Low-fat, increased fruit, vegetable, and grain dietary pattern, fractures, and bone mineral density: the Women’s Health Initiative Dietary Modification Trial\(^1\)–\(^3\)

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ABSTRACT

Background: The effects of dietary changes on osteoporosis, low bone density, and frequent falls are unestablished.

Objective: We assessed the effect of the Women’s Health Initiative Dietary Modification low-fat and increased fruit, vegetable, and grain intervention on incident hip, total, and site-specific fractures and self-reported falls, and, in a subset, on bone mineral density (BMD).

Design: Postmenopausal women (\(n = 48,835\)) aged 50–79 y (18.6\% of minority race-ethnicity) were randomly assigned to receive the Dietary Modification intervention (40\%, \(n = 19,541\)) (daily goal: ≤20\% of energy as fat, ≥5 servings of vegetables and fruit, and ≥6 servings of grains) or to a comparison group that received no dietary changes (60\%; \(n = 29,294\)).

Results: After a mean 8.1 y of follow-up, 215 women in the intervention group and 285 women in the comparison group (annualized rate: 0.14\% and 0.12\%, respectively) experienced a hip fracture (hazard ratio: 1.12; 95\% CI: 0.94, 1.34; \(P = 0.21\)). The intervention group (\(n = 5423\); annualized rate: 3.44\%) had a lower rate of reporting ≥2 falls than did the comparison group (\(n = 8695\); annualized rate: 3.67\%) (HR: 0.92; 95\% CI: 0.89, 0.96; \(P < 0.01\)). There was a significant interaction according to hormone therapy use; those in the comparison group receiving hormone therapy had the lowest incidence of hip fracture. In a subset of 3951 women, hip BMD at years 3, 6, and 9 was 0.4–0.5% lower in the intervention group than in the comparison group (\(P = 0.003\)).

Conclusions: A low-fat and increased fruit, vegetable, and grain diet intervention modestly reduced the risk of multiple falls and slightly lowered hip BMD but did not change the risk of osteoporotic fractures. This trial was registered at clinicaltrials.gov as NCT00000611. Am J Clin Nutr 2009;89:1864–76.

INTRODUCTION

Approximately 13–17 million postmenopausal women in the United States have low bone mass or osteoporosis (1, 2), and nearly 1.5 million fractures occur annually in older women (3). There are limited data regarding the effect of changing certain lifestyle factors, such as diet, on risk of fracture. The most extensively studied nutritional factor has been the effect of supplemental calcium plus vitamin D, and recent results from the Women’s Health Initiative (WHI) Calcium plus Vitamin D Trial indicate that supplemental calcium plus vitamin D may reduce the risk of hip fractures among adherent women and in women ≥60 y of age (4).

The increased risks of osteoporosis and fracture in postmenopausal women have been linked to declining concentrations of circulating estrogens (5, 6). Treatment with estrogen therapy results in increased bone mineral density (BMD) and a lower risk of osteoporotic fractures (7, 8). The WHI Dietary Modification Trial tested the effect of a low-fat, increased fruit, vegetable, and grain diet on breast cancer and other outcomes. The WHI Dietary Modification intervention resulted in a mean decrease in serum estrogens (9), which could raise the risk of bone loss and fractures. Furthermore, some women adopting a low-fat diet may reduce their intake of dairy foods, with a resulting reduction in dietary calcium and vitamin D intakes (10). Weight loss through calorie reduction has previously been found to reduce BMD (11, 12). Although weight loss was not an objective of the study (13), a small reduction in weight occurred in the study, which may explain the reduction in endogenous estrone concentrations (9). On the other hand, the Dietary Modification intervention might improve BMD and reduce fracture risk because of the beneficial effects of a low-fat dietary pattern on bone resorption and remodeling (14). Also, a low-fat dietary pattern could have beneficial effects on overall health and frailty.

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resulting in fewer falls and therefore a lower risk of fractures. In support of this, observational studies have suggested that high-fat dietary patterns may be associated with an increased risk of fractures (15).

The objective of this article was to describe the effect of the WHI Dietary Modification intervention on incident osteoporosis-related fractures, falls, and on BMD in a subset of women. Secondary objectives were to assess possible effect modification of this relation by other factors, including randomization to the WHI Hormone Therapy Trial or the Calcium plus Vitamin D Trial, age, body mass index (BMI), weight loss during follow-up, and other risk factors for osteoporotic fractures.

SUBJECTS AND METHODS

Study population

The design of the WHI Dietary Modification Trial, including detailed eligibility criteria and recruitment methods, was described previously (9, 16–18). All women were postmenopausal and aged 50–79 y at enrollment, with no evidence of medical conditions associated with a predicted survival of <3 y and no safety, adherence, or retention risks. Women were recruited into 40 clinical centers from across the United States. Participants enrolled in the WHI Dietary Modification Trial or the Hormone Therapy Trial were invited to join the Calcium plus Vitamin D Trial at their first or second annual follow-up visit. The Hormone Therapy Trial components were stopped early, as previously reported (19, 20). The main results from the Dietary Modification (9, 13, 21) and Calcium plus Vitamin D (4, 22) trials were also previously reported.

Major exclusions for the WHI Dietary Modification Trial included prior diagnosis of breast cancer, colorectal cancer, or other cancer (except nonmelanoma skin cancer) in the past 10 y or a diet at baseline with a fat intake <32% of total calories as estimated by the WHI food-frequency questionnaire (FFQ) (23). Use of estrogen (with or without a progestin) was by randomization for those women who were also enrolled in the Hormone Therapy trials. Independent use of hormone therapy or selective estrogen receptor modulators (SERMs) was permitted for women enrolled in the WHI Dietary Modification trials. The WHI Dietary Modification Trial and Hormone Therapy trials participants were all allowed to use bone-health medications, including calcium, vitamin D, bisphosphonates, and calcitonin.

Eligible women were randomly assigned with a computer to an intervention group (40%) or to a comparison group (60%) by stratification for those women who were also enrolled in the Hormone Therapy trials. Stratification by clinical center and age group (50–54, 55–59, 60–69, and 70–79 y). The randomization rate for the intervention group and the comparison group was chosen to minimize study cost while maintaining the specified trial power. The protocol and consent forms were approved by the institutional review boards for each participating institution, and all women provided written informed consent.

