

# Low-Fat Dietary Pattern and Risk of Cardiovascular Disease

## The Women's Health Initiative Randomized Controlled Dietary Modification Trial

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**C**LINICAL TRIALS AND OBSERVATIONAL studies have identified strong associations between low-density lipoprotein cholesterol (LDL-C) level and other cardiovascular disease (CVD) risk factors and dietary intake of fats, particularly

See also pp 629, 643, and 693.

**Context** Multiple epidemiologic studies and some trials have linked diet with cardiovascular disease (CVD) prevention, but long-term intervention data are needed.

**Objective** To test the hypothesis that a dietary intervention, intended to be low in fat and high in vegetables, fruits, and grains to reduce cancer, would reduce CVD risk.

**Design, Setting, and Participants** Randomized controlled trial of 48 835 postmenopausal women aged 50 to 79 years, of diverse backgrounds and ethnicities, who participated in the Women's Health Initiative Dietary Modification Trial. Women were randomly assigned to an intervention (19 541 [40%]) or comparison group (29 294 [60%]) in a free-living setting. Study enrollment occurred between 1993 and 1998 in 40 US clinical centers; mean follow-up in this analysis was 8.1 years.

**Intervention** Intensive behavior modification in group and individual sessions designed to reduce total fat intake to 20% of calories and increase intakes of vegetables/fruits to 5 servings/d and grains to at least 6 servings/d. The comparison group received diet-related education materials.

**Main Outcome Measures** Fatal and nonfatal coronary heart disease (CHD), fatal and nonfatal stroke, and CVD (composite of CHD and stroke).

**Results** By year 6, mean fat intake decreased by 8.2% of energy intake in the intervention vs the comparison group, with small decreases in saturated (2.9%), monounsaturated (3.3%), and polyunsaturated (1.5%) fat; increases occurred in intakes of vegetables/fruits (1.1 servings/d) and grains (0.5 serving/d). Low-density lipoprotein cholesterol levels, diastolic blood pressure, and factor VIIc levels were significantly reduced by 3.55 mg/dL, 0.31 mm Hg, and 4.29%, respectively; levels of high-density lipoprotein cholesterol, triglycerides, glucose, and insulin did not significantly differ in the intervention vs comparison groups. The numbers who developed CHD, stroke, and CVD (annualized incidence rates) were 1000 (0.63%), 434 (0.28%), and 1357 (0.86%) in the intervention and 1549 (0.65%), 642 (0.27%), and 2088 (0.88%) in the comparison group. The diet had no significant effects on incidence of CHD (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.90-1.06), stroke (HR, 1.02; 95% CI, 0.90-1.15), or CVD (HR, 0.98; 95% CI, 0.92-1.05). Excluding participants with baseline CVD (3.4%), the HRs (95% CIs) for CHD and stroke were 0.94 (0.86-1.02) and 1.02 (0.90-1.17), respectively. Trends toward greater reductions in CHD risk were observed in those with lower intakes of saturated fat or *trans* fat or higher intakes of vegetables/fruits.

**Conclusions** Over a mean of 8.1 years, a dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains did not significantly reduce the risk of CHD, stroke, or CVD in postmenopausal women and achieved only modest effects on CVD risk factors, suggesting that more focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk.

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saturated and *trans* fats, cholesterol, plant products, and grains or fiber. Epidemiologic studies have demonstrated that diets low in saturated fat and cholesterol are associated with lower rates of CVD and have implicated several nutrients as determinants of CVD risk.<sup>1-6</sup> Replacing saturated fat with polyunsaturated fat reduced cardiovascular events in some early trials.<sup>7-9</sup> In more recent secondary prevention trials, a Mediterranean-type dietary pattern<sup>10,11</sup> or a very low-fat eating pattern<sup>12</sup> prevented recurrent events, and meta-analyses<sup>13,14</sup> of recent trials of lipid-lowering drugs have documented a strong relationship between changes in LDL-C level and decreased incidence of coronary heart disease (CHD).

Whether a single “healthy” diet could result in decreased risks of cancer and CVD has not been previously evaluated. The primary aim of the Women’s Health Initiative (WHI) Dietary

Modification Trial was to test whether behavioral intervention intended to produce a dietary pattern low in total fat, along with increased intakes of vegetables, fruits, and grains, would decrease the incidence of breast and colorectal cancer in postmenopausal women.<sup>15</sup> A secondary aim was to test whether such a dietary intervention, which did not focus on the intake of specific fats, would also reduce the risk of CVD. This report compares incidence of CHD and CVD among postmenopausal women randomly assigned to either the dietary modification intervention or usual-diet comparison group during a mean of 8.1 years of follow-up.

**METHODS**

**Recruitment and Dietary Intervention**

Details of the study design and methods have been published.<sup>16,17</sup> All women

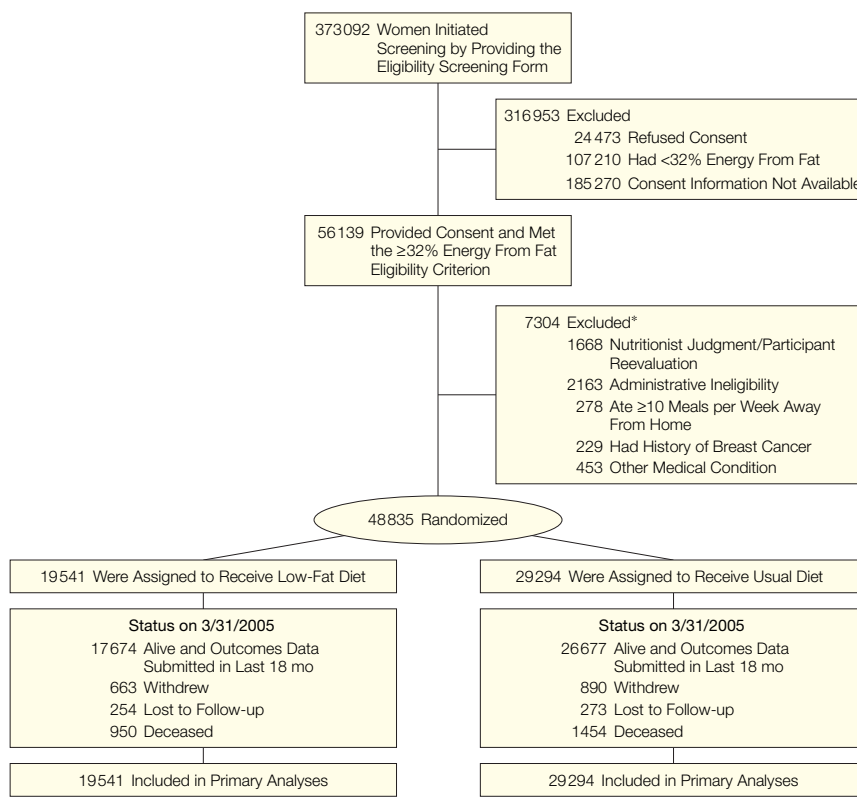
provided written informed consent, and the study was approved by the local institutional review boards as well as by the Coordinating Center institutional review board and the National Institutes of Health. Briefly, 48 835 women between the ages of 50 and 79 years were enrolled between 1993 and 1998 at 40 US clinical centers and were randomly assigned to an intervention group (40%, n=19 541) or a usual-diet comparison group (n=29 294) (FIGURE 1) using a randomized permuted block algorithm with blocks of size 5, 10, or 15, stratified by clinical center site and age group. Race/ethnicity was classified by self-report, using options outlined on the personal data form completed by all participants at baseline.

