Effects of a low-fat dietary intervention on glucose, insulin, and insulin resistance in the Women's Health Initiative (WHI) Dietary Modification trial[1–3]

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ABSTRACT

Background: Glycemic effects of the Women's Health Initiative (WHI) low-fat dietary intervention are unknown.

Objective: Our objective was to analyze the effects of the WHI low-fat dietary intervention on serum glucose and insulin and insulin resistance up to 6 y after random assignment.

Design: Postmenopausal WHI Dietary Modification trial intervention (DM-I) and comparison (DM-C) participants with blood measures at least at baseline and year 1 (n = 2263) were included. Anthropometric measures, dietary assessments, serum glucose and insulin concentrations, homeostasis model assessment of insulin resistance (HOMA-IR) measures, and quantitative insulin sensitivity check index (QUICKI) values were obtained at baseline, year 1, year 3, and year 6. Changes in measures were compared between groups at years 1, 3, and 6 overall and within stratified analyses.

Results: Mean (±SD) differences in changes at year 1 between the DM-I and DM-C groups were as follows: glucose, −1.7 ± 17.9 mg/dL; insulin, −0.7 ± 5.1 μIU/mL; HOMA-IR, −0.2 ± 1.9; and QUICKI, 0.004 ± 0.019 (all $P < 0.05$). Similar findings resulted from repeated-measures analyses comparing the intervention and comparison groups over the 6 y. Whereas normoglycemic women at baseline had a decrease in glucose at year 1 that was 1.9 ± 17.2 mg/dL greater in the DM-I than in the DM-C group, diabetic women had an increase in glucose that was 7.9 ± 20.3 mg/dL greater in the DM-I than in the DM-C group (P for interaction <0.001).

Conclusions: A low-fat diet was not significantly associated with adverse glycemic effects up to 6 y after random assignment in postmenopausal women. However, diabetic women experienced adverse glycemic effects of the low-fat diet. This trial is registered at clinicaltrials.gov as NCT00000611. *Am J Clin Nutr* 2011;94:75–85.

INTRODUCTION

The optimal macronutrient content of the diet for human health remains a major controversy in nutritional science. Low-fat diets in general, and the Women's Health Initiative (WHI) low-fat dietary intervention in particular, have been criticized for their potential to substitute unhealthy carbohydrates for fat, potentially contributing to hyperglycemia, hyperinsulinemia, and insulin resistance (1).

The WHI Dietary Modification (DM) trial was designed to test the effects of a dietary pattern low in total fat, along with increased vegetables, fruit, and grains, on primarily breast cancer and colorectal cancer incidence in postmenopausal women during a mean follow-up of 8.1 y. Despite the increased intake of carbohydrate in the intervention group, and question of associated increased risk of diabetes, no increase in diabetes risk was observed. Subgroup analysis suggested that greater decreases in percentage of energy from total fat reduced diabetes risk (P for trend = 0.04); however, that finding was not statistically significant after adjustment for weight loss—a common effect of eating a low-fat diet (2).

Details of the effects of the WHI diet intervention on glucose, insulin, and insulin resistance have not been reported. The aim of this report was to analyze the effect of the overall diet intervention, and the specific effects of fiber and whole grain intakes, and dietary glycemic index (GI) and glycemic load (GL) on glucose, insulin, and insulin resistance in the WHI DM trial.

SUBJECTS AND METHODS

WHI DM trial

Recruitment

Details of the study design and methods were published previously (3). All women provided written informed consent, and

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the study was approved by the National Institutes of Health and the institutional review boards at each of the clinical centers and the Clinical Coordinating Center. Briefly, 48,835 postmenopausal women between the ages of 50 and 79 y were enrolled between 1993 and 1998 at 40 clinical centers across the United States (4). Participants were assigned randomly to an intervention group (40%, n = 19,541) or a usual-diet comparison group (60%, n = 29,294), stratified by clinical center site and age group.

Eligibility criteria included consumption of a baseline a diet with a total fat intake $\geq$32% of total energy, as assessed by a food-frequency questionnaire (FFQ). Major exclusions for the WHI included prior breast or colorectal cancer, other cancers (except nonmelanoma skin cancer) in the past 10 y, medical conditions with a predicted survival $<$3 years, and compliance concerns such as alcoholism. Additional DM trial-specific exclusions included type 1 diabetes and frequent consumption of meals prepared away from home.

Dietary intervention

The DM intervention was designed to promote dietary change, with the goals of reducing intake of total fat to 20% of energy and increasing vegetable and fruit consumption to $\geq$5 servings and grains to $\geq$6 servings daily (5). The intervention did not include total energy reduction or weight-loss goals. The intensive behavioral-modification program involved 18 group sessions in the first year and quarterly maintenance sessions thereafter, led by specially trained and certified nutritionists. Group activities were supplemented during the intervention period by individual contacts, completed by telephone or mail. Each participant was assigned her own fat gram goal, calculated on the basis of height. Participants self-monitored total fat gram intake and also servings of vegetables, fruit, and grains. No formal intervention regarding saturated fat, cholesterol, *trans* fatty acids, or other known atherogenic factors was provided.

Comparison-group participants received a copy of the *Dietary Guidelines for Americans* (6) and other health-related materials available to all WHI participants (such as information about Pap tests and breast exams and guides to quitting smoking), but had no contact with the nutrition interventionists. Interested and eligible women were allowed to join 1, 2, or all 3 of the WHI clinical trial components: DM trial, Hormone Therapy trial, or Calcium and Vitamin D trial (7). Of the total DM enrollment of 48,836, 10,553 (21.6%) participated in only the DM trial, 8050 (16.5%) in the DM and the Hormone Therapy trial, 25,210 (51.6%) in the DM and the Calcium and Vitamin D trial, and 5017 (10.3%) in all 3 trials.

Participants were followed from the date of entry until the trial's planned completion date, loss to follow-up, the time that a participant requested no further contact, or death, regardless of their compliance with the dietary intervention. DM trial participants were contacted by clinic staff at 6-mo intervals to provide information on health outcomes.