Low-fat dietary pattern intervention

Details of the WHI Dietary Modification Trial were published previously (24). Briefly, the intervention was designed to promote dietary change with the goals of reducing intake of total fat to 20% of energy, increasing vegetable and fruit intakes to ≥5 servings/d, and increasing grain intake to ≥6 servings/d. The intervention did not include total energy intake reduction or weight-loss goals. Although not a separate focus of the intervention, it was presumed that by reducing the total fat intake to 20% of energy; saturated fat would be reduced to ≈7% of energy.

The intervention was an intensive behavioral modification program consisting of 18 group sessions in the first year and quarterly maintenance sessions thereafter. Groups consisted of 8–15 women and were led by specially trained and certified nutritionists (17). Each participant was given her own fat gram goal, according to height. The intervention emphasized self-monitoring techniques and introduced other tailored and targeted strategies, such as motivational interviewing to lower fat intake throughout the intervention period. Comparison group participants received a copy of the Dietary Guidelines for Americans and other health-related materials, but were not asked to make dietary changes. Neither group was asked to make changes in their use of dietary supplements or in other health-related behaviors.

Follow-up and data collection

Dietary intake for all participants was monitored by using the WHI FFQ, which was designed specifically for the study. This FFQ was administered at baseline and at 1 y after randomization and thereafter to about one-third of the participants each year in a rotating sample. Study participants were contacted every 6 mo for outcome ascertainment. Height, weight, waist circumference, and blood pressure were measured by using standardized procedures at the annual clinic visits. A fasting blood specimen was collected at baseline and 1 y after randomization, and details of change in diet-related biomarkers in the intervention and comparison groups were published previously (9). Risk factors for fracture were assessed by questionnaire, interview, and clinical examination.

Outcome ascertainment

Outcomes were ascertained by annual clinic visits and telephone or clinic visits at intervening 6-mo intervals. The participants were followed for major outcomes regardless of their adherence to the WHI Dietary Modification Trial (eg, session attendance and reported dietary intake) until death, loss to follow-up or study end. Total fractures were defined as all reported clinical fractures other than those of the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae. Fractures were verified by review of radiology, magnetic resonance imaging (MRI), or operative reports by centrally trained and masked physician adjudicators at each clinical center (25). In addition, final adjudication of hip fractures was performed centrally by blinded adjudicators with 94% agreement between central and local adjudication. Incidence and frequency of falls was determined from semi-annual participant self-reports. In a random subset of 1092 WHI participants, a 3-mo repeat administration of a questionnaire on number of falls in the previous year yielded a κ of 0.45, which indicated a moderate level of reproducibility (26).

A subset of women at 3 clinical centers (Pittsburgh, PA; Birmingham, AL; and Tucson/Phoenix, AZ) (n = 1580 intervention participants and 2371 comparison participants) underwent dual-
energy X-ray absorptiometry (DXA) of the lumbar spine (L2-L4), total hip, and total body (QDR 2000, 2000+, or 4500W; Hologic Inc, Waltham, MA). BMD was measured at the time of randomization and repeated at annual visits 1, 3, 6, and 9 according to standard protocols (27). Three Hologic phantoms (spine, hip, and block) were sent between BMD centers and measured in array mode 5 times once each day for 5 consecutive days to assess cross-calibration. Spine, hip, and block phantoms were in close agreement (interscanner variability: <1.5% spine, 4.8% hip, and 1.7% linearity).

**Statistical analyses**

Comparisons of event rates between the intervention and comparison groups were based on the intent-to-treat principle by using time-to-event methods (28). The time-to-event for an outcome was defined as the number of days from randomization to the first postrandomization diagnosis of the designated event (eg, hip fracture). Follow-up time was censored at the time of a woman’s last documented follow-up contact or death. Quantitative comparisons of event rates between the intervention and comparison groups are presented as hazard ratios (HRs) with nominal 95% CIs from Cox proportional hazards regression (28), stratified by age, prior fracture, and randomization status in the Hormone Therapy trials. Additionally, participation in the Calcium plus Vitamin D Trial was adjusted as a time-dependent variable because women joined the Calcium plus Vitamin D trial 1 to 2 y after Dietary Modification Trial randomization. Annualized event rates were also calculated for absolute disease rate comparisons. Cumulative HRs were estimated by the Kaplan-Meier method.

HRs for the intervention compared with the comparison groups were estimated among women who participated actively in the Dietary Modification trials. Because of the limited reliability of individual dietary assessment, and because dietary data were available only on a subset of women during follow-up, we chose to define adherence in terms of participation in trial activities. Thus, a comparison group woman became nonadherent the first time an annual visit was missed. An intervention group woman became nonadherent at the earliest of a missed annual visit, failure to participate in ≥9 of the 18 first-year intervention sessions, or failure to participate in ≥2 of the 4 maintenance sessions in subsequent years. In a previous publication, WHI investigators showed that attendance at group sessions was significantly associated (P < 0.01) with dietary adherence, and the magnitude of the association was greater than for any of the participant characteristics, including age, race-ethnicity, income, education, or BMI (29).

To examine the effect of nonadherence, Cox proportional hazards regression analyses were performed among women who continued to be adherent using an HR estimation procedure weighted by the inverse of each woman’s estimated adherence probability. This method yields a valid HR estimator among women meeting adherence criteria, provided censoring probabilities can be accurately estimated (30). Under these criteria, the comparison group adherence rates (estimated from a Cox regression model) were 87% at year 3, 75% at year 6, and 65% at year 9, whereas the corresponding intervention group adherence rates were 57%, 31%, and 19%. The weighting procedure aims to produce valid HR estimates, even when adherence rates differ between the 2 groups. Time to nonadherence was modeled separately for the intervention and comparison groups by using Cox regression models. These methods are described in greater detail by Prentice et al (9). Unweighted adherence analyses were conducted for comparison with the weighted adherence analyses.