Eligibility criteria included being postmenopausal and consuming at baseline a diet with fat intake of 32% or more of total calories, as assessed by a food frequency questionnaire (FFQ). Major exclusions for WHI included prior breast or colorectal cancer, other cancers except nonmelanoma skin cancer in the last 10 years, medical conditions with predicted survival less than 3 years, and adherence concerns such as alcoholism. Additional trial-specific exclusions included type 1 diabetes and frequent consumption of meals prepared away from home.

The intervention was designed to promote dietary change with the goals of reducing intake of total fat to 20% of energy intake (in kilocalories) by increasing intake of vegetables and fruits to at least 5 servings daily and of grains to at least 6 servings daily. The intervention did not include total energy reduction or weight loss goals. Although not a separate focus of the intervention, it was presumed that by reducing total fat intake to 20% kcal, intake of saturated fat would also be reduced (7% energy intake).

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. Each participant was as-

**Figure 1.** Participant Flow in the Dietary Modification Component of the Women’s Health Initiative



\*Categories are presented for which exclusions are known. More than 1 reason could be given for exclusion.

signed her own fat-gram goal, calculated on the basis of height. Participants self-monitored total fat-gram intake and also servings of vegetables, fruits, and grains. No formal intervention regarding saturated fat, cholesterol, *trans* fatty acids, or other known atherogenic factors was provided. Details of the dietary intervention have been published.<sup>16-18</sup>

Group activities were supplemented during the intervention period by individual interviews that used validated reflective listening techniques,<sup>19</sup> targeted-message campaigns, and personalized feedback on fat intake. Individual contacts were completed by telephone or mail.

Women in the comparison group received a copy of the *Dietary Guidelines for Americans*,<sup>20</sup> as well as other health-related materials, but had no contact with the nutrition interventionists.

All participants were also invited to participate concurrently in one of the other WHI controlled trials of hormone therapy (HT) (estrogen alone or with progestin),<sup>21</sup> Participation in a trial of calcium and vitamin D supplementation (CaD) was offered after 1 year.<sup>22</sup> In total, 20 592 (42.2%) joined only the Dietary Modification Trial, 8050 (16.5%) the Dietary Modification plus HT Trial, 25 210 (51.6%) the Dietary Modification plus CaD Trial, and 5017 (10.3%) all 3 trials. Details of the HT and CaD trials have been published.<sup>15,21,22,24</sup>

Based on the intent-to-treat criteria, participants were followed up from the date of entry until death, loss to follow-up, time of a request for no further contact, or until the trial's planned completion date, regardless of their adherence to the dietary intervention. All participants were contacted by clinic staff at 6-month intervals to provide information on health outcomes. Height, weight, waist circumference, and blood pressure were measured at annual visits using standardized procedures. Fasting blood samples were collected at baseline and at year 1 from all participants and from a 5.8% (n=2816) subsample of women at years 3 and 6. The subsample was randomly chosen with

oversampling of minority women in which the odds for selection were 6-fold higher than for white women. Physical activity was assessed at baseline and at years 1, 3, 6, and 9; questions assessed walking and participation in sports, and hours of activity per week were calculated for each participant. Physical activity was expressed as metabolic equivalent tasks per week for the analysis.

All participants completed an FFQ designed specifically for the study<sup>23</sup> at baseline and 1 year. 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 follow-up dietary intake were computed from FFQs administered from years 5 through 7 (designated as year 6 follow-up), thus including all participants. Four-day food records were provided by all women prior to randomization.

#### Outcome Ascertainment

Methods for ascertaining and classifying outcomes have been published previously.<sup>24-26</sup> Electrocardiograms (ECGs) were digitally acquired every 3 years and analyzed by a core laboratory. Women completed a medical update questionnaire every 6 months; medical records for all overnight hospitalizations and outpatient coronary revascularization procedures were reviewed by central physician adjudicators (for CHD death) or trained local adjudicators (for all other coronary end points), all blinded to treatment assignment. For this analysis, major CHD, the outcome variable that was designated in the trial design, was defined as acute myocardial infarction (MI) requiring overnight hospitalization or silent MI determined from serial ECGs or CHD death; composite CHD was defined to include MI, CHD death, and coronary revascularization. Cardiovascular disease includes composite CHD and ischemic and hemorrhagic stroke.

The diagnosis of acute MI was established according to an algorithm that included cardiac pain, enzyme levels, and ECG readings. Aborted MIs and

those occurring during surgery were included if they met established criteria. Silent MI was diagnosed by comparing baseline and follow-up ECGs at 3, 6, and 9 years after randomization. Coronary heart disease death was defined as death consistent with CHD as the underlying cause plus 1 or more of the following: preterminal hospitalization with MI within 28 days of death; previous angina or MI and no potentially lethal noncoronary disease process; death resulting from a procedure related to coronary artery disease; or death certificate consistent with CHD as the underlying cause. Stroke diagnosis was based on the rapid onset of a neurologic deficit lasting more than 24 hours or until death, requiring hospitalization and supported by imaging studies when available. Coronary revascularization procedures were validated by medical record review.

#### Design and Data Analysis

Adherence assumptions included 13% lower percentage energy intake from fat in the intervention compared with the comparison group 1 year after randomization, diminishing to an 11% energy difference at 9 years. These assumptions led to a projected 14% lower CHD incidence in the intervention vs the comparison group. However, the achieved difference in percentage energy from fat was only about 70% of design assumptions. This reduction, along with a comparison group incidence rate that is about two thirds of the design rate, leads to a projected power of only approximately 40% over the 8.1-year follow-up period, under other design assumptions.

All primary analyses were based on the intent-to-treat principle and used time-to-event methods, defined to be the number of days from randomization to the first postrandomization diagnosis. For silent MIs, the date of the follow-up ECG applied. A woman with self-report but without the diagnosis was censored for that event at the time of her last follow-up contact.

Primary outcome comparisons are presented as hazard ratios (HRs) and

**Table 1.** Baseline Characteristics of the Dietary Modification Trial Participants (N = 48 835)

Characteristic	No. (%)		P Value
	Intervention (n = 19 541)	Comparison (n = 29 294)	
Age group at screening, y			
50-59	7206 (36.9)	10 797 (36.9)	.99
60-69	9086 (46.5)	13 626 (46.5)	
70-79	3249 (16.6)	4871 (16.6)	
Mean (SD)	62.3 (6.9)	62.3 (6.9)	.99
Race/ethnicity			
White	15 869 (81.2)	23 890 (81.6)	.76
Black	2137 (10.9)	3129 (10.7)	
Hispanic	755 (3.9)	1099 (3.8)	
American Indian/Alaskan Native	88 (0.5)	115 (0.4)	
Asian/Pacific Islander	433 (2.2)	674 (2.3)	
Unknown	259 (1.3)	387 (1.3)	
Annual family income, \$			
<10 000	683 (3.7)	1100 (4.0)	.40
10 000-19 999	2091 (11.4)	3203 (11.6)	
20 000-34 999	4501 (24.5)	6814 (24.7)	
35 000-49 999	3954 (21.5)	5868 (21.3)	
50 000-74 999	3887 (21.1)	5662 (20.5)	
≥75 000	3293 (17.9)	4948 (17.9)	
Body mass index*			
<25	5072 (26.1)	7585 (26.0)	.94
25-<30	6940 (35.7)	10 446 (35.8)	
≥30	7442 (38.3)	11 126 (38.2)	
First-degree relative with premature MI			
No	14 064 (81.3)	21 079 (81.2)	.79
Yes	3239 (18.7)	4887 (18.8)	
Postmenopausal hormone therapy, y			
Estrogen alone			.36
None	12 262 (62.8)	18 452 (63.0)	
<5	2711 (13.9)	3933 (13.4)	
≥5	4568 (23.4)	6909 (23.6)	
Estrogen plus progestin			.92
None	14 196 (72.7)	21 299 (72.7)	
<5	2768 (14.2)	4114 (14.0)	
≥5	2576 (13.2)	3881 (13.3)	
Smoking			
Never or past	18 039 (93.4)	27 009 (93.2)	.33
Current	1273 (6.6)	1977 (6.8)	
Hypertension (treated or BP ≥140/90 mm Hg)			
No	10 315 (57.5)	15 271 (56.8)	.15
Yes	7617 (42.5)	11 596 (43.2)	
History of hypercholesterolemia requiring medication			
No	15 231 (88.2)	22 761 (87.9)	.29
Yes	2034 (11.8)	3138 (12.1)	
Treated for diabetes (pills or injections)			
No	18 673 (95.6)	27 955 (95.4)	.50
Yes	866 (4.4)	1336 (4.6)	
History of cardiovascular disease			
MI	363 (1.9)	548 (1.9)	.92
Stroke	205 (1.0)	328 (1.1)	.46
CABG surgery or PCI	241 (1.2)	321 (1.1)	.17
Aspirin use (≥80 mg/d)			
No	16 149 (82.7)	23 980 (81.9)	.03
Yes	3391 (17.4)	5314 (18.1)	
The metabolic syndrome†			
No	679 (64.4)	1056 (64.0)	.94
Yes	393 (35.6)	608 (36.0)	