Dietary assessment

All DM participants completed an FFQ, designed specifically for the study, at baseline and at 1 y (8). Thereafter, one-third of the participants completed the FFQ each year in a rotating sample; completion rates were 100% at baseline and 81% thereafter. Data on dietary intake for the year 6 follow-up were computed from the FFQs administered from years 5 through 7, thus including all participants. The methods for assigning GI and GL values used in the WHI FFQ were reported elsewhere (9). Briefly, GI values were taken from published reports or were imputed from GI values of foods with similar composition and preparation, by using glucose as the reference standard. A composite GI was computed by a weighted average for FFQ line items with multiple foods. The GL was computed by multiplying the GI by grams of carbohydrate consumed according to the number and frequency of servings and portion size.

Analytic cohort

The current study uses data from the 5.8% (n = 2816) subset of DM trial participants for whom blood samples were collected, and serum was analyzed at baseline and years 1, 3, and 6. The subsample for blood sample collection was randomly chosen from all 40 WHI clinical centers, with oversampling of minority women and Hormone Therapy trial participants, where the odds for selection were 6-fold higher than for white women and higher among the Hormone Therapy trial participants (8.6% sampling rate) than among the DM participants (4.3% sampling rate). Excluded from the analyses were participants without glucose and insulin results at least at baseline and year 1 (n = 504), who self-reported taking insulin at baseline (n = 46) (although participants with diabetes at baseline not taking insulin were included), with baseline insulin $>$170 μIU/mL (n = 1), and having a change in insulin between baseline and year 1 $>$100 μIU/mL (n = 2), which resulted in a final analytic cohort of 2263 participants.

Laboratory methods

Blood samples were collected in the fasting state ($\geq$12 h) and were maintained at 4°C for up to 1 h until plasma or serum was separated from cells. Centrifuged aliquots were stored in freezers (at −70°C) within 2 h of collection and sent on dry ice to the central repository, where storage at −70°C was maintained. Serum glucose was measured by using the hexokinase method on the Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) (10). Serum insulin was measured by using a step-wise sandwich enzyme-linked immunoassay procedure on an ES 300 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) (11). Insulin resistance was calculated from fasting glucose and insulin according to the homeostasis model assessment of insulin resistance (HOMA-IR) (12). We also conducted analyses using another method of calculating insulin sensitivity—the quantitative insulin sensitivity check index (QUICKI) (13).

Statistical methods

Descriptive statistics for baseline characteristics were compared by randomization assignment with the use of chi-square tests. Means and standard deviations were computed for nutrient intake data from the FFQ, physical activity levels collected from standardized questionnaires, physical measurements, and laboratory data at baseline, year 1, year 3, and year 6. Differences in means between intervention and comparison groups for baseline, year 1, year 3, and year 6 were computed and tested for significance by using a 2-sample paired t test. Because of non-normal distributions, means and t tests of insulin and HOMA-IR were

based on log-transformed values. Geometric means are reported in the tables. In addition, an analysis of changes in glucose, insulin, HOMA-IR, and QUICKI over the entire 6 y of follow-up was performed by using a repeated-measures linear regression model with an unstructured covariance matrix.

We compared changes in glucose, insulin, and the insulin resistance/sensitivity indexes between the intervention and comparison groups stratified by baseline characteristics [age, race-ethnicity, body mass index (BMI; in kg/m^2), diabetes status, insulin concentration, and presence or absence of the metabolic syndrome as defined by National Cholesterol Education Program (14) criteria] and baseline dietary intakes of fiber and whole grains, GI, and GL categorized into tertiles. Tests for an interaction between each characteristic and the effect of the DM intervention on the change were performed by using a linear regression model that included the 2 main effects and a cross-product term. When available, the continuous form of the characteristic was used. The model assumption of a linear relation between the independent and dependent variables was checked by including a spline term for the dependent variable in a generalized additive model and evaluating the analysis of deviance. If indicated, models were rerun including quadratic terms. Heterogeneity of variance was evaluated by visual inspection of residual plots; no significant departures were detected.

Diabetes was considered to be present at baseline on the basis of either self-reported physician diagnosis or a fasting glucose $\geq$126 mg/dL (15). Among women in the WHI DM who self-reported treatment of diabetes, 80% were confirmed to have an antidiabetic medication in their baseline medication inventory. Among women who self-reported ever having been told by a physician they had diabetes, 91% were found to have diabetes by medical record review (16).

We examined the relation in the intervention group between glucose and insulin changes at years 1, 3, and 6 by achieved nutrient intakes at these time points (% of energy from total fat, saturated fat, polyunsaturated fat, and *trans* fat; total carbohydrate; sugars; fiber; vegetables and fruit; whole grains; and dietary GI and GL). The maximum change in dietary intake had been reported at year 1 by the intervention group. The changes in glucose, insulin, HOMA-IR, and QUICKI were compared by quartiles of intake in the intervention group, by using the overall intake in the comparison group as reference. Linear regression models were run to test for linear trends across quartiles of intake.

The analyses described above evaluating the changes in insulin, glucose, HOMA-IR, and QUICKI were run unadjusted and adjusted for many baseline characteristics, including age, race-ethnicity, education, BMI, and randomization arm in the Hormone Therapy trial. Baseline levels of the specific change of interest were also added to the models, as was weight change at year 1. All reported *P* values are 2-sided. The analyses were performed by using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Of the 2263 WHI DM participants included in these analyses, the intervention and comparison groups had similar baseline demographic characteristics, physical measurements, health habits, and comorbidities (**Table 1**). However, in the subgroup of 219 women with diabetes at baseline (based on either self-report or fasting serum glucose $\geq$126 mg/dL), BMI (31.5 compared with 33.9; $P = 0.005$) and waist circumference (95.2 cm compared with 101.0 cm; $P = 0.002$) were significantly lower in the intervention than in the comparison group, although other baseline characteristics were similar (data not shown).