The possibility of differential intervention effects across subsets of the study population were also explored by including product terms between randomization assignment and indicator variables for the subsets in Cox proportional hazards regression models and testing equality of the product term coefficients with a likelihood ratio test. In addition to baseline indicator variables, subgroup analyses by participation in the Hormone Therapy and Calcium plus Vitamin D trials were conducted. Analyses were also done according to personal intakes of hormone therapy and calcium and vitamin D combined with trial assignment to the active arms of the Hormone Therapy and Calcium plus Vitamin D trials. Because 20 interactions with baseline characteristics are reported, one significant test at the 0.05 level would be expected based on chance alone. Cox models examining subgroup interactions were stratified by age, prevalent condition, and randomization assignment in the Hormone Therapy and Calcium plus Vitamin D trials.

Generalized estimating equation methods were conducted for the analysis of BMD data. We compared estimated mean percentage changes in BMD from baseline across follow-up time by randomization arm, while adjusting for clinical center, race-ethnicity, and weight (kg) at the corresponding visit.

**RESULTS**

Between 1993 and 1998, a total of 48,835 women were randomly assigned into the Dietary Modification trial, 19,541 and 29,294 to the intervention and comparison groups, respectively (Figure 1). Baseline characteristics of the participant were previously described (17). Briefly, the mean age of the participants was 62.3 y, 18.6% of the participants were of a minority race-ethnicity, and the mean BMI (kg/m²) was 29.1. Fracture risk characteristics were comparable in the 2 study groups, including age; race-ethnicity; previous use of menopausal hormone therapy; smoking status; alcohol intake; physical activity [MET (metabolic equivalents)-h/wk]; low body weight (<127 lb, or 57.15 kg); BMI; personal history of fractures or falls; family history of fracture after age 40 y; parity; self-reported health status; mean daily intakes of vitamin D (both dietary intake alone and dietary intake plus supplements), caffeine, fruit and vegetables, and grains; percentage of energy from protein, fat, and total energy; and mean daily intakes of total fat, saturated fat, omega-3 (n–3) fatty acids, and omega-6 fatty acids. Comparison participants were slightly more likely to have a calcium intake < 800 mg/d from diet and supplements (P = 0.04) (Table 1).

A total of 8050 participants in the WHI Dietary Modification trial were also enrolled in the WHI Hormone Therapy trials, and a total of 25,210 were also enrolled in the WHI Calcium plus Vitamin D trial (20,592 in the Dietary Modification trial only; 3,033 in the Dietary Modification and Hormone Therapy trials; 20,193 in the Dietary Modification trial and Calcium plus Vitamin D trials; and 5017 in all 3 trials). A calculated variable that reflected both Hormone Therapy trial randomization and baseline menopausal hormone therapy use did not differ between the
intervention and comparison groups. Similarly, there was no difference between the intervention and comparison women in use of hormone therapy at the 3-y follow-up point (37.5% and 37.8%, respectively; data not shown). No difference was found in assignment when the analyses were restricted to those also in the Hormone Therapy or Calcium plus Vitamin D trial. However, a calculated variable that reflected both Calcium plus Vitamin D Hormone Therapy or Calcium plus Vitamin D trial. Women in the intervention group experienced a modest weight loss early in the trial and maintained a greater weight change from baseline throughout follow-up than did the women in the comparison group (−2.2, −1.3, and −0.8-kg differences between the intervention and control women at year 1, year 3, and year 6, respectively (all P < 0.001)). Dietary differences were similar to those reported from FFQs when the assessment was based on a 4-d food record or 24-h dietary recall. For example, based on 4-d food record assessments, the percentage of energy from fat was 11.3% lower and the intake of fat was 26.3 g lower in the intervention group than in the comparison group at year 1. At year 3, based on 24-h recall assessments, the percentage of energy from fat was 8.2% (19.4 g) lower in the intervention group than in the comparison group and at year 6 was 7.5% (24 g) lower, respectively, in the intervention group.

Clinical outcomes

The mean follow-up time was 8.1 y in both the intervention and comparison groups. Over the course of the trial, 4.7% of the women in the intervention group withdrew from participation or were lost to follow-up compared with 4.0% of the women in the comparison group (Figure 1).

There were a total of 500 hip fractures among participants in the WHI Dietary Modification trial: 215 (0.14% annualized rate) in the intervention group and 285 (0.12% annualized rate) in the comparison group (HR: 1.12; 95% CI: 0.94, 1.34; P = 0.28) (Table 2). There were a total of 552 clinical vertebral fractures among the WHI Dietary Modification trial participants: 208 (annualized rate 0.13%) in the intervention group and 344 (annualized rate 0.15%) in the comparison group (HR: 0.91; 95% CI: 0.77, 1.08; P = 0.28). A similar number of intervention and comparison group participants developed lower arm/wrist or other fractures, and the total numbers of fractures were similar between arms. During the follow-up period, ≥2 self-reported falls were noted in a smaller number of intervention participants (n = 5423, annualized rate 3.44%) than comparison participants (n = 8695, annualized rate 3.67%) (HR: 0.92; 95% CI: 0.89, 0.96; P < 0.01). This lower risk of ≥2 falls in the intervention women than in the comparison women was not affected by adjustment for total physical activity (MET-h/wk) reported at the year 1 follow-up point (P for interaction = 0.82).

Additional adjustment for Calcium plus Vitamin D trial participation as a time-dependent variable and for baseline intake of omega-3- and omega-6-fatty acids yielded almost identical results. Therefore, the data are not shown.

