[2] *P*-value was calculated from logistic model with use of hypertension of cholesterol medications (yes/no) as outcome and DM treatment as the independent variable, adjusted for baseline hypertension/cholesterol use.

[3] *P*-value was calculated from generalized linear model with repeated measurements (GEE), using hypertension of cholesterol medications (yes/no) as outcome. DM treatment and years post-randomization (1, 3, 6) as independent variables, adjusted for baseline hypertension/cholesterol use.