At year 1, weight, BMI, waist circumference, glucose, insulin, and HOMA-IR (insulin resistance) had decreased significantly more in the intervention group than in the comparison group, whereas QUICKI (insulin sensitivity) increased more in the intervention group than in the comparison group (**Table 2**). At year 3, the differences in change in these measures had decreased, and only the difference in waist circumference remained statistically significant. None of the differences remained significant at year 6. In repeated-measures analyses over the 6-y study period, we observed greater decreases [mean (95% CI)] in glucose (-1.4; -2.8, 0.0) mg/dL, insulin (-0.6; -1.0, -0.2) μIU/mL, and HOMA-IR (-0.2; -0.3, -0.0) and a significantly greater increase in QUICKI (0.003; 0.002, 0.005) in the intervention than in the comparison group, although the glucose finding was not quite statistically significant ($P = 0.05$). A significantly greater increase in physical activity in the intervention than in the control group was found at year 6.

Similar to the overall findings in the WHI DM trial, women in the intervention group had significantly lower self-reported intakes of energy, total fat, saturated fat, polyunsaturated fat, and *trans* fat than did women in the comparison group at year 1 (**Table 3**). The intervention group had higher mean intakes of carbohydrate, sugars, fiber, vegetables and fruit, grains, and whole grains and a higher GL at year 1. Generally, these findings were similar at year 3. The differences were smaller but still statistically significant at year 6, except for the difference in total energy intake, which was greater at year 6, and in GL, which was no longer statistically significant. No difference in dietary GI was observed at any time point.

We examined changes in serum glucose and insulin concentrations in WHI DM intervention and comparison group participants at year 1 by various baseline subgroups, adjusted for age at screening, race-ethnicity, education, Hormone Therapy trial treatment arm, BMI, baseline concentration of glucose or insulin, and weight change at year 1 (**Table 4**). No differences in glucose or insulin change by age, race-ethnicity, metabolic syndrome, insulin concentration, total fat intake, whole grain intake, GI, or GL were observed. However, whereas women without diabetes at baseline had a mean (95% CI) decrease in glucose at year 1 that was 1.9 (0.3, 3.6) mg/dL (in women with normoglycemia) and 1.8 (-1.0, 4.6) mg/dL (in women with impaired fasting glucose) greater in the intervention group than in the comparison group, and women with diabetes had an increase in glucose at year 1 that was 7.9 (3.5, 12.4) mg/dL greater in the intervention group than in the comparison group (P for interaction <0.001). Similar but less pronounced trends toward greater decreases in glucose in the intervention than in the comparison group were found, with lower baseline HOMA-IR (less insulin resistance) and higher baseline QUICKI (higher insulin sensitivity) scores in the intervention than in the comparison group with lower baseline fiber intakes. There was a small difference in insulin change by BMI, with obese women in the intervention group having virtually no change in insulin compared with a mean 1.2-μIU/mL increase in obese women in the comparison group. The results were similar regardless of the adjustment for baseline variables and without adjustment for weight change at year 1. Because testing indicated the

TABLE 1
Baseline characteristics of Dietary Modification trial intervention (DM-I) and comparison (DM-C) participants with glucose and insulin measurements[1]

	DM-I	DM-C	P^2
Subjects randomly assigned [*n* (%)]	892 (100.0)	1371 (100.0)	
Age group at screening [*n* (%)]			0.46
50–59 y	375 (42.0)	544 (39.7)	
60–69 y	391 (43.8)	636 (46.4)	
70–79 y	126 (14.1)	191 (13.9)	
Age (y)	61.5 ± 6.9[3]	61.6 ± 6.8	0.58
Race-ethnicity [*n* (%)]			0.86
White	437 (49.0)	691 (50.4)	
Black	242 (27.1)	384 (28.0)	
Hispanic	100 (11.2)	146 (10.7)	
American Indian/Alaskan Native	22 (2.5)	30 (2.2)	
Asian/Pacific Islander	71 (8.0)	93 (6.8)	
Unknown	20 (2.2)	27 (2.0)	
BMI [*n* (%)]			0.44
<25 kg/m^2	192 (21.7)	295 (21.6)	
25 to <30 kg/m^2	327 (36.9)	470 (34.4)	
≥30 kg/m^2	368 (41.5)	600 (44.0)	
Waist circumference [*n* (%)]			0.98
<88 cm	429 (48.2)	658 (48.1)	
≥88 cm	462 (51.9)	710 (51.9)	
Smoking [*n* (%)]			0.19
Never or past	811 (92.1)	1268 (93.5)	
Current	70 (8.0)	88 (6.5)	
Moderate or strenuous physical activity [*n* (%)]			0.92
None	175 (22.7)	263 (21.6)	
<2 episodes/wk	341 (44.2)	551 (45.3)	
2 to <4 episodes/wk	120 (15.5)	194 (16.0)	
≥4 episodes/wk	136 (17.6)	208 (17.1)	
Hypertension, treated or BP ≥140/90 mm Hg [*n* (%)]			0.10
No	454 (57.5)	671 (53.8)	
Yes	335 (42.5)	577 (46.2)	
Taking cholesterol-lowering medication [*n* (%)]			0.82
No	676 (89.2)	1060 (88.9)	
Yes	82 (10.8)	133 (11.2)	
Self-reported diabetes [*n* (%)]			0.98
No	833 (93.4)	1280 (93.4)	
Yes	59 (6.6)	91 (6.6)	
Diabetes [*n* (%)]			0.22
Normoglycemic, fasting glucose <100 mg/dL	579 (64.9)	925 (67.5)	
Impaired fasting glucose, fasting glucose 100–125 mg/dL	230 (25.8)	310 (22.6)	
Yes, self-report or fasting glucose ≥126 mg/dL	83 (9.3)	136 (9.9)	
History of cardiovascular disease [*n* (%)]			0.41
No	864 (97.4)	1304 (96.8)	
Yes	23 (2.6)	43 (3.2)	
Metabolic syndrome [*n* (%)][4]			0.56
No	567 (63.6)	888 (64.8)	
Yes	325 (36.4)	483 (35.2)	

[1] BP, blood pressure.
[2] From a chi-square test of independence.
[3] Mean ± SD (all such values).
[4] Metabolic syndrome defined by Adult Treatment Panel III criteria (14).