When we assessed the intervention effect according to adherence to the dietary intervention, based on an adherence model (described in the statistical analysis section), the HRs for outcome

Low-fat dietary pattern adoption and maintenance

Previously, the WHI investigators reported on dietary pattern changes in the intervention and comparison participants in the Dietary Modification trial (9). On the basis of data from women who provided FFQs, the average reductions in percentage of energy from fat for the intervention group compared with the comparison group was 10.7 at year 1, which decreased to 8.1 at year 6 (both P < 0.001). The absolute difference in the percentage of energy from fat on the FFQ between adherent women in the intervention group and adherent women in the comparison group was 12.1 percentage points at year 1, 11.8 percentage points at year 3, 11.1 percentage points at year 6, and 10.1 percentage points at year 9. Between baseline and year 1, the

FIGURE 1. Participant screening and randomization.
### TABLE 1

Descriptive characteristics of participants randomly assigned to the Women’s Health Initiative Dietary Modification (DM) intervention or to a comparison group

|                          | DM intervention (n = 19,541) | Comparison (n = 29,294) | P value $^2$ |
|--------------------------|------------------------------|-------------------------|-------------|
| No. of subjects          | 19,541                       | 29,294                  | 0.99        |
| Age at screening (y)     |                              |                         | >0.99       |
| 50–59 y                  | 7206                         | 10,792                  | 36.8        |
| 60–69 y                  | 9083                         | 13,632                  | 46.5        |
| 70–79 y                  | 3252                         | 4870                    | 16.6        |
| Race-ethnicity (%)       |                              |                         | 0.76        |
| White                    | 15,869                       | 23,890                  | 81.2        |
| Black                    | 2137                         | 3129                    | 10.9        |
| Hispanic                 | 755                          | 1099                    | 3.9         |
| American Indian          | 88                           | 115                     | 0.5         |
| Asian/Pacific Islander   | 433                          | 674                     | 2.2         |
| Unknown                  | 259                          | 387                     | 1.3         |
| BMI (kg/m²)              | 19,454                       | 29,157                  | 29.1 ± 5.9  |
| Weight <127 lb (%)       | 1730                         | 2600                    | 8.9         |
| Any fracture over age 55 y, before enrollment (%) | 2078                     | 3098                    | 10.6        |
| Number of falls in last 12 mo (%) | 7117                   | 10,790                  | 36.8        |
| General health, self-reported (%) |                  |                         | 0.93        |
| Excellent                | 3115                         | 4499                    | 15.9        |
| Very good                | 7946                         | 12,022                  | 40.7        |
| Good                     | 6798                         | 10,282                  | 34.8        |
| Fair                     | 1475                         | 2200                    | 7.5         |
| Poor                     | 89                           | 151                     | 0.5         |
| Parity (%)               |                              |                         | 0.69        |
| Never pregnant           | 1618                         | 2482                    | 8.3         |
| Never had term pregnancy | 505                          | 745                     | 2.6         |
| 1                        | 1682                         | 2463                    | 8.6         |
| 2                        | 4766                         | 7002                    | 24.4        |
| 3                        | 4714                         | 7183                    | 24.1        |
| 4                        | 3120                         | 4666                    | 16.0        |
| ≥5                       | 3039                         | 4628                    | 15.6        |
| Baseline menopausal HT (%) |                              |                         | 0.96        |
| Never used               | 8076                         | 12,104                  | 41.3        |
| Past user                | 2810                         | 4186                    | 14.3        |
| Current user             | 8640                         | 12,972                  | 44.3        |
| Duration of prior menopausal HT (%) |                  |                         | 0.71        |
| Nonuser                  | 8076                         | 12,104                  | 41.3        |
| <5 y                     | 4468                         | 6656                    | 22.9        |
| 5–10 y                   | 2559                         | 3938                    | 13.1        |
| >10 y                    | 4438                         | 6596                    | 22.7        |
| E-alone trial treatment assignment (%) $^5$ |                        |                         | 0.41        |
| E-alone placebo          | 670                          | 1068                    | 52.1        |
| E-alone                  | 615                          | 1039                    | 47.9        |
| E-P trial treatment assignment (%) $^6$ |                        |                         | 0.30        |
| E-P placebo              | 972                          | 1457                    | 51.2        |
| E+P                      | 925                          | 1304                    | 48.8        |

(Continued)
variables were largely unchanged (Table 2), although the HR for experiencing ≥2 falls for intervention group compared with the comparison group was slightly more apparent (0.87; 95% CI: 0.82, 0.93; P < 0.01).

Assessment of the intervention effect by various risk factors for osteoporotic fractures showed no evidence of a consistent interaction across types of fractures. Of note, women with a history of a fracture after age 55 y (but before randomization) had a statistically significant greater risk of hip fracture if they participated in the WHI Dietary Modification intervention compared with the comparison group (HR: 1.63; 95% CI: 1.15, 2.31; P for interaction = 0.01) (Table 3). We conducted similar analyses for the clinical vertebral and total fractures, but found no significant interactions.

We assessed interactions by menopausal hormone therapy use. We analyzed data by personal hormone use at baseline, hormone use at baseline plus active hormone trial arm assignment, and in the subset participating in the hormone trials, according to trial assignment. A significant interaction effect was observed (Table 3). There was no apparent interaction by personal hormone use.
at baseline. However, among women who were randomly assigned to the active arms of the estrogen-alone (E-alone) trial and estrogen plus progestin (E+P) trials, the risk of hip fracture increased: E-alone (HR 3.82; 95% CI 1.18, 12.40) and E+P (HR 2.89; 95% CI 1.22, 6.82). Overall, the risk associated with randomization to the Dietary Modification intervention for E-alone or E+P active arm participants was increased by a factor of 3.20 (95% CI: 1.60, 6.40). Of note, the HRs observed were largely influenced by a reduced annualized incidence in the Dietary Modification comparison groups, rather than as a result of an increase in the annualized incidence in the Dietary Modification intervention group receiving hormone therapy.

When we partitioned women into those who were randomly assigned to active treatment in the Calcium plus Vitamin D trial (including 1000 mg Ca/d plus dietary intake) or whose calcium intake from dietary and supplemental means was ≥1200 mg/d at study enrollment compared with those with lower intakes, there was no significant interaction effect (Table 3). Among women who were in the high intake group, the risk of hip fractures associated with randomization to the Dietary Modification intervention was not notably or statistically significantly different from that of women with lower calcium intakes. In addition, no interaction was seen when the analysis was restricted to those randomly assigned to the Calcium plus Vitamin D trial.