Abbreviations: BP, blood pressure; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.  
 \*Calculated as weight in kilograms divided by the square of height in meters.  
 †Defined retrospectively by Adult Treatment Panel III criteria and determined on a 5.8% subsample.

95% confidence intervals (CIs) from Cox proportional hazard analyses, stratified by age at screening, prevalent disease, and randomization status in the hormone trials. Assumptions of proportionality were met and tested by testing for a treatment by time-to-event interaction. Outcomes were also evaluated after exclusion of women with CVD at baseline (n=1656 [3.4%]). No time-dependent variables were included in the analyses.

Changes in individual LDL-C levels in the 5.8% subsample were compared with those predicted using the equation of Mensink and Katan<sup>27</sup>:

$$\Delta\text{LDL-C} = 1.28(\Delta\text{sat}) - 0.24(\Delta\text{mono}) - 0.55(\Delta\text{poly})$$

where sat indicates saturated fat; mono, monounsaturated fat; and poly, polyunsaturated fat.

Secondary analyses compared event rates in the intervention and comparison groups in women stratified by baseline characteristics (eg, ethnicity, age, and body mass index [BMI]), as well as other health characteristics known to influence CVD. For the analysis of baseline percentage energy from fat, data from baseline 4-day food records of those women who developed CHD were also used as described previously.<sup>28</sup>

The possibility of important subgroup effects was explored by testing for interactions in expanded Cox models. Twenty-seven subgroups were tested; thus, at least 1 would be expected to be significant by chance alone at the .05 level of significance.

Secondary analyses were also conducted, using Cox models, examining the relationship in the intervention group between CHD events after year 1 and quartiles of specific nutrient intakes at year 1 (ie, percentage energy from intakes of fat, vegetables and fruits, and grains). Other dietary components not specific to the intervention but believed to influence CVD were similarly assessed, including saturated fats, *trans* fatty acids, cholesterol, fiber, and the ratio of polyunsaturated to saturated fat. The analysis

provided adjustment for energy intake, for known correlates of trial adherence, and for characteristics known to influence CVD risk; the CVD rate in the comparison group was used as the reference. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

**RESULTS**

**Baseline Characteristics**

The mean (SD) age of the 48 835 participants was 62.3 (6.9) years. Demographic characteristics, medical history, and behavioral characteristics of the study population have been described in detail<sup>16</sup> and appear in TABLE 1 by intervention group. The cohort was ethnically diverse (18.6% minority) and in-

cluded a range of education and income levels; 3.4% reported a history of CVD. No significant differences were found between the randomization groups for any of the measures presented in Table 1 and TABLE 2, except for a 0.4-mm Hg difference in systolic blood pressure and a 0.7% difference in use of aspirin. The women in this trial reflect the characteristics of the general population of women of this age throughout the United States, except that they had somewhat higher obesity measures, income, and education and lower rates of smoking.<sup>16</sup> Baseline levels of lipids and other biomarkers measured in a 5.8% sample were similar between the 2 groups, except that high-density lipoprotein cholesterol (HDL-C) level in the compar-

ison group was 1.7 mg/dL (0.04 mmol/L) lower (Table 2).

TABLE 3 presents overall baseline and follow-up nutrient data for both groups based on the FFQ. No meaningful changes were seen in any of the dietary factors in the comparison group. Compared with the comparison group, the intervention group reported significant changes in all dietary components, resulting in year 6 in an 8.2% lower mean total fat intake ( $P < .001$ ) and a 2.9% lower mean saturated fat intake ( $P < .001$ ), as well as reduced intakes of *trans*, mono-unsaturated, and polyunsaturated fat and cholesterol (but no change in ratio of polyunsaturated to saturated fat) and increased intakes of fiber, vegetables and fruits, total and whole grains, and soy.

**Table 2.** Differences Between the Mean Changes in Cardiovascular Disease Risk Factors From Baseline to Year 3 in the Intervention vs the Comparison Group

Risk Factor	Baseline, Mean (SD)		Year 3, Mean (SD)		Change at Year 3		
	Intervention	Comparison	Intervention	Comparison	Intervention, Mean (SD)	Comparison, Mean (SD)	Difference, Mean (95% CI)
<b>Clinical Values</b>							
Weight, kg	76.8 (16.6)	76.7 (16.5)	75.7 (17.1)	76.7 (16.8)	-0.7 (9.0)	0.6 (9.2)	-1.29 (-1.47 to -1.11)*
Body mass index†	29.1 (5.9)	29.1 (5.9)	28.8 (6.0)	29.2 (5.9)	-0.2 (2.7)	0.3 (2.7)	-0.49 (-0.54 to -0.44)*
Waist circumference, cm	89.0 (13.9)	89.0 (13.7)	88.2 (13.9)	89.3 (14.1)	-0.4 (7.3)	0.5 (7.7)	-0.98 (-1.19 to -0.76)*
Physical activity, METs/wk	10.0 (11.7)	10.1 (12.0)	11.6 (13.0)	11.3 (12.8)	1.4 (11.7)	1.0 (11.4)	0.39 (0.16 to 0.63)*
Blood pressure, mm Hg							
Systolic	127.5 (17.2)	127.9 (17.2)	125.1 (16.9)	125.7 (16.8)	-2.2 (16.3)	-2.1 (16.4)	-0.17 (-0.49 to 0.15)
Diastolic	75.9 (9.1)	76.0 (9.1)	73.1 (9.4)	73.6 (9.3)	-2.6 (9.4)	-2.3 (9.4)	-0.31 (-0.50 to -0.13)*
<b>Laboratory Values</b>							
Cholesterol, mg/dL							
Total‡	224.0 (36.5)	224.2 (39.2)	214.1 (35.3)	216.6 (35.9)	-10.2 (32.0)	-6.9 (31.9)	-3.26 (-6.53 to -0.00)§
LDL-C‡	133.3 (35.3)	134.2 (35.1)	123.2 (33.1)	127.0 (34.0)	-9.7 (29.3)	-6.2 (29.1)	-3.55 (-6.58 to -0.52)§
HDL-C‡	60.1 (16.1)	58.4 (15.4)	59.7 (15.8)	58.2 (15.5)	-0.7 (9.4)	-0.3 (10.2)	-0.43 (-1.42 to 0.57)
Total cholesterol-HDL-C ratio‡	4.0 (1.2)	4.1 (1.3)	3.8 (1.1)	4.0 (1.2)	-0.2 (0.8)	-0.1 (1.0)	-0.04 (-0.13 to 0.5)
Non-HDL-C‡	163.9 (39.5)	165.8 (41.1)	154.3 (36.5)	158.4 (37.0)	-9.7 (32.0)	-6.6 (32.6)	-3.08 (-6.37 to 0.22)
Triglycerides, mg/dL‡	138.6 (65.1)	141.1 (66.3)	142.3 (67.5)	144.6 (63.7)	1.0 (0.4)	1.0 (0.3)	0.00 (-0.03 to 0.04)
Lipoprotein(a), mg/dL‡	15.7 (17.5)	15.4 (17.0)	13.2 (15.1)	13.8 (15.5)	0.9 (0.5)	0.9 (0.5)	-0.01 (-0.07 to 0.05)
Glucose, mg/dL‡	100.4 (26.6)	100.0 (26.9)	98.8 (25.6)	99.5 (27.3)	-1.7 (19.9)	-0.7 (21.6)	-1.06 (-3.06 to 0.93)
Insulin, µU/mL‡	9.9 (4.9)	10.2 (5.3)	10.5 (5.3)	11.2 (5.9)	1.1 (0.5)	1.1 (0.5)	-0.03 (-0.07 to 0.02)
HOMA insulin resistance‡	2.4 (1.4)	2.5 (1.6)	2.5 (1.5)	2.7 (1.7)	1.1 (0.5)	1.1 (0.6)	-0.04 (-0.09 to 0.01)
Total carotenoids, µg/mL‡	0.7 (0.4)	0.7 (0.4)	0.7 (0.4)	0.6 (0.4)	0.0 (0.3)	-0.0 (0.3)	0.04 (0.01 to 0.07)§
Factor Vllc, %‡	131.0 (33.3)	129.1 (29.0)	130.0 (35.7)	131.6 (32.7)	-1.9 (27.3)	2.4 (28.7)	-4.29 (-7.29 to -1.29)*
Fibrinogen, mg/dL‡	301.5 (59.3)	298.7 (61.7)	288.0 (58.1)	290.2 (60.0)	-11.1 (49.9)	-10.2 (54.0)	-0.97 (-6.41 to 4.47)