possibility of nonlinear relations between the change in insulin and baseline HOMA-IR and QUICKI, the models testing for interactions with these factors were also run including quadratic terms. This resulted in the *P* value for the interaction between the change in insulin at year 1 and baseline HOMA-IR changing from 0.15 to 0.02 and that for the interaction with baseline QUICKI changing from 0.15 to 0.13. An analysis of the changes in glucose and insulin concentrations between year 3 and year 6 in the same baseline subgroups showed no significant interactions by these subgroups, except for a significant interaction of baseline HOMA-IR with glucose concentration in year 3, with a mean change in glucose of −1.3 (95% CI: −4.3, 1.8) mg/dL in the intervention compared with the comparison women in the lowest category of baseline HOMA-IR and a mean change in glucose of 1.3 (95% CI: −1.7, 4.4) mg/dL in the intervention compared with the comparison women in the highest category of HOMA-IR (data not

TABLE 2
Baseline and follow-up anthropometric, blood glucose and insulin, and insulin resistance/sensitivity measures at years 1, 3, and 6 in Dietary Modification trial intervention (DM-I) and comparison (DM-C) participants with glucose and insulin measurements[1]

	Measure estimate										
	Baseline		Year 1		Year 3		Year 6		Difference in change between groups		
	DM-I	DM-C	DM-I	DM-C	DM-I	DM-C	DM-I	DM-C	Year 1	Year 3	Year 6
Weight (kg)	77.2 ± 15.9 (890)	78.2 ± 17.5 (1370)	75.8 ± 17.3 (882)	77.8 ± 17.4 (1352)	76.8 ± 18.1 (810)	78.3 ± 18.2 (1240)	77.0 ± 16.8 (743)	78.4 ± 18.2 (1162)	−1.0 ± 7.5[2]	−0.5 ± 10.2	−0.4 ± 9.4
BMI (kg/m^2)	29.6 ± 5.8 (887)	30.0 ± 6.1 (1365)	29.0 ± 6.1 (874)	29.9 ± 6.1 (1350)	29.4 ± 6.3 (806)	30.0 ± 6.1 (1230)	29.7 ± 6.1 (742)	30.1 ± 6.1 (1151)	−0.4 ± 2.4[3]	−0.1 ± 2.8	−0.0 ± 2.9
Waist circumference (cm)	89.6 ± 12.9 (891)	90.1 ± 14.1 (1368)	87.9 ± 13.0 (871)	89.8 ± 13.8 (1342)	89.4 ± 13.2 (701)	91.0 ± 14.5 (1060)	90.7 ± 13.4 (577)	91.4 ± 14.6(879)	−1.5 ± 6.2[3]	−0.9 ± 7.6[2]	0.1 ± 8.4
Physical activity (MET-h/wk)	9.6 ± 11.6 (772)	9.4 ± 11.9 (1216)	10.7 ± 12.7 (482)	9.8 ± 11.6 (694)	11.1 ± 13.3 (783)	10.4 ± 12.5 (1187)	11.7 ± 13.5 (799)	10.3 ± 12.5 (1258)	0.2 ± 11.0	0.2 ± 11.5	1.6 ± 12.5[2]
Glucose (mg/dL)	100.6 ± 25.4 (892)	100.3 ± 25.6 (1371)	99.0 ± 27.3 (892)	100.3 ± 25.9 (1371)	100.2 ± 25.8 (748)	100.5 ± 26.2 (1158)	102.2 ± 27.0 (646)	102.3 ± 28.0 (990)	−1.7 ± 7.9[2]	−0.6 ± 20.3	−0.6 ± 24.9
Insulin (μIU/mL)[4]	10.3 ± 5.0 (892)	10.5 ± 5.3 (1371)	9.5 ± 4.6 (892)	10.3 ± 5.3 (1371)	11.1 ± 5.6 (712)	11.5 ± 5.8 (1111)	8.2 ± 5.1 (645)	8.6 ± 5.8 (989)	−0.7 ± 5.1[2]	0.0 ± 7.3	−0.3 ± 7.6
HOMA-IR[4]	2.5 ± 1.5 (892)	2.6 ± 1.6 (1371)	2.3 ± 1.3 (892)	2.5 ± 1.6 (1371)	2.7 ± 1.6 (712)	2.8 ± 1.7 (1110)	2.0 ± 1.5 (645)	2.1 ± 1.6(988)	−0.2 ± 1.9[2]	−0.0 ± 2.6	−0.1 ± 2.8
QUICKI	0.335 ± 0.028 (892)	0.334 ± 0.029 (1371)	0.340 ± 0.028 (892)	0.335 ± 0.029 (1371)	0.332 ± 0.028 (712)	0.330 ± 0.028 (1110)	0.348 ± 0.038 (645)	0.346 ± 0.040 (988)	0.004 ± 0.019[3]	0.001 ± 0.024	0.001 ± 0.032

[1] All values are means ± SDs; *n* in parentheses. HOMA-IR, homeostasis model assessment of insulin resistance; MET, metabolic equivalent; QUICKI, quantitative insulin sensitivity check index.
[2] $P < 0.05$ (2-sample paired *t* test).
[3] $P < 0.001$ (2-sample paired *t* test).
[4] Values were based on log-transformed values and reported as geometric means. Values used for computing change were not transformed.