There was differential weight loss by treatment arm (a mean decrease of 0.8 kg in the Dietary Modification intervention group compared with a mean decrease of 0.1 kg in the comparison group; P < 0.001) (31). When we assessed fracture risk by intervention status with weight during follow-up, adjusted as a time-dependent variable, the overall results did not change, although the HR for hip fracture decreased to 0.88 (95% CI: 0.68, 1.14; P = 0.34) (Table 4). The results were similar when weight change was used as the adjustment variable.

The baseline BMD values at the hip, spine, and total body are shown in Table 1, which were not significantly different between the intervention and comparison groups. The effect of intervention status on BMD is shown in Figure 2. After adjustment for clinical center, race-ethnicity, and weight at baseline and at each annual follow-up visit, the difference in the percentage change in hip BMD was consistently significantly lower in the intervention group (by 0.4–0.5%) than in the comparison group (P = 0.003). There was little discernable effect of intervention on the percentage change in total-body or spine BMD (P = 0.58 and 0.78, respectively).

DISCUSSION

The WHI Dietary Modification trial is the first large-scale randomized trial to test the effect of a low-fat, increased fruit, vegetable, and grain dietary pattern on the risk of osteoporotic fractures in postmenopausal women. The WHI intervention resulted in significant and sustained reduction in fat intake and increased intakes of vegetables and fruit (9). After ≈8 y of follow-up, there was no significant effect of the intervention on hip, clinical vertebral, lower arm/wrist, or total osteoporotic-related fractures. Similarly, in the subset of women who underwent BMD testing, there was no significant effect of the intervention on change in vertebral or total-body BMD. There was, however, a statistically significant yet very small decrease in hip BMD in the intervention group compared with the comparison group that persisted throughout follow-up. In addition, women in the Dietary Modification intervention had a slightly lower risk of falling ≥2 times during follow-up than did the women in the comparison group.

Few studies of the effects of diets low in fat or high in vegetables and fruit on BMD or fractures in postmenopausal women have been published. In the New York Women’s Health Study cohort of 6250 postmenopausal women, 1025 new incident bone fractures were reported after a mean 7.6 y of follow-up (15). Compared with women in the lowest quintile of calorie-adjusted daily dietary fat intake, women in the highest quintile of calorie-adjusted daily dietary fat intake had a 23% greater risk of all fractures (relative risk: 1.23; 95% CI: 1.0. 1.5; P for trend = 0.005) and a 43% greater risk of wrist or hip fracture (relative risk: 1.43; 95% CI: 0.9, 2.3; P for trend = 0.06).

A 3-mo Dietary Approaches to Stopping Hypertension (DASH) intervention study involving 186 men and women aged 23–76 y found that a diet high in fruit and vegetables significantly reduced bone turnover (32). The DASH diet emphasizes an increased

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**TABLE 2**

Incidence (annualized rate) of fractures and falls, according to Dietary Modification (DM) treatment

| Variable                  | DM intervention | Comparison | Intent-to-treat analysis | Sensitivity analysis for adherence |
|---------------------------|-----------------|------------|--------------------------|-----------------------------------|
|                           | (n = 19,541)    | (n = 29,294) | HR (95% CI) | P value | HR (95% CI) | P value |
| Hip                       | 215 (0.14)      | 285 (0.12)  | 1.12 (0.94, 1.34)        | 0.21                              | 1.17 (0.85, 1.59) | 0.34 |
| Clinical vertebral        | 208 (0.1)       | 344 (0.15)  | 0.91 (0.77, 1.08)        | 0.28                              | 0.79 (0.58, 1.09) | 0.15 |
| Lower arm or wrist        | 652 (0.41)      | 950 (0.40)  | 1.03 (0.93, 1.14)        | 0.56                              | 1.04 (0.88, 1.23) | 0.65 |
| Total                     | 2400 (1.52)     | 3695 (1.56) | 0.97 (0.92, 1.02)        | 0.28                              | 0.99 (0.90, 1.08) | 0.76 |
| Two or more falls         | 5423 (3.44)     | 8695 (3.67) | 0.92 (0.89, 0.96)        | <0.01                             | 0.87 (0.82, 0.93) | <0.01 |

1 Hazard ratios (HRs), 95% CIs, and P values are from Cox proportional hazards regression models stratified according to age group, Hormone Therapy trial randomization arm, and history of fractures and adjusted for time-dependent Calcium plus Vitamin D trial randomization arm.

2 HRs, 95% CIs, and P values are from Cox proportional hazards regression models stratified according to age group, Hormone Therapy trial randomization arm, and history of fractures and weighted by using inverse probability weights from an adherence model. Time to nonadherence was modeled separately for intervention and comparison groups and was adjusted for age, ethnicity, education, BMI, physical activity (metabolic equivalent hours/wk), alcohol intake, smoking, income, total energy intake, percentage of energy from fat, family history of fracture, social support, optimism, life events, hostility, negative emotion construct, use of multivitamins, Hormone Therapy trial randomization arm, and number of fruit, vegetable, and grain servings per day.
### TABLE 3
Incidence (annualized rate) of hip fracture, according to baseline characteristics and treatment group