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol; METs, metabolic equivalent tasks.

SI conversion factors: To convert total cholesterol, LDL-C, and HDL-C to mmol/L, multiply values by 0.0259; triglycerides to mmol/L, by 0.0113; lipoprotein(a) to µmol/L, by 0.0357; glucose to mmol/L, by 0.0555; insulin to pmol/L, by 6.945; and fibrinogen to µmol/L, by 0.0294.

\*Difference significant at  $P < .001$  from a 2-sample test.

†Calculated as weight in kilograms divided by the square of height in meters.

‡Blood measures were performed on a 5.8% subsample at year 3. Means and SDs have been weighted by ethnicity using the ethnicity distribution of participants randomized to the entire clinical trial. Tests for differences between the randomization groups are performed on the weighted means and SDs.

§Difference significant at  $P < .05$  from a 2-sample test.

||Means shown are geometric means.

**Follow-up**

At trial conclusion, 2404 women (4.9%) were deceased, 1553 (3.2%) had stopped follow-up, and 527 (1.1%) were lost to follow-up. Five percent (4.7%) of women in the intervention and 4.0% in the comparison group withdrew, were considered lost to follow-up, or had stopped providing outcomes information for longer than 18 months (Figure 1). Eleven percent (11.4%) of women had terminated the intervention, as defined by neither attending group sessions nor providing self-monitoring information through phone or individual visits for 18 months.

**CVD Risk Factors**

At year 3, women in the intervention group compared with those in the comparison group showed small but significant decreases in body weight,<sup>29</sup> waist circumference,<sup>29</sup> diastolic blood

pressure, LDL-C level (3.55 mg/dL [0.09 mmol/L]), and factor VIIc level (Table 2). The dietary intervention had no statistically significant effects on levels of triglycerides or HDL-C; ratio of total cholesterol to HDL-C; levels of non-HDL-C, lipoprotein(a), glucose, or insulin; or insulin resistance as estimated by homeostasis model assessment<sup>30</sup>; in the latter 3 factors, there were trends toward improvement. The observed absolute LDL-C change of 2.7 mg/dL (0.07 mmol/L) after 6 years was similar to the 2.3-mg/dL (0.06-mmol/L) change predicted using current equations based on differences in fatty acid intakes.<sup>27</sup> Carotenoid levels, a reflection of increased vegetable consumption, were significantly higher.

**CVD Outcomes**

After a mean of 8.1 years of follow up, the observed incidence rate for major

CHD (MI/CHD death, 3.6 per 1000 person-years) in the comparison group was 30% lower than projected in the design. No significant effects of the dietary intervention were observed for major CHD (HR, 0.98; 95% CI, 0.88-1.09) or composite CHD (CHD/revascularization; HR, 0.97; 95% CI, 0.90-1.06) vs the comparison group (TABLE 4). The incidences of total, fatal, or nonfatal stroke were not influenced by the dietary intervention (HR, 1.02; 95% CI, 0.90-1.15), nor was a composite measure of CVD (CHD/revascularization/stroke; HR, 0.98; 95% CI, 0.92-1.05). The monitoring plan for the Dietary Modification Trial specified 2 primary outcomes (breast and colorectal cancer) and 2 secondary outcomes (major CHD and death from other causes). The 95% CI for major CHD, adjusted for these 4 outcomes using a Bonferroni correction,