TABLE 3
Baseline and follow-up nutrient intakes at years 1, 3, and 6 in Dietary Modification trial intervention (DM-I) and comparison (DM-C) participants with glucose and insulin measurements

	Nutrient intake estimate										
	Baseline		Year 1		Year 3		Year 6		Difference in change between groups		
	DM-I (n = 888)	DM-C (n = 1366)	DM-I (n = 865)	DM-C (n = 1329)	DM-I (n = 631)	DM-C (n = 940)	DM-I (n = 765)	DM-C (n = 1171)	Year 1	Year 3	Year 6
Total energy (kcal)	1817 ± 755	1761 ± 756	1523 ± 593	1591 ± 739	1503 ± 589	1558 ± 670	1431 ± 538	1534 ± 670	−131 ± 676[1]	−128 ± 657[1]	−169(718)[1]
Total fat (% of energy)	37.6 ± 4.9	38.1 ± 5.1	25.4 ± 7.7	35.6 ± 7.0	26.8 ± 8.0	36.5 ± 6.8	29.2 ± 8.5	37.1 ± 7.3	−9.8 ± 7.3[1]	−9.1 ± 7.3[1]	−7.4 ± 7.8[1]
Saturated fat (% of energy)	12.3 ± 2.3	12.6 ± 2.5	8.2 ± 2.8	11.8 ± 2.9	8.7 ± 3.0	12.0 ± 2.9	9.4 ± 3.2	12.2 ± 3.1	−3.2 ± 3.0[1]	−3.0 ± 3.0[1]	−2.5 ± 3.2[1]
Polyunsaturated fat (% of energy)	7.8 ± 2.0	7.8 ± 2.0	5.4 ± 1.8	7.4 ± 2.1	5.7 ± 1.8	7.5 ± 2.1	6.3 ± 2.4	7.6 ± 2.1	−1.9 ± 2.2[1]	−1.8 ± 2.3[1]	−1.4 ± 2.5[1]
trans Fat (% of energy)	2.8 ± 1.2	2.8 ± 1.1	1.7 ± 0.9	2.6 ± 1.2	1.7 ± 0.8	2.5 ± 1.1	1.8 ± 0.9	2.4 ± 1.1	−0.9 ± 1.1[1]	−0.8 ± 1.2[1]	−0.6 ± 1.2[1]
Carbohydrate (% of energy)	46.2 ± 6.1	45.7 ± 6.3	58.0 ± 8.9	48.0 ± 8.2	56.6 ± 9.5	47.1 ± 8.0	54.0 ± 10.0	46.2 ± 8.9	9.5 ± 8.2[1]	9.0 ± 8.3[1]	7.6 ± 9.1[1]
Sugars (% of energy)	21.6 ± 6.1	21.6 ± 5.9	28.2 ± 7.9	23.4 ± 7.3	27.9 ± 7.9	22.9 ± 7.0	26.8 ± 7.8	22.8 ± 7.7	4.8 ± 6.8[1]	4.9 ± 7.0[1]	4.2 ± 7.3[1]
Glycemic index	53.0 ± 3.4	53.2 ± 3.5	52.8 ± 3.4	52.8 ± 3.8	52.1 ± 3.5	52.3 ± 3.8	51.3 ± 4.3	51.6 ± 4.5	0.3 ± 3.5	0.0 ± 3.7	0.0 ± 4.5
Glycemic load (g/d)	102.7 ± 45.0	99.2 ± 45.6	107.1 ± 45.9	92.2 ± 44.5	100.9 ± 41.4	88.0 ± 41.1	90.6 ± 37.9	83.4 ± 38.5	11.1 ± 42.8[1]	8.7 ± 41.6[1]	4.0 ± 44.2
Dietary fiber (g/d)	15.6 ± 6.7	14.8 ± 6.6	17.9 ± 8.2	14.4 ± 6.9	17.9 ± 8.1	14.3 ± 6.7	16.9 ± 7.5	14.1 ± 6.8	2.7 ± 6.6[1]	2.5 ± 6.7[1]	1.8 ± 7.1[1]
Vegetables and fruit (servings/d)	3.6 ± 1.8	3.4 ± 1.8	4.9 ± 2.4	3.6 ± 1.9	5.2 ± 2.5	3.7 ± 2.1	5.0 ± 2.5	3.7 ± 2.0	1.1 ± 2.0[1]	1.2 ± 2.1[1]	1.0 ± 2.2[1]
Grains (servings/d)	4.9 ± 2.8	4.7 ± 2.6	5.2 ± 3.0	4.2 ± 2.6	4.7 ± 2.6	4.0 ± 2.4	4.3 ± 2.4	3.7 ± 2.2	0.7 ± 2.8[1]	0.5 ± 2.7[1]	0.3 ± 2.7[2]
Whole grains (servings/d)	1.2 ± 0.8	1.2 ± 0.8	1.4 ± 1.0	1.1 ± 0.8	1.3 ± 0.9	1.0 ± 0.8	1.3 ± 0.9	1.0 ± 0.7	0.3 ± 0.8[1]	0.2 ± 0.8[1]	0.2 ± 0.9[1]

[1] $P < 0.001$ (2-sample paired t test).
[2] $P < 0.05$ (2-sample paired t test).

TABLE 4
Changes in glucose and insulin at year 1 in Dietary Modification trial intervention (DM-I) and comparison (DM-C) participants by baseline demographic and dietary characteristics[1]