| Variable                                | DM intervention | Comparison | HR (95% CI)     | P value for interaction |
|-----------------------------------------|-----------------|------------|-----------------|------------------------|
| overall                                 | 215 (0.14)      | 285 (0.12) | 1.13 (0.95, 1.35)|                        |
| age at enrollment                       |                 |            |                 |                        |
| 50–59 y                                 | 14 (0.02)       | 30 (0.03)  | 0.70 (0.37, 1.32)| 0.08                   |
| 60–69 y                                 | 88 (0.12)       | 107 (0.10) | 1.24 (0.93, 1.64)|                        |
| 70–79 y                                 | 113 (0.45)      | 148 (0.39) | 1.14 (0.89, 1.45)|                        |
| race-ethnicity                          |                 |            |                 |                        |
| white                                   | 198 (0.15)      | 266 (0.14) | 1.10 (0.92, 1.33)| 0.31                   |
| black                                   | 6 (0.04)        | 9 (0.04)   | 0.98 (0.35, 2.76)|                        |
| hispanic                                | 6 (0.10)        | 3 (0.04)   | 2.87 (0.71, 11.54)|                        |
| american indian                         | 0 (0.00)        | 2 (0.22)   | NA              |                        |
| asian or pacific islander               | 2 (0.06)        | 1 (0.02)   | 3.54 (0.32, 39.10)|                        |
| unknown/other                           | 3 (0.15)        | 2 (0.07)   | 2.00 (0.33, 11.97)|                        |
| bmi                                      |                 |            |                 |                        |
| <18.5 kg/m²                              | 1 (0.19)        | 3 (0.43)   | NA              | 0.15                   |
| 18.5 to <25 kg/m²                       | 67 (0.16)       | 99 (0.16)  | 1.00 (0.74, 1.37)|                        |
| 25 to <30 kg/m²                         | 82 (0.15)       | 115 (0.14) | 1.10 (0.83, 1.47)|                        |
| ≥30 kg/m²                               | 65 (0.11)       | 68 (0.08)  | 1.42 (1.01, 1.99)|                        |
| weight <127 lb                           |                 |            |                 |                        |
| no                                       | 188 (0.13)      | 248 (0.11) | 1.14 (0.94, 1.38)| 0.83                   |
| yes                                      | 27 (0.19)       | 37 (0.18)  | 1.09 (0.66, 1.79)|                        |
| any fracture over age 55 y               |                 |            |                 |                        |
| no                                       | 99 (0.11)       | 159 (0.11) | 0.93 (0.73, 1.20)| 0.01                   |
| yes                                      | 67 (0.42)       | 61 (0.25)  | 1.63 (1.15, 2.31)|                        |
| parent had fracture after age 40 y       |                 |            |                 |                        |
| no                                       | 112 (0.13)      | 146 (0.11) | 1.15 (0.90, 1.46)| 0.90                   |
| yes                                      | 87 (0.15)       | 119 (0.14) | 1.11 (0.84, 1.46)|                        |
| number of falls in past 12 mo            |                 |            |                 |                        |
| none                                     | 122 (0.13)      | 156 (0.11) | 1.17 (0.92, 1.48)| 0.78                   |
| 1 time                                   | 41 (0.14)       | 59 (0.13)  | 1.05 (0.70, 1.56)|                        |
| 2 times                                  | 23 (0.19)       | 28 (0.15)  | 1.28 (0.73, 2.22)|                        |
| ≥3 times                                 | 10 (0.18)       | 16 (0.19)  | 1.04 (0.46, 2.32)|                        |
| smoking                                  |                 |            |                 |                        |
| never smoked                             | 102 (0.13)      | 158 (0.13) | 0.99 (0.77, 1.27)| 0.29                   |
| past smoker                              | 93 (0.14)       | 102 (0.11) | 1.34 (1.01, 1.78)|                        |
| current smoker                           | 17 (0.17)       | 21 (0.13)  | 1.23 (0.65, 2.34)|                        |
| alcohol intake                           |                 |            |                 |                        |
| nondrinker                               | 19 (0.12)       | 26 (0.11)  | 1.08 (0.60, 1.95)| 0.92                   |
| past drinker                             | 42 (0.15)       | 56 (0.13)  | 1.10 (0.74, 1.65)|                        |
| <1 drink/mo                              | 29 (0.14)       | 48 (0.15)  | 0.91 (0.58, 1.45)|                        |
| <1 drink/wk                              | 47 (0.14)       | 60 (0.12)  | 1.22 (0.83, 1.78)|                        |
| 1 to <7 drinks/wk                        | 52 (0.12)       | 68 (0.11)  | 1.16 (0.81, 1.66)|                        |
| ≥7 drinks/wk                             | 23 (0.15)       | 25 (0.11)  | 1.34 (0.76, 2.36)|                        |
| general health, self-reported            |                 |            |                 |                        |
| excellent                                | 24 (0.09)       | 35 (0.09)  | 1.04 (0.62, 1.74)| 0.60                   |
| very good                                | 80 (0.12)       | 100 (0.10) | 1.21 (0.90, 1.63)|                        |
| good                                     | 82 (0.15)       | 121 (0.15) | 1.00 (0.76, 1.33)|                        |
| fair                                     | 26 (0.23)       | 25 (0.15)  | 1.57 (0.91, 2.73)|                        |
| poor                                     | 1 (0.16)        | 2 (0.17)   | 0.93 (0.08, 10.32)|                        |
| parity                                   |                 |            |                 |                        |
| never pregnant                           | 20 (0.15)       | 20 (0.10)  | 1.48 (0.79, 2.76)| 0.43                   |
| never had term pregnancy                 | 2 (0.05)        | 7 (0.12)   | 0.42 (0.08, 2.08)|                        |
| 1                                        | 23 (0.17)       | 29 (0.15)  | 1.11 (0.64, 1.92)|                        |
| 2                                        | 50 (0.13)       | 72 (0.13)  | 1.07 (0.74, 1.53)|                        |
| 3                                        | 59 (0.15)       | 63 (0.11)  | 1.40 (0.98, 2.00)|                        |
| 4                                        | 33 (0.13)       | 45 (0.12)  | 1.05 (0.67, 1.65)|                        |
| ≥5                                       | 28 (0.12)       | 48 (0.13)  | 0.89 (0.56, 1.43)|                        |
| prior menopausal HT at baseline          |                 |            |                 |                        |
| nonuser                                  | 116 (0.18)      | 152 (0.16) | 1.14 (0.89, 1.45)| 0.98                   |
| past user                                | 32 (0.14)       | 41 (0.12)  | 1.18 (0.74, 1.87)|                        |
| current user                             | 67 (0.10)       | 92 (0.09)  | 1.11 (0.81, 1.52)|                        |

(Continued)
intake of fruit, vegetables, low-fat dairy foods, whole grains, poultry, fish, and nuts and a reduced intake of fats, red meat, sweets, and sugar-containing beverages. In addition, the DASH diet emphasizes low amounts of total fat, saturated fat, and cholesterol and increased amounts of potassium, calcium, magnesium, dietary fiber, and protein. The DASH diet reduced serum osteocalcin by 8–11% and C-terminal telopeptide of type I collagen by 16–18% (both $P < 0.001$ compared with controls). It is not clear, however, whether the effect of the DASH diet on bone markers was observed in the subgroup of women who were postmenopausal.