**Table 3.** Baseline and Follow-up Nutrient Intakes\*

	Baseline, Mean (SD)		Year 1, Mean (SD)			Year 6, Mean (SD)		
	Intervention	Comparison	Intervention	Comparison	Difference, Mean (95% CI)†	Intervention	Comparison	Difference, Mean (95% CI)†
Total energy, kcal/d	1790.2 (710.1)	1789.4 (703.0)	1500.5 (544.2)	1593.8 (644.0)	-93.4 (-104.8 to -81.9)	1431.8 (551.7)	1546.2 (639.5)	-114.3 (-126.8 to -101.8)
Daily intakes, % of energy								
Total fat	37.8 (5.1)	37.8 (5.0)	24.3 (7.5)	35.1 (6.9)	-10.7 (10.9 to -10.6)	28.8 (8.4)	37.0 (7.3)	-8.2 (-8.3 to -8.0)
Saturated fat	12.7 (2.5)	12.7 (2.5)	8.1 (2.8)	11.8 (2.9)	-3.7 (-3.7 to -3.6)	9.5 (3.2)	12.4 (3.1)	-2.9 (-3.0 to -2.8)
Monounsaturated fat	14.4 (2.3)	14.4 (2.3)	8.9 (3.1)	13.3 (2.9)	-4.4 (-4.5 to -4.4)	10.8 (3.5)	14.2 (3.1)	-3.3 (-3.4 to -3.3)
Polysaturated fat	7.8 (2.0)	7.8 (2.0)	5.2 (1.8)	7.2 (2.1)	-2.0 (-2.0 to -2.0)	6.1 (2.1)	7.5 (2.1)	-1.5 (-1.5 to -1.4)
P/S fat ratio	0.6 (0.2)	0.6 (0.2)	0.7 (0.2)	0.6 (0.2)	0.0 (0.0 to 0.0)	0.7 (0.2)	0.6 (0.2)	0.0 (0.0 to 0.0)
Total trans fatty acid	2.7 (1.1)	2.8 (1.1)	1.6 (0.8)	2.5 (1.1)	-0.8 (-0.9 to -0.8)	1.8 (0.9)	2.4 (1.1)	-0.6 (-0.6 to -0.6)
Protein	16.5 (3.0)	16.4 (3.0)	17.7 (3.1)	16.9 (3.2)	0.8 (0.8 to 0.9)	17.7 (3.4)	17.1 (3.3)	0.6 (0.5 to 0.6)
Carbohydrate	45.6 (6.3)	45.6 (6.2)	58.3 (8.9)	48.0 (8.0)	10.3 (10.2 to 10.5)	53.9 (9.9)	45.9 (8.8)	8.1 (7.9 to 8.3)
Dietary fiber, g/d	15.4 (6.4)	15.4 (6.4)	18.1 (7.5)	14.9 (6.5)	3.2 (3.0 to 3.3)	16.9 (7.5)	14.4 (6.4)	2.4 (2.3 to 2.6)
Soluble fiber, g/d	4.2 (1.7)	4.2 (1.8)	4.9 (2.0)	4.0 (1.8)	0.8 (0.8 to 0.9)	4.5 (2.0)	3.8 (1.7)	0.6 (0.6 to 0.7)
Dietary folate equivalent, µg/d	259.2 (136.6)	259.3 (138.1)	398.5 (215.0)	346.1 (195.1)	52.4 (48.6 to 56.2)	469.1 (205.9)	422.5 (189.0)	46.6 (42.5 to 50.6)
Cholesterol, mg/d	260.5 (139.0)	260.0 (135.6)	172.4 (99.3)	229.8 (128.7)	-57.5 (-59.7 to -55.3)	193.6 (118.7)	243.5 (143.2)	-49.9 (-52.7 to -47.2)
Intakes, servings/d								
Vegetables and fruits	3.6 (1.8)	3.6 (1.8)	5.1 (2.3)	3.9 (2.0)	1.2 (1.2 to 1.2)	4.9 (2.4)	3.8 (2.0)	1.1 (1.1 to 1.2)
Grains	4.7 (2.5)	4.8 (2.5)	5.1 (2.7)	4.2 (2.3)	0.8 (0.8 to 0.9)	4.3 (2.4)	3.8 (2.2)	0.5 (0.4 to 0.5)
Whole grains	1.1 (0.8)	1.1 (0.8)	1.4 (0.9)	1.1 (0.7)	0.3 (0.3 to 0.3)	1.2 (0.9)	1.0 (0.7)	0.2 (0.2 to 0.2)
Intakes, servings/wk								
Soy‡	0.1 (0.7)	0.1 (0.7)	0.2 (0.8)	0.2 (0.7)	0.0 (0.0 to 0.0)	0.3 (1.0)	0.2 (0.9)	0.0 (0.0 to 0.1)
Nuts	1.5 (2.3)	1.5 (2.3)	0.5 (1.1)	1.3 (1.9)	-0.8 (-0.8 to -0.7)	1.0 (1.7)	1.8 (2.5)	-0.8 (-0.9 to -0.8)
Fish	1.9 (1.8)	1.9 (1.7)	1.9 (1.7)	1.8 (1.7)	0.1 (0.0 to 0.1)	2.0 (1.7)	2.0 (1.9)	0.0 (-0.1 to 0.0)

Abbreviations: CI, confidence interval; P/S, ratio of polyunsaturated fat to saturated fat.

\*Nutrient intakes were available on 19 470 and 29 216 participants at baseline, and 18 058 and 26 743 at year 1 and 14 885 and 22 958 at year 6 in the intervention and comparison groups, respectively. Data on servings of types of food was available on 19 470 and 29 216 participants at baseline, 18 057 and 26 743 at year 1, and 14 774 and 22 713 at year 6 in the intervention and comparison groups respectively.

†All differences significant at  $P < .001$  from a 2-sample test except for soy at year 3 ( $P = .02$ ), and fish at year 6 ( $P = .40$ ).

‡No soy intake was reported by 87.0%, 84.9%, and 80.1% of participants at baseline, year 1, and year 6, respectively.

was 0.86 to 1.12. After women with history of CVD at baseline were removed (n=1656 [3.4%]), HRs (95% CIs) for major CHD, composite CHD, stroke, and total CVD were 0.93 (0.83-1.05), 0.94 (0.86-1.02), 1.02 (0.90-1.17), and 0.96 (0.89-1.03), respectively. The HR for the 3.4% of women with CVD at baseline was 1.26 (95% CI, 1.03-1.54). We considered the potential confounding effects of changing medication use during the trial by examining use of statins, aspirin, and angiotensin-converting enzyme inhibitors at year 6. All differences in medication use between groups were less than 1%.

In examining trends over time (FIGURE 2), there was no apparent influence of the dietary intervention on stroke at any point up to 9 years of follow-up. There appeared to be a slight, nonsignificant trend toward decreased CHD rates in the intervention group in the later years, and this was more pronounced for women with no CVD at baseline. Likewise, exploratory analyses of CHD outcomes in groups stratified by race/ethnicity, age, BMI, waist circumference, smoking, statin use, diabetes, randomization to the HT and CaD trials, and baseline fat

intake revealed no significant interactions between the intervention group and any of these variables (FIGURE 3), either in the group as a whole or if women with baseline CVD were excluded. A significant interaction was observed between the intervention effect and baseline disease (P=.006).

**Additional Analyses**

When the effect of the intervention was assessed using adherence criteria based on participation in intervention activities,<sup>28</sup> the HRs did not change. Trends for changes in specific components of the diet were examined by evaluating CHD risk in individuals stratified by quartiles of achieved levels of key nutrients at year 1, using the rate in the comparison group as the reference. Analyses were adjusted for age, baseline CHD, and HT randomization group; full models included CVD risk factors (age, BMI, hypertension, high cholesterol level, smoking, diabetes, physical activity, and energy expenditure) and correlates of adherence (ethnicity, education, income, and psychosocial factors).

Compared with those in the entire comparison group, a trend was ob-

served toward reduction of CHD risk among those in the intervention group who reached the lowest levels of saturated fat (HR, 0.81; 95% CI, 0.69-0.96 in the group that consumed <6.1% energy; P<.001 [adjusted HR, 0.82; 95% CI, 0.67-0.99; P=.05]) and trans fat (HR, 0.81; 95% CI, 0.69-0.95 in group consuming <1.1% energy intake; P<.001 [adjusted HR, 0.84; 95% CI, 0.69-1.02; P=.10]) or the highest intakes of vegetables and fruits (HR, 0.88; 95% CI, 0.76-1.03 in the group that consumed ≥6.5 servings/d; P<.001 [adjusted HR, 0.89; 95% CI, 0.74-1.06; P=.11]). While these additional analyses are subject to residual confounding because of reporting bias or the lack of a comparable comparison group, some confidence in their validity is supported by parallel patterns of LDL-C reductions in participants stratified by changes in saturated fat at year 1 (-10.1; 95% CI, -13.5 to -6.6 mg/dL [0.26; 95% CI, -0.36 to -0.17 mmol/L] in the quartile with the greatest reduction; P=.005 for trend), and trans fat (-9.0; 95% CI, -12.5 to -5.6 mg/dL [0.23; 95% CI, -0.32 to -0.14 mmol/L] in the quartile with the greatest reduction; P=.03).