	Glucose				Insulin			
	Change				Change			
	DM-I (n = 878)	DM-C (n = 878)	Difference in change between groups	P for interaction[2]	DM-I (n = 1338)	DM-C (n = 1338)	Difference in change between groups	P for interaction[2]
	mg/dL		*mg/dL*		*μIU/mL*		*μIU/mL*	
Obesity, BMI (in kg/m^2) ≥30				0.73				0.04
Yes	0.9 ± 16.8	2.3 ± 17.0	−1.5 ± 16.9		−0.1 ± 4.8	1.2 ± 5.0	−1.3 ± 4.9	
No	−3.0 ± 16.8	−2.0 ± 16.9	−1.0 ± 16.8		−1.6 ± 4.8	−1.2 ± 4.9	−0.4 ± 4.9	
Diabetes				<0.001				0.40
Normoglycemic, fasting glucose <100 mg/dL	−4.3 ± 17.0	−2.4 ± 17.4	−1.9 ± 17.2		−0.9 ± 4.7	−0.3 ± 4.8	−0.6 ± 4.7	
Impaired fasting glucose, fasting glucose 100–125 mg/dL	−2.4 ± 16.2	−0.6 ± 16.4	−1.8 ± 16.3		−1.0 ± 4.7	0.2 ± 4.8	−1.2 ± 4.8	
Yes, self-report or fasting glucose ≥126 mg/dL	23.3 ± 19.3	15.4 ± 20.9	7.9 ± 20.3		−1.2 ± 4.7	−0.1 ± 4.8	−1.0 ± 4.8	
Baseline HOMA-IR				0.01				0.15
<1.88	−1.8 ± 17.4	−0.1 ± 17.7	−1.7 ± 17.6		−2.5 ± 5.9	−2.1 ± 6.4	−0.4 ± 6.2	
1.88 to <3.14	−2.4 ± 16.6	−0.9 ± 16.7	−1.5 ± 16.7		−0.7 ± 4.6	0.1 ± 4.6	−0.8 ± 4.6	
≥3.14	0.4 ± 17.4	0.6 ± 18.4	−0.2 ± 18.0		0.4 ± 5.8	1.6 ± 6.7	−1.2 ± 6.3	
Baseline QUICKI				0.03				0.15
<0.3223	0.4 ± 17.4	0.6 ± 18.4	−0.2 ± 18.0		0.4 ± 5.8	1.6 ± 6.7	−1.2 ± 6.3	
0.3223 to <0.3472	−2.4 ± 16.6	−0.9 ± 16.7	−1.5 ± 16.7		−0.7 ± 4.6	0.1 ± 4.6	−0.8 ± 4.6	
≥0.3472	−1.8 ± 17.4	−0.1 ± 17.7	−1.7 ± 17.6		−2.5 ± 5.9	−2.1 ± 6.4	−0.4 ± 6.2	
Baseline fiber (g/d)				0.02				0.30
<11.6	−2.3 ± 16.6	0.6 ± 16.7	−2.8 ± 16.7		−1.4 ± 4.6	0.2 ± 4.6	−1.5 ± 4.6	
11.6 to <16.9	−0.7 ± 16.6	−0.5 ± 16.6	−0.2 ± 16.6		−0.5 ± 4.6	−0.3 ± 4.6	−0.2 ± 4.6	
≥16.9	−1.0 ± 16.6	−0.5 ± 16.7	−0.5 ± 16.6		−1.0 ± 4.6	−0.5 ± 4.6	−0.6 ± 4.6	

[1] Values were adjusted for age at screening, race-ethnicity, education, Hormone Therapy trial arm, baseline BMI, baseline glucose or insulin, and weight change at year 1. HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

[2] From a linear regression model testing for an interaction between the DM group and each baseline factor separately by using obesity and diabetes coded as above and log-transformed HOMA-IR, QUICKI, and fiber as continuous variables.

shown). In repeated-measures analyses, we observed similar trends over the entire study period. In particular, we noted a significant difference in change in glucose between the intervention and comparison groups with normoglycemia or impaired fasting glucose and those with diabetes at baseline: −2.0 (95% CI: −2.9, −1.1) mg/dL compared with 3.4 (95% CI: −8.7, 15.5) mg/dL, respectively (P for interaction = 0.03).

No differences were found in the number of diabetes medications reported by the intervention and comparison groups at baseline or year 1 (ie, the differences in glucose cannot likely be explained by differences in diabetes treatment intensity of the 2 groups in this unblinded trial). Also, no significant differences in HOMA-IR or QUICKI changes were found between participants in the intervention and comparison groups according to whether they were normoglycemic or had impaired fasting glucose or diabetes (data not shown).

A graded decrease in the insulin concentration and an increase in QUICKI at year 1 was found in women in the intervention group who achieved progressively lower levels of fat intake relative to women in the comparison group after adjustment for age, race-ethnicity, education, Hormone Therapy trial arm, baseline BMI, baseline glucose concentration, and baseline insulin concentration (**Table 5**). After further adjustment for weight change at year 1, the result for change in insulin concentration was

TABLE 5
Changes in glucose, insulin, insulin resistance, and insulin sensitivity by achieved intake in dietary components in Dietary Modification trial intervention participants at years 1, 3, and 6[1]