Some epidemiologic and experimental studies have suggested that a high intake of omega-3 fatty acids is associated with

| Variable | DM intervention | Comparison | HR (95% CI)$^3$ | $P$ value for interaction$^3$ |
|----------|-----------------|------------|-----------------|------------------------------|
| Duration of prior HT reported at baseline | | | | |
| Nonuser | 116 (0.18) | 152 (0.16) | 1.14 (0.89, 1.45) | 0.61 |
| <5 y | 36 (0.10) | 38 (0.07) | 1.41 (0.89, 2.23) | 0.13 |
| 5–10 y | 21 (0.10) | 27 (0.08) | 1.24 (0.70, 2.19) | 0.36 |
| >10 y | 42 (0.12) | 68 (0.13) | 0.94 (0.64, 1.38) | 0.82 |
| HT active arms or baseline personal HT current users | | | | |
| No | 125 (0.16) | 182 (0.16) | 1.02 (0.81, 1.28) | 0.72 |
| Yes | 90 (0.11) | 105 (0.08) | 1.34 (1.01, 1.78) | 0.41 |
| Baseline total calcium intake | | | | |
| <800 mg/d | 80 (0.14) | 93 (0.10) | 1.34 (0.99, 1.81) | 0.87 |
| 800–1200 mg/d | 43 (0.10) | 62 (0.10) | 1.00 (0.67, 1.47) | 0.51 |
| >1200 mg/d | 92 (0.16) | 130 (0.15) | 1.04 (0.80, 1.36) | 0.13 |
| Baseline total vitamin D intake | | | | |
| <200 IU/d | 84 (0.13) | 96 (0.10) | 1.35 (1.00, 1.81) | 0.82 |
| 200 to <400 IU/d | 37 (0.11) | 51 (0.11) | 1.04 (0.68, 1.58) | 0.94 |
| 400 to <800 IU/d | 77 (0.14) | 121 (0.15) | 0.96 (0.72, 1.27) | 0.56 |
| ≥800 IU/d | 17 (0.22) | 17 (0.15) | 1.48 (0.75, 2.91) | 0.31 |
| CaD active arms or baseline calcium intake >1200 mg/d | | | | |
| No | 101 (0.14) | 125 (0.11) | 1.17 (0.90, 1.52) | 0.72 |
| Yes | 114 (0.14) | 160 (0.12) | 1.10 (0.87, 1.40) | 0.83 |
| Physical activity | | | | |
| <1.5 MET-h/wk | 58 (0.17) | 57 (0.11) | 1.53 (1.06, 2.21) | 0.41 |
| 1.5 to <6.3 MET-h/wk | 54 (0.15) | 67 (0.13) | 1.13 (0.79, 1.61) | 0.37 |
| ≥6.3 to <14.8 MET-h/wk | 36 (0.11) | 76 (0.15) | 0.74 (0.50, 1.10) | 0.09 |
| ≥14.8 MET-h/wk | 44 (0.13) | 54 (0.10) | 1.21 (0.81, 1.80) | 0.01 |
| Daily caffeine intake | | | | |
| <76.8 mg | 52 (0.13) | 63 (0.11) | 1.23 (0.85, 1.77) | 0.31 |
| 76.8 to <177.4 mg | 60 (0.16) | 70 (0.12) | 1.32 (0.93, 1.86) | 0.24 |
| 177.4 to <196.8 mg | 57 (0.14) | 80 (0.14) | 1.07 (0.76, 1.50) | 0.43 |
| ≥196.8 mg | 46 (0.12) | 70 (0.12) | 0.97 (0.67, 1.41) | 0.75 |
| Women in HT active arms (n = 8050) | | | | |
| Placebo | 19 (0.15) | 34 (0.18) | 0.82 (0.47, 1.44) | 0.01 |
| E-alone or E+P | 24 (0.19) | 13 (0.06) | 3.20 (1.60, 6.40) | 0.14 |
| E-alone trial arms only (n = 3392)$^3$ | Placebo | 10 (0.19) | 13 (0.15) | 1.34 (0.59, 3.05) | 0.14 |
| E-alone | 9 (0.18) | 5 (0.06) | 3.82 (1.18, 12.40) | 0.04 |
| E+P trial arms only (n = 4658)$^4$ | Placebo | 9 (0.12) | 21 (0.20) | 0.55 (0.25, 1.20) | 0.004 |
| E+P | 15 (0.19) | 8 (0.07) | 2.89 (1.22, 6.82) | 0.04 |
| CaD treatment assignment (n = 25,210)$^5$ | Placebo | 51 (0.13) | 79 (0.12) | 1.01 (0.71, 1.44) | 0.40 |
| Intervention | 42 (0.11) | 57 (0.09) | 1.26 (0.85, 1.88) | 0.47 |

$^1$ Hazard ratios (HRs), 95% CIs, and $P$ values are from Cox proportional hazards regression models stratified by age, Hormone Therapy trial randomization arm, and prior fracture. $P$ values are from a likelihood ratio test comparing Cox proportional hazards regression models with and without the interaction terms between treatment assignment and the potential risk factor of interest. The interaction was evaluated as a continuous linear trend when possible. HT, hormone therapy; MET, metabolic equivalents; CaD, Calcium plus Vitamin D trial; E, estrogen; P, progestin; NA, cannot be estimated; DM, Dietary Modification.

$^2$ Includes only DM trial participants who also participated in the E-alone Hormone Therapy trial.

$^3$ Includes only DM trial participants who also participated in the E+P Hormone Therapy trial.

$^4$ Includes only DM trial participants who also participated in the CaD trial.

$^5$ Includes only DM trial participants who also participated in the CaD trial.
increased BMD (33). Adjustment for baseline intake did not change any of the fracture outcomes, however. There was a statistically significant interaction between use of menopausal hormone therapy at baseline or randomization into the active arms of the Hormone Therapy trial. Those in the Dietary Modification comparison group who were also taking menopausal hormone therapy had the lowest annualized incidence of hip fracture. One possible explanation is that the women who consumed a low-fat diet may have had greater concentrations of sex hormone–binding globulin than the women in the comparison group (9), which resulted in less free estradiol available for bone remodeling and thus more hip fractures.