**Table 4.** Clinical Outcomes (Annualized Percentage) of the Dietary Modification Trial Participants by Randomization Assignment

	All Participants, No. (%)			Participants Without History of CVD, No. (%)		
	Intervention (n = 19 541)	Comparison (n = 29 294)	HR (95% CI)*	Intervention (n = 18 633)	Comparison (n = 27 925)	HR (95% CI)*
Mean follow-up time, mo	96.9	97.1		97.2	97.4	
Major CHD (nonfatal MI or CHD death)†‡	559 (0.35)	863 (0.36)	0.98 (0.88-1.09)	452 (0.30)	733 (0.32)	0.93 (0.83-1.05)
Nonfatal MI	435 (0.28)	671 (0.28)	0.98 (0.87-1.11)	353 (0.23)	581 (0.26)	0.91 (0.80-1.04)
CHD death	158 (0.10)	234 (0.10)	1.02 (0.84-1.25)	124 (0.08)	185 (0.08)	1.01 (0.81-1.27)
CABG/PCI	717 (0.45)	1113 (0.47)	0.96 (0.88-1.06)	569 (0.38)	935 (0.41)	0.91 (0.82-1.01)
Composite CHD (nonfatal MI, CHD death, or CABG/PCI)	1000 (0.63)	1549 (0.65)	0.97 (0.90-1.06)	806 (0.53)	1292 (0.57)	0.94 (0.86-1.02)
Stroke	434 (0.28)	642 (0.27)	1.02 (0.90-1.15)	384 (0.25)	564 (0.25)	1.02 (0.90-1.17)
Fatal§	55 (0.03)	86 (0.04)	0.97 (0.69-1.36)	46 (0.03)	73 (0.03)	0.94 (0.65-1.35)
Nonfatal	379 (0.24)	556 (0.23)	1.03 (0.90-1.17)	338 (0.22)	491 (0.22)	1.04 (0.90-1.19)
Stroke class						
Ischemic	256 (0.16)	383 (0.16)	1.01 (0.86-1.18)	228 (0.15)	334 (0.15)	1.03 (0.87-1.22)
Hemorrhagic	67 (0.04)	113 (0.05)	0.90 (0.66-1.22)	62 (0.04)	106 (0.05)	0.88 (0.64-1.20)
Total cardiovascular disease	1357 (0.86)	2088 (0.88)	0.98 (0.92-1.05)	1132 (0.75)	1777 (0.78)	0.96 (0.89-1.03)

Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

\*From an unweighted proportional hazards model stratified by prevalent condition, age, and hormone therapy randomization group.

†MI includes clinical MI and silent MI. Fifty-five and 47 MIs were identified only by serial electrocardiography among all participants and those without history of CVD, respectively.

‡Nonfatal MI is defined as no definite CHD death within 28 days of MI.

§Fatal stroke is defined as death within 30 days of stroke, or source of outcome is cause of death only.

||Total cardiovascular disease includes clinical MI, silent MI, death due to CHD, CABG/PCI, and stroke.

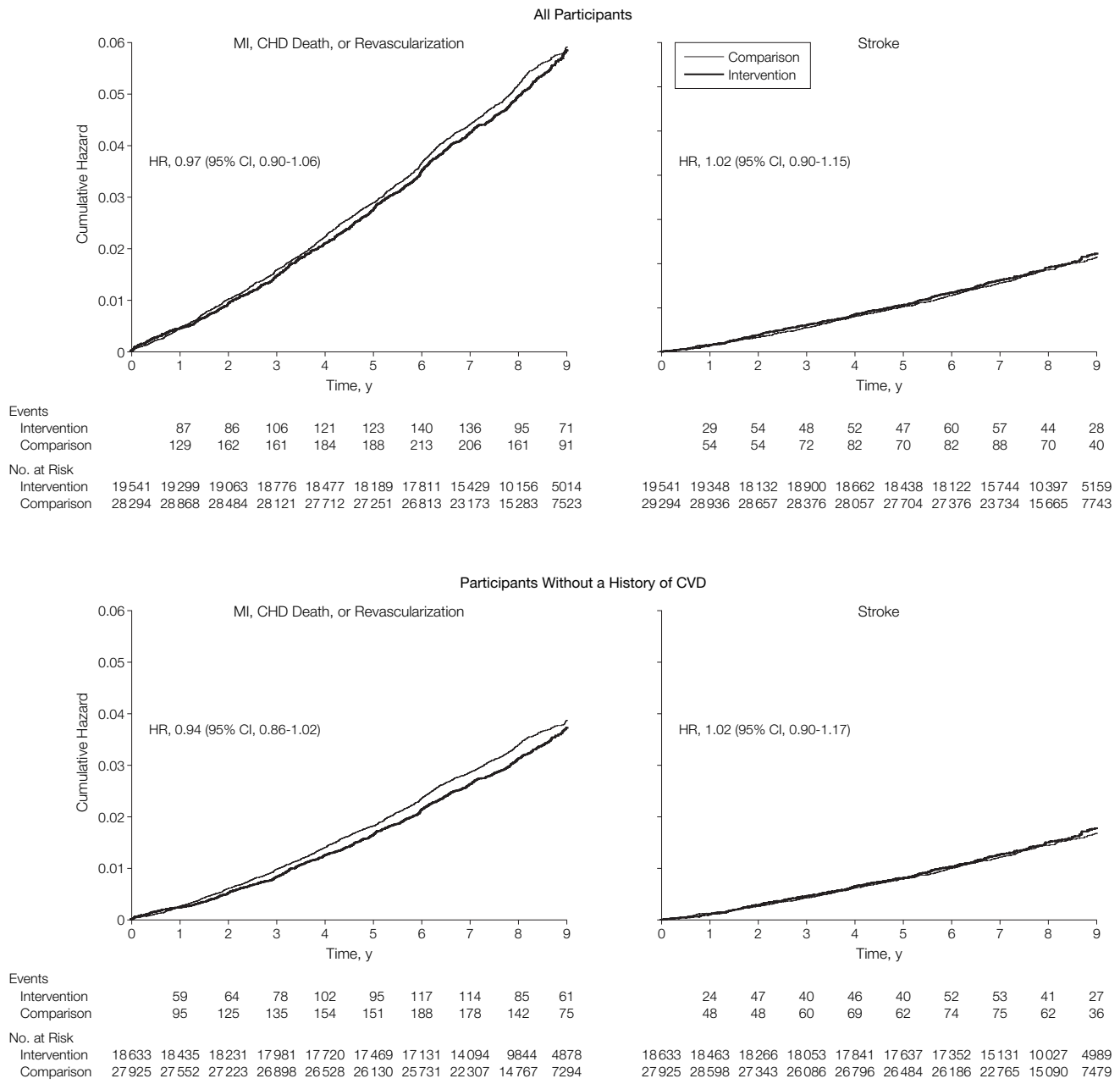
**COMMENT**

The WHI Dietary Modification Trial is the largest long-term randomized trial of a dietary intervention ever conducted to our knowledge, and it achieved an 8.2% reduction at year 6 in total fat intake and a mean daily increase of 1.1 servings of vegetables and fruits and 0.5 serving of grains. No sig-

nificant effects on incidence of CHD or stroke were observed during 8.1 years of follow-up. Analysis of subcomponents of CVD, including MI, coronary interventions, and stroke separately showed no beneficial or adverse effects of the dietary changes. Although power was limited for subgroup analyses, stratification by ethnicity, age, BMI,

or the presence of baseline CVD risk factors did not reveal any subgroup in which there were significant effects. An interaction with prior CVD was observed; women without baseline CVD had an HR close to significant, but the absolute reduction was only 7%. The intervention was associated with increased risk in the 3.4% of women with