	Glucose	Insulin	HOMA-IR	QUICKI
	mg/dL	*μIU/mL*		
Change in measure estimate, baseline to year 1				
No. of subjects	2152	2152	2152	2152
Total fat				
<19.6% of energy	−2.87 (−5.25, −0.49)	−1.54 (−2.22, −0.85)	−0.42 (−0.68, −0.17)	0.007 (0.005, 0.010)
19.6% to <24.4% of energy	−1.92 (−4.29, 0.45)	−0.58 (−1.26, 0.10)	−0.14 (−0.39, 0.11)	0.004 (0.002, 0.007)
24.4% to <30.0% of energy	−1.02 (−3.41, 1.37)	−0.55 (−1.24, 0.13)	−0.15 (−0.41, 0.10)	0.002 (−0.001, 0.004)
≥30.0% of energy	−0.16 (−2.56, 2.23)	−0.44 (−1.13, 0.25)	−0.16 (−0.41, 0.10)	0.002 (−0.001, 0.004)
P for trend	0.08	0.02	0.14	0.0004
Carbohydrate				
<52.4% of energy	0.53 (−1.86, 2.92)	−0.39 (−1.08, 0.30)	−0.10 (−0.36, 0.15)	0.002 (−0.001, 0.004)
52.4% to <58.7% of energy	−2.12 (−4.50, 0.26)	−0.84 (−1.53, −0.16)	−0.27 (−0.53, −0.02)	0.004 (0.001, 0.006)
58.7% to <63.8% of energy	−1.50 (−3.88, 0.87)	−0.59 (−1.27, 0.10)	−0.16 (−0.41, 0.09)	0.003 (0.000, 0.005)
≥63.8% of energy	−2.87 (−5.24, −0.50)	−1.28 (−1.97, −0.60)	−0.34 (−0.59, −0.08)	0.008 (0.005, 0.010)
P for trend	0.06	0.09	0.27	0.001
Change in measure estimate, baseline to year 3				
No. of subjects	1377	1316	1315	1315
Total fat				
<20.7% of energy	−4.38 (−7.69, −1.07)	−0.83 (−2.04, 0.39)	−0.41 (−0.85, 0.04)	0.005 (0.001, 0.009)
20.7% to <26.2% of energy	0.05 (−3.25, 3.36)	−0.22 (−1.45, 1.00)	−0.11 (−0.55, 0.34)	0.002 (−0.002, 0.006)
26.2% to <32.1% of energy	−1.43 (−4.80, 1.93)	−0.39 (−1.61, 0.83)	−0.16 (−0.60, 0.28)	0.005 (−0.002, 0.006)
≥32.1% of energy	2.79 (−0.56, 6.15)	1.08 (−0.16, 2.31)	0.28 (−0.16, 0.73)	−0.004 (−0.008, −0.000)
P for trend	0.005	0.03	0.03	0.001
Carbohydrate				
<50.5% of energy	3.10 (−0.29, 6.49)	0.22 (−1.03, 1.48)	0.06 (−0.40, 0.52)	−0.002 (−0.006, 0.002)
50.5% to <57.2% of energy	−0.29 (−3.62, 3.04)	0.65 (−0.57, 1.86)	0.11 (−0.33, 0.55)	−0.002 (−0.006, 0.002)
57.2% to <63.1% of energy	−2.04 (−5.34, 1.26)	−0.50 (−1.71, 0.71)	−0.17 (−0.60, 0.27)	0.004 (0.001, 0.008)
≥63.1% of energy	−3.64 (−6.95, −0.34)	−0.73 (−1.95, 0.49)	−0.39 (−0.83, 0.05)	0.004 (0.000, 0.008)
P for trend	0.002	0.12	0.08	0.004
Change in measure estimate, baseline to year 6				
No. of subjects	1528	1526	1525	1525
Total fat				
<23.1% of energy	−1.89 (−5.55, 1.77)	−1.48 (−2.73, −0.24)	−0.38 (−0.83, 0.07)	0.008 (0.003, 0.014)
23.1% to <28.7% of energy	0.33 (−3.27, 3.92)	0.28 (−0.94, 1.51)	0.06 (−0.38, 0.51)	−0.001 (−0.006, 0.004)
28.7% to <33.9% of energy	−0.41 (−4.11, 3.29)	−0.52 (−1.78, 0.75)	−0.25 (−0.70, 0.21)	−0.002 (−0.008, 0.003)
≥33.9% of energy	0.76 (−3.13, 4.65)	−0.59 (−1.92, 0.73)	−0.03 (−0.51, 0.45)	0.002 (−0.004, 0.007)
P for trend	0.37	0.47	0.45	0.05
Carbohydrate				
<47.9% of energy	2.98 (−0.89, 6.84)	−0.15 (−1.47, 1.18)	0.19 (−0.28, 0.67)	−0.002 (−0.008, 0.003)
47.9% to <54.6% of energy	−1.63 (−5.33, 2.06)	−0.71 (−1.97, 0.56)	−0.34 (0.79, 0.12)	0.002 (−0.004, 0.007)
54.6% to <60.4% of energy	−0.54 (−4.15, 3.07)	−0.46 (−1.69, 0.78)	−0.16 (−0.60, 0.28)	−0.000 (−0.005, 0.005)
≥60.4% of energy	−1.73 (−5.37, 1.90)	−0.92 (−2.16, 0.33)	−0.25 (−0.70, 0.19)	0.007 (0.001, 0.012)
P for trend	0.11	0.45	0.26	0.03

[1] All values are means; 95% CI in parentheses. Values were adjusted for age at screening, race-ethnicity, education, Hormone Therapy trial arm, baseline BMI, and baseline glucose or insulin concentration. HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index. Means and 95% CIs are based on least-squares means estimated from linear regression models.

no longer significant, but the change in QUICKI remained significant. These patterns were similar for intakes of saturated fat and polyunsaturated fat (data not shown). Similarly, women in the intervention group who consumed the greatest amount of carbohydrate as a percentage of energy at year 1 had the greatest increases in QUICKI and trends toward greater decreases in glucose and insulin. No differences in changes in glucose, insulin, HOMA-IR, or QUICKI were observed by achieved intake of *trans* fat, vegetables and fruit, fiber, sugars, GI, or GL at year 1 (data not shown). At year 3, women with the greatest reductions in total fat intake had statistically significant trends toward decreasing glucose and insulin concentrations and HOMA-IR and increasing QUICKI. Also at year 3, women with the greatest increases in carbohydrate intake had significant trends toward decreasing glucose concentrations and increasing QUICKI. Women in the intervention group who consumed the greatest amount of carbohydrate as a percentage of energy at year 6 had the greatest increases in QUICKI, which was significant with and without adjustment for weight change at year 6.

DISCUSSION

Our results showed that, whereas consumption of a diet low in fat and high in vegetables, fruit, and grains resulted in an increase in dietary carbohydrate, no significant adverse effects on blood glucose or insulin concentrations or on insulin sensitivity were apparent in postmenopausal women without diabetes at baseline. In fact, women who best complied with the diet (based on their self-reported fat and carbohydrate intakes at year 1) had the greatest decreases in insulin and the greatest increase in insulin sensitivity, even after adjustment for weight change resulting from the diet. Consistent with the overall lack of deleterious effects of the low-fat intervention on fasting glucose and insulin and measures of insulin sensitivity seen in the current study, Tinker et al (2) observed no difference in self-reported incident diabetes in WHI DM intervention and comparison subjects without prevalent diabetes at baseline after a mean follow-up of 8.1 y.

A recent report by Carty et al (17) in a subset of WHI DM participants who received whole-body dual-energy X-ray absorptiometry (DXA) scans found modest body-composition changes with the intervention. This report included women from only the 3 WHI clinical centers performing DXA scans (in contrast with the current study, which included a sample of women from all 40 WHI clinical centers), and only 7% of the 2263 women analyzed in the current study were also in the subset with DXA measurements. Therefore, it was not possible to evaluate the effect of the body-composition changes on glucose, insulin, and insulin resistance. However, the current study augments the report of Carty et al and other previous reports of the WHI DM trial, by describing additional long-term effects of a low-fat dietary intervention.