The intervention participants lost slightly more weight than did the comparison women (0.8 kg compared with 0.1 kg). We found no association between amount of weight loss and risk of bone fracture or change in BMD in a comparison of the intervention and comparison groups. However, previous studies have shown that weight loss through calorie reduction results in a reduction in BMD and an increase in frailty fracture risk; thus, larger amounts of weight loss than those observed with the WHI Dietary Modification intervention could be detrimental to bone health (12, 34, 35).

It is not clear why the incidence of ≥2 falls was lower in the intervention group than in the comparison group. Previous research has shown an effect of exercise training and other lifestyle changes in preventing falls among the elderly (36), but little research has been done on the influence of diet on falling. An increase in vitamin D intake is associated with a reduced risk of falling (37); however, there was no interaction between the WHI dietary intervention status and baseline (before randomization) vitamin D intake on the risk of falling. Possible reasons for fewer falls in the WHI Dietary Modification intervention group include the following: better cognitive function resulting from improved socialization as a result of group dietary meetings, dietary change–induced weight loss resulting in improved balance, dietary change–induced reductions in arteriosclerosis resulting in better neurological control of balance, or reduced sarcopenia due to increased circulating carotenoids. The mean difference in total carotenoids between the intervention and comparison groups at 3 y was 0.04 μg/mL; P < 0.05 (31), which could lead to improved strength and balance (38, 39). Given the

### TABLE 4
Incidence (annualized rate) of fractures and falls, according to Dietary Modification (DM) treatment group adjusted for weight during follow-up

| Variable      | DM intervention (n = 19,541) | Comparison (n = 29,294) | Hazard ratio (95% CI) | P value |
|---------------|-------------------------------|-------------------------|-----------------------|---------|
| no. of events (annualized %) | Hip 215 (0.14) 285 (0.12) 0.88 (0.68, 1.14) 0.34 | | | |
|               | Clinical vertebral 208 (0.13) 344 (0.15) 0.93 (0.75, 1.16) 0.54 | | | |
|               | Lower arm or wrist 652 (0.41) 950 (0.40) 1.06 (0.95, 1.19) 0.28 | | | |
|               | Total 2400 (1.52) 3695 (1.56) 0.96 (0.91, 1.02) 0.21 | | | |
|               | ≥2 Falls 5423 (3.44) 8695 (3.67) 0.91 (0.88, 0.95) <0.01 | | | |

1 Hazard ratios, 95% CIs, and P values are from Cox proportional hazards regression models stratified according to age group, Hormone Therapy trial randomization arm, and history of fractures and adjusted for weight (kg) reported at annual visits as a time-dependent variable.

### FIGURE 2
Mean (±SE) percentage changes from baseline in hip bone mineral density (BMD), spine BMD, and total-body BMD in a subset of participants in the Women’s Health Initiative Dietary Modification trial from 3 clinical centers who were randomly assigned to the Dietary Modification intervention group (n = 1580) or to a comparison group (n = 2371). Generalized estimating equations were used to compare the mean percentage changes in BMD from baseline by visit, with adjustment for clinical center, race-ethnicity, and weight (kg) at the corresponding visit. Mean (±SD) change in hip BMD from baseline: 0.87 ± 0.14 in the intervention group and 0.88 ± 0.14% in the comparison group. Mean (±SD) change in spine BMD from baseline: 0.99 ± 0.17 in the intervention group and 0.99 ± 0.17% in the comparison group. Mean (±SD) change in total-body BMD from baseline: 1.02 ± 0.11% in the intervention group and 1.03 ± 0.11 in the comparison group.
number of comparisons made, we cannot rule out the possibility that this observed association was due to chance alone. Although there was a significant interaction according to Hormone Therapy Trial assignment, the total number of hip fractures seen was small. In addition, the HRs were largely influenced by a reduced number of hip fractures in women assigned to active hormone therapy who were in the comparison group.

The present study had limitations. The WHI Dietary Modification Trial was designed to test the effect of a particular dietary pattern on risk of breast cancer and cardiovascular disease and was not designed specifically to test the effects on osteoporotic fractures. The WHI Dietary Modification cohort of women was not chosen based on risk of fractures, and the overall annual incidence of hip fractures (0.13%) was lower than that observed in other cohorts of postmenopausal women (40). Among the subset of women for whom BMD was measured, the baseline mean values of 0.87, 0.99, and 1.03 g/cm², respectively, for hip, spine, and total-body BMD were higher than the value for the general US population of postmenopausal women (1); therefore, on average, they did not have an elevated risk of osteoporotic fractures. The difference in percentage energy from fat between intervention and comparison women was only ∼70% of the design goal, and relatively few women met the dietary target of 20% of energy from fat: 31.4% at year 1 and 14.4% at year 6 (9). On average, the participants in this study were calcium replete at baseline, most of whom continued to be so throughout the study. As such, the dietary changes made may not have reflected a reduction in calcium intake that would be associated with risk of fracture. Given that the intervention goals included a reduction of all dietary fats and an increased intake of all vegetables, fruit, and grains, it is not possible to identify any one dietary factor as causally related to any study outcome.

The reliance on self-reported methods to assess differences in dietary consumption between the intervention and comparison groups was also a limitation. However, the relative changes in blood γ-tocopherol concentrations between the randomization groups were consistent with reports of decreased intakes of added fats and oils in the intervention participants and the changes in carotenoids were consistent with FFQ-reported differences in vegetable and fruit intakes (10).

In conclusion, although the WHI Dietary Modification low-fat dietary intervention resulted in fewer falls and in a significant reduction in hip BMD in the subset of women who underwent DXA testing, there was no significant difference in the risk of osteoporotic fractures over a mean 8.1-y period. The results of this study indicate that a low-fat dietary pattern such as the WHI Dietary Modification intervention does not have an overall detrimental effect on the risk of osteoporotic fractures.

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