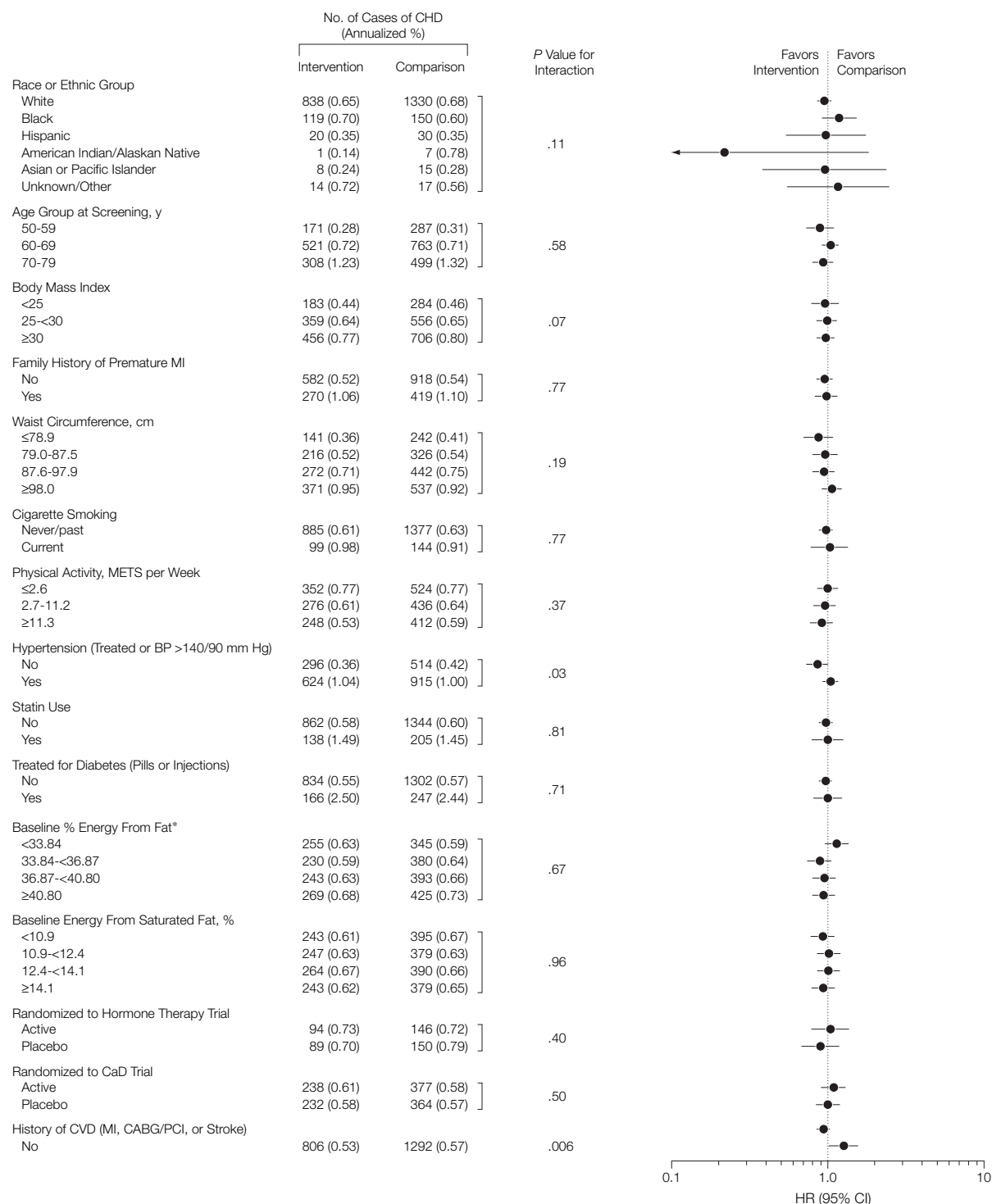
**Figure 2.** Kaplan-Meier Estimates of Cumulative Hazards for CHD (MI, CHD Death, or Revascularization) and Stroke



CHD indicates coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.



**Figure 3.** Risk of Composite Coronary Heart Disease (CHD) in Various Subgroups



Body mass index was calculated as weight in kilograms divided by the square of height in meters. BP indicates blood pressure; CABG, coronary artery bypass graft; CaD, calcium and vitamin D; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; HT, hormone therapy; METs, metabolic equivalent tasks; MI, myocardial infarction; PCI, percutaneous coronary intervention.

\*Conclusions do not change if results from 4-day food records are used.

baseline CVD; this may be a chance observation, or rates in this small subset may be confounded by concurrent therapy or comorbid conditions.

The primary focus of the WHI Dietary Modification Trial intervention was on lowering rates of breast and colorectal cancer, not those of CVD, by targeting total dietary fat reduction.<sup>28,31</sup> Women in the intervention group achieved intakes of saturated fat and cholesterol that were less than 10% of energy intake and less than 300 mg/d, respectively. However, intakes of polyunsaturated fat, vegetables and fruits, and fiber were lower than now recommended,<sup>32-34</sup> and there was no focus on consumption of fish. However, while the WHI Dietary Modification Trial intervention was not specifically designed to lower rates of CVD, at least 3 findings relevant to CVD are worth noting.

First, contrary to previous suggestions about adverse effects of increasing carbohydrate intake on CVD risk factors,<sup>35,36</sup> no long-term adverse effects were observed on lipid profiles or levels of glucose or insulin. There were no significant increases in triglycerides levels or decreases in HDL-C levels, and trends for glucose and insulin levels and for estimated insulin resistance all were slightly favorable. Body weight, waist circumference, and diastolic blood pressure were significantly lower, as were levels of factor VIIc. Because there are no apparent changes that would have mitigated a potentially favorable effect on CVD, the lack of an appreciable CVD effect may be attributable to the limited decrease (only 2.7 mg/dL [0.07 mmol/L]) in LDL-C level, as well as the modest differences in other potentially favorable dietary components. Based on a large body of evidence from LDL-C-lowering trials,<sup>13,14</sup> this magnitude of change in LDL-C level would be predicted to produce only a small (2%-4%) decrease in CVD risk, a value far below the power for detection in the current study. As delivered, the dietary intervention was not expected to have substantial effects on lipoprotein

levels, but it is possible that a diet specifically lower in saturated and *trans* fat combined with increased intakes of vegetables, fruits, and grains might have led to a decrease in CVD risk. The trial is not a test of the dietary guidelines currently recommended for prevention of CVD<sup>32-34</sup> that specify a plant-based, high-fiber diet rich in vegetables, fruits, whole grains, nuts, beans, low-fat dairy products, and fish and replacement of saturated and *trans* fat with monounsaturated and polyunsaturated fat and plant sterols.

Second, there is value in the comparison of these results to the limited existing clinical trial results. Six previous randomized dietary trials, conducted many years ago, examined the effect of dietary fat on rates of CVD with at least 2 years of follow-up.<sup>7-9,37-39</sup> In 4 of these trials,<sup>7-9,39</sup> individuals started with diets extremely high in saturated fat; saturated fat intake was decreased by approximately 10% of energy intake, resulting in a 12% to 15% decrease in blood levels of total cholesterol and a significant reduction in CHD. In 2 other studies in which total cholesterol levels were reduced by only 3% to 4%, no reduction was seen in CHD.<sup>37,38</sup> These previous studies further support the implication that the lack of effect on CVD in the current study was attributable to the small decrease in saturated fat and reduced intakes of monounsaturated and polyunsaturated fat that yielded the subsequent minimal change in LDL-C levels. These data further imply that, because the current mean saturated fat intake in the United States is now approximately 11% kcal vs 18% to 20% in the 1970s,<sup>40</sup> very aggressive and targeted dietary intervention would be required to achieve substantial LDL-C lowering through dietary approaches. This might be difficult to attain within the context of the general societal framework of food processing and availability.

Third, this study provides the opportunity for subgroup analyses. These results show no effect of this diet on stroke, but a possible trend toward benefit with regard to CHD

was observed. The large diverse cohort and long duration provide the unique opportunity to evaluate the effects of different levels of dietary adherence and to examine whether specific qualitative and quantitative changes in the diet affected CVD outcomes. Stratification by attainment of lowest levels of saturated or *trans* fat or highest intakes of vegetables and fruits showed positive trends, with women who achieved the more optimal levels showing lower LDL-C levels and rates of CHD. Several previous observational studies have indicated that intakes of specific fatty acids are more strongly related to CHD risk than is total fat intake.<sup>1,2,6</sup> Collectively, these analyses, despite their inherent limitations, suggest that a diet lower in saturated and *trans* fat intake and higher in intakes of vegetables and fruits and polyunsaturated fat than what was achieved in this trial might show significant benefit in preventing CHD.