Women with diabetes at baseline appeared to obtain no glycemic benefit from a reduced fat intake and appeared to show deterioration in glucose homeostasis. Women in the intervention group had a significantly greater increase in mean serum glucose at year 1 than did women in the comparison group over the entire study period in the repeated-measures analysis. This difference was not evident in women with impaired fasting glucose, whose results were similar to women with normoglycemia. This finding agrees with some, but not all, previous studies evaluating the effects of high- and low-carbohydrate diets in persons with diabetes. Several randomized clinical trials (RCTs) in persons with diabetes have shown that higher-carbohydrate, lower-fat diets result in higher blood glucose concentrations than do lower-carbohydrate, higher-fat diets (18–20), although one RCT comparing such diets found no difference in the effects on plasma glucose between the diets (21). Two RCTs of low- and high-carbohydrate diets with equal proportions of fat (but different proportions of protein) showed no differences in mean fasting glucose concentrations at the conclusion of the dietary interventions (22, 23), whereas a nonrandomized clinical study of low- and high-carbohydrate diets with equal proportions of fat resulted in a significant reduction in plasma glucose on the low-carbohydrate diet (24). The studies that compared higher-carbohydrate, lower-fat diets with lower-carbohydrate, higher-fat diets seem to be most relevant to the current study, because a reduction in the percentage of total energy from fat in the DM intervention group was accompanied by an increase in the percentage of total energy from carbohydrate (Table 2). In a meta-analysis of clinical studies of restricted-carbohydrate diets in patients with type 2 diabetes, a greater mean reduction in hyperglycemia was observed with the lower- than with the higher-carbohydrate diets in all 13 studies included (25).

A low-GI/GL diet resulted in significantly greater decreases in fasting glucose and glycosylated hemoglobin concentrations than did a high-cereal fiber diet in a 6-mo RCT in subjects with type 2 diabetes (26). In the current study, whereas GI was equal in both the intervention and comparison participants at years 1, 3, and 6, GL was significantly higher in intervention participants at all 3 time points. However, the higher GL in the intervention participants did not result in higher fasting glucose concentrations at years 1, 3, or 6, nor were changes in fasting glucose and insulin related to baseline GI or GL in the intervention or comparison participants.

We used 2 surrogate indexes of insulin sensitivity derived from blood glucose and insulin concentrations under fasting (steady state) conditions in this study: HOMA-IR and QUICKI (27). HOMA-IR, which has been used extensively in large epidemiologic studies and clinical trials, is a model of interactions between glucose and insulin dynamics that is used to predict steady state glucose and insulin concentrations for a wide range of possible combinations of insulin resistance and β cell function. HOMA-IR is useful for evaluation of insulin resistance in persons with glucose intolerance, mild-to-moderate diabetes, and other insulin-resistant conditions (28). QUICKI is an empirically derived mathematical transformation of fasting blood glucose and plasma insulin concentrations that provides a reliable, reproducible, and accurate index of insulin sensitivity with excellent predictive power (28). Over a wide range of insulin sensitivity/resistance, QUICKI has been shown to have a substantially better linear correlation with insulin sensitivity, as determined by the reference standard glucose clamp than by HOMA-IR (27). Our study seemed to confirm the utility of both indexes. Both HOMA-IR and QUICKI values were significantly better in the intervention than in the comparison participants at year 1, whereas no significant differences in the change in either measure were found between the groups at years 3 and 6. In addition, baseline insulin resistance/sensitivity, assessed by either HOMA-IR or QUICKI, significantly modified the effect of the WHI low-fat intervention on change in glucose concentrations

between baseline and year 1; those in the lowest tertile of HOMA-IR or the highest tertile of QUICKI had greater reductions in glucose concentrations in the intervention than in the comparison participants. However, whereas there were significant trends of higher QUICKI in the intervention participants, with greater reductions in fat intake and greater increases in carbohydrate intake in all years, this was not the case with HOMA-IR.

The strengths of this study included the large and diverse sample (ie, in race-ethnicity and BMI), the comprehensive characterization of the participants that took place within the WHI, and the inclusion of a significant proportion of women with diabetes or impaired fasting glucose. Few diabetic subjects have been included in trials comparing varying macronutrient compositions; in fact, many studies have specifically excluded persons with diabetes. Because there were differences in some baseline characteristics (race-ethnicity, history of hypercholesterolemia requiring medication, and history of cardiovascular disease) between the participants included in this analysis (those with a minimum of baseline and year 1 glucose and insulin measures) and those not included (participants missing at least one of these measures), there was the possibility that some degree of bias was introduced. However, because these differences were small in magnitude, we believe that any resulting bias was minimal. Another limitation was the inclusion of only postmenopausal women; thus, generalizing our results to other populations may not be possible. The well-documented limitations associated with assessing diet with FFQs in general also must be noted. Differences in changes in GI and GL over time between the groups were not statistically significant, which was not surprising considering that the intervention did not target GI and GL. Finally, the overall differences in changes in glucose, insulin, and insulin resistance/sensitivity between the 2 groups in this study were somewhat small in magnitude. Even with small effects, whereas the diminution in risk of a given individual may not be clinically important, because the whole distribution is shifted down, the effect on the population risk can be substantial. Most importantly, although the changes were small, they strongly suggest that eating a low-fat, higher-carbohydrate diet does not result in deleterious effects on glucose or insulin in women without diabetes.

In summary, a reduced-fat dietary pattern with a corresponding increase in the proportion of carbohydrate overall was not significantly associated with adverse effects on glucose or insulin concentrations, or on insulin sensitivity/resistance, in this group of postmenopausal women. However, women with diabetes at baseline did experience adverse glycemic effects of the low-fat diet, which indicated that caution should be exercised in recommending a reduction in overall dietary fat in women with diabetes unless accompanied by additional recommendations to guide carbohydrate intake.

The authors' responsibilities were as follows—KLM: designed the research; MP: analyzed the data; JMS, KLM, RDJ, MCL, SL, LSP, and LFT: wrote the manuscript; and JMS: had primary responsibility for the final content. All authors read and approved the final manuscript. None of the authors reported a conflict of interest.

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