Strengths of this study include its randomized design, long-term follow-up, large sample size, ethnic and socioeconomic diversity, and high retention rate. Limitations include the lack of targeting key nutrients relevant to CVD and the focus on women aged between 50 and 79 years; the possibility that the effect might have been greater in men or if the diet had been initiated at younger ages cannot be ruled out. Why trends toward protective effects for CHD events were observed only in women without baseline disease also needs further consideration. Limitations associated with the FFQ methodology include bias caused by self-report<sup>41</sup> and the need to recall food intake throughout a 3-month period; also, our validation study suggested that baseline percentage of energy from fat may have been overestimated by 2% to 3%.<sup>42</sup>

In conclusion, this long-term dietary intervention in postmenopausal women, intended to reduce fat intake and increase intake of vegetables, fruits, and grains, achieved an 8.2% of energy decrease in total fat intake but only a 2.9% of energy

decrease in saturated fat intake and only modest increases in intakes of vegetables, fruits, and grains. The intervention did not reduce risk of CHD or stroke. To achieve a significant public health impact on CVD events, a greater magnitude of change in multiple macronutrients and micronutrients and other behaviors that influence CVD risk factors may be necessary.

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**Author Contributions:** Dr Howard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Acquisition of data:** Howard, Van Horn, Hsia, Manson, Stefanick, Wassertheil-Smoller, LaCroix, Langer, Lasser, Lewis, Limacher, Margolis, Mysiw, Ockene, Parker, Perri, Phillips, Prentice, Robbins, Sarto, Schatz,

Sneltselaar, Stevens, Tinker, Trevisan, Assaf, Bassford, Beresford, Black, Brunner, Brzyski, Caan, Chlebowski, Gass, Granek, Greenland, Hays, Heber, Heiss, Hendrix, Hubbell, Johnson, Kotchen.

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**Drafting of the manuscript:** Howard, Van Horn, Stefanick, Rossouw, Trevisan, Vitolins.

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**Critical input to representation of the intervention program:** Tinker.

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**WHI Investigators:** For a complete list of the WHI investigators, see the companion article in this issue, "Dietary Pattern and Risk of Invasive Breast Cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial" (*JAMA*. 2006;296:629-642).

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## REFERENCES

1. Keys A. From Naples to seven countries—a sentimental journey. *Prog Biochem Pharmacol*. 1983;19:1-30.
2. Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. *Am J Epidemiol*. 2005;161:672-679.
3. Liu S, Stampfer MJ, Hu FB, et al. Whole grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. *Am J Clin Nutr*. 1999;70:412-419.
4. Liu S, Manson JE, Lee I-M, et al. Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *Am J Clin Nutr*. 2000;72:922-928.
5. Fung TT, Stampfer MJ, Manson JE, Rexrode KM, Willett WC, Hu FB. Prospective study of major dietary patterns and stroke risk in women. *Stroke*. 2004;35:2014-2019.
6. Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease [published correction appears in *Circulation*. 2003;107:512]. *Circulation*. 2002;21:2747-2757.
7. Dayton S, Pearce ML, Hashimoto S, Cixon WJ, Tomiyasu U. A controlled trial of a diet high in unsaturated fat for preventing complications of atherosclerosis. *Circulation*. 1969;60(suppl 2):111-163.
8. Leren P. The Oslo Diet-Heart Study: eleven year report. *Circulation*. 1970;42:935-942.
9. Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Elosuo R, Paavilainen E. Dietary prevention of coronary heart disease: the Finnish Mental Hospital Study. *Int J Epidemiol*. 1979;8:99-118.
10. de Lorgeril M, Salen P, Martin JL, Monjaud I, Demaille J, Marmelle N. Mediterranean diet, traditional risk factors and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99:779-785.
11. de Lorgeril M, Renaud S, Marmelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease [published correction appears in *Lancet*. 1995;345:738]. *Lancet*. 1994;343:1454-1459.
12. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA*. 1998;280:2001-2007.
13. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267-1278.
14. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. *JAMA*. 1997;278:313-321.
15. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19:61-109.
16. Ritenbaugh C, Patterson R, Chlebowski RT, et al. The Women's Health Initiative Dietary Modification Trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13:S87-S97.
17. Patterson RE, Kristal A, Rodabough R, et al. Changes in food sources of dietary fat in response to an intensive low-fat dietary intervention: early results from the Women's Health Initiative. *J Am Diet Assoc*. 2003;103:454-460.
18. Tinker LF, Burrows ER, Henry H, Patterson R,

- Rupp L, Van Horn L. The Women's Health Initiative: overview of the nutrition components. In: Krummel D, Kris-Etherton P, eds. *Nutrition in Women's Health*. Gaithersburg, Md: ASPEN Publishers; 1996:510-542.
19. Bowen D, Ehret C, Pedersen M, et al. Results of an adjunct dietary intervention program in the Women's Health Initiative. *J Am Diet Assoc*. 2002;102:1631-1637.
20. US Department of Agriculture. *Dietary Guidelines for Americans*. 3rd ed. Washington, DC: US Dept of Health and Human Services; 1990.
21. Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9 suppl):S78-S86.
22. Jackson RD, LaCroix AZ, Cauley JA, McGowan J. The Women's Health Initiative calcium-vitamin D trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9 suppl):S98-S106.
23. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Argus-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol*. 1999;9:178-187.
24. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.
25. Manson JE, Hsia J, Johnson KC, et al; Women's Health Initiative Investigators. Estrogen plus progestin and risk of CHD. *N Engl J Med*. 2003;349:523-534.
26. Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13: S122-S128.
27. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials. *Arterioscler Thromb*. 1992;12:911-918.
28. Prentice RL, Caan B, Chlebowski R, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295: 629-642.
29. Howard BV, Manson JE, Stefanick ML, et al. Low-fat dietary pattern and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial. *JAMA*. 2006;295:39-49.
30. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and b-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28: 412-419.
31. Beresford SAA, Johnson KC, Rittenbaugh C, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295:643-654.
32. Krauss RM, Eckel RH, Howard B, et al. AHA Dietary Guidelines, Revision 2000: a statement for health-care professionals from the nutrition committee of the American Heart Association. *Circulation*. 2000;102: 2284-2299.
33. Franz MJ, Bantle JP, Beebe CA, Brunzeu JD, Chason JL. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*. 2002;25:148-198.
34. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
35. Pereira MA, Liu S. Types of carbohydrates and risk of cardiovascular disease. *J Womens Health (Larchmt)*. 2003;12:115-122.
36. Hellerstein MK. Carbohydrate-induced hypertriglyceridemia: modifying factors and implications for cardiovascular risk. *Curr Opin Lipidol*. 2002;13:33-40.
37. Low-fat diet in myocardial infarction: a controlled trial. *Lancet*. 1965;2:501-504.
38. Controlled trial of soya-bean oil in myocardial infarction. *Lancet*. 1968;2:693-700.
39. Watts GF, Lewis B, Brunt JNH, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St. Thomas' Atherosclerosis Regression Study (STARS). *Lancet*. 1992;339:563-569.
40. Chanmugam P, Guthrie JF, Cecilio S, Morton JF, Basiotis P, Anand R. Did fat intake in the United States really decline between 1989-1991 and 1994-1996? *J Am Diet Assoc*. 2003;103:867-872.
41. Subar AF, Kipnis V, Troiano RP, et al. Using intake of biomarkers to evaluate the extent of dietary misreporting in a large sample of adults: the OPEN Study. *Am J Epidemiol*. 2003;158:1-13.
42. Wang C-Y, Anderson GL, Prentice RL. Estimation of the correlation between nutrient intake measures under restricted sampling. *Biometrics*. 1999;55: 711-717.

I may as well tell you, here and now, that if you are going about the place thinking things pretty, you will never make a modern poet. Be poignant, man, be poignant!

—P. G. Wodehouse (1881-1975)