

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 8, 2003

VOL. 348 NO. 19

## Effects of Estrogen plus Progestin on Health-Related Quality of Life

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### ABSTRACT

#### BACKGROUND

The Women's Health Initiative (WHI) and other clinical trials indicate that significant health risks are associated with combination hormone use. Less is known about the effect of hormone therapy on health-related quality of life.

#### METHODS

The WHI randomly assigned 16,608 postmenopausal women 50 to 79 years of age (mean, 63) with an intact uterus at base line to estrogen plus progestin (0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate, in 8506 women) or placebo (in 8102 women). Quality-of-life measures were collected at base line and at one year in all women and at three years in a subgroup of 1511 women.

#### RESULTS

Randomization to estrogen plus progestin resulted in no significant effects on general health, vitality, mental health, depressive symptoms, or sexual satisfaction. The use of estrogen plus progestin was associated with a statistically significant but small and not clinically meaningful benefit in terms of sleep disturbance, physical functioning, and bodily pain after one year (the mean benefit in terms of sleep disturbance was 0.4 point on a 20-point scale, in terms of physical functioning 0.8 point on a 100-point scale, and in terms of pain 1.9 points on a 100-point scale). At three years, there were no significant benefits in terms of any quality-of-life outcomes. Among women 50 to 54 years of age with moderate-to-severe vasomotor symptoms at base line, estrogen and progestin improved vasomotor symptoms and resulted in a small benefit in terms of sleep disturbance but no benefit in terms of the other quality-of-life outcomes.

#### CONCLUSIONS

In this trial in postmenopausal women, estrogen plus progestin did not have a clinically meaningful effect on health-related quality of life.

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N Engl J Med 2003;348.

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THE RECENT FINDINGS OF SEVERAL large-scale randomized clinical trials have demonstrated that protection from cardiovascular disease is not an indication for the use of estrogen plus progestin among postmenopausal women.<sup>1-3</sup> The Women's Health Initiative (WHI) found that women taking estrogen (conjugated equine estrogen) plus progestin (medroxyprogesterone acetate) were at increased risk for myocardial infarction, stroke, venous thromboembolism, and breast cancer as compared with women taking placebo. In spite of the decreased risk of osteoporotic fractures and colorectal cancer, there was an unfavorable global risk-benefit profile in the hormone-treatment group, and the planned 8.5-year randomized clinical trial was stopped after women had been followed for an average of 5.2 years. The estrogen-alone trial is scheduled to continue until March 2005.

These findings have prompted revisions in guidelines for hormone therapy that limit the use of estrogen plus progestin to short-term relief of vasomotor or urogenital symptoms or for the prevention of osteoporosis after careful consideration of alternatives.<sup>4-6</sup> There is evidence that treatment with estrogen plus progestin produces relief from vasomotor symptoms,<sup>7,8</sup> and women report that quality of life is a consideration in their decision to use hormones.<sup>9,10</sup> However, results of the few randomized trials that have assessed the effect of hormone replacement on health-related quality of life are inconsistent, particularly when hormones are prescribed specifically for the prevention of disease rather than the relief of symptoms.<sup>11</sup> Randomized trials have found a substantial placebo effect, with approximately 25 percent of women in placebo groups reporting improvements in health-related quality of life.<sup>12</sup> Hormone use has also been reported to affect depression,<sup>13</sup> sexual functioning,<sup>14</sup> and cognitive functioning.<sup>15</sup> Again, findings are inconsistent, depending on the study design, population, and test instruments.<sup>16</sup>

In research on health-related quality of life, small differences can be statistically significant yet clinically unimportant, especially in studies using large samples.<sup>17</sup> The concept of a minimal clinically meaningful difference, defined as "the smallest effect size that would lead [clinicians] to recommend therapy to their patients,"<sup>18</sup> can be applied in the interpretation of results related to health-related quality of life in large, randomized clinical trials. The WHI trial of estrogen plus progestin, a ran-

domized, double-blind, placebo-controlled trial involving 16,608 postmenopausal women, provides an excellent opportunity to assess the relations between the use of estrogen plus progestin and health-related quality of life and other psychosocial measures in postmenopausal women.

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## METHODS

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### STUDY PARTICIPANTS

The criteria for eligibility, recruitment procedures, and main study outcomes have been published previously.<sup>3,19,20</sup> Briefly, women 50 to 79 years of age with an intact uterus were potentially eligible for this component of the trial. Women were excluded if their last menstrual period occurred less than 6 months before they enrolled in the study (less than 12 months for women 50 to 54 years of age) or if they had medical conditions associated with a life expectancy of less than 3 years, a history of breast cancer or melanoma, other cancers within the previous 10 years (except nonmelanoma skin cancer), a low hematocrit or platelet count, or conditions that would interfere with acceptable adherence to the assigned regimen and retention in the study (e.g., alcoholism or dementia). Potential participants who were using postmenopausal hormones at the initial screening visit were required to undergo a three-month "washout" period before data collection, screening, and enrollment. Women who reported moderate or severe menopausal symptoms during the washout period were discouraged from participating in the study but were not excluded.

Women were seen at a clinic at three screening visits over a period of several months, at which initial consent forms and questionnaires were completed, blood was drawn after a 12-hour fast, standardized physical measurements were taken, and breast and pelvic examinations were performed. Women were required to take lead-in placebo pills for at least four weeks during the screening process so that their compliance with pill taking could be assessed. At randomization, women were assigned to take either a combination of estrogen and progestin (0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate [Prempro, Wyeth]) or a matching placebo pill. Both participating women and members of the clinic staff were unaware of the study-group assignments. Women were seen in the clinics 6 and 12 months after randomization and annually thereafter. Base-line questionnaire items were repeated at the first annual vis-

it for all participants and for a subgroup of 1511 women at the third annual visit. The protocol and all consent forms were approved by the National Institutes of Health and the institutional review boards of all participating institutions.

#### ASSESSMENT OF QUALITY-OF-LIFE-RELATED VARIABLES

##### *Quality of Life and Functional Status*

Quality of life and functional status were assessed with the use of the RAND 36-Item Health Survey (RAND-36).<sup>21,22</sup> The RAND-36 contains eight subscales that include general health (5 items), physical functioning (10 items), limitations on usual role-related activities due to physical health problems (4 items), bodily pain (2 items), energy and fatigue (vitality, 4 items), limitations on usual role-related activities due to emotional or mental problems (3 items), social functioning (2 items), and emotional or mental health (5 items). Scores on all eight subscales range from 0 to 100, with higher scores indicating better health or function. In addition, we used a single health-transition question from the RAND-36, asking women to compare their current general health with their general health a year earlier. Although the RAND-36<sup>22</sup> contains the same items as the Medical Outcomes Study 36-item Short Form General Health Survey (SF-36),<sup>21</sup> it uses a slightly different scoring algorithm for two of the eight subscales.

##### *Depression Score*

Depressive symptoms were assessed according to an eight-item scale developed by Burnam and colleagues.<sup>23</sup> This scale was developed to screen for depressive disorders (major depression and dysthymia) and is composed of six items from the depression scale of the Center for Epidemiologic Studies (CES-D)<sup>24</sup> and two items from the National Institute of Mental Health Diagnostic Interview Schedule.<sup>25</sup> Scores range from -8.2 (best) to 4.0 (worst).

##### *Sleep Disturbance*

Quality of sleep was assessed by the five-item WHI Insomnia Rating Scale,<sup>26</sup> which was developed and validated for use in the WHI. Items in this instrument referred to sleep during the "past four weeks." Four items assessed the problems with the initiation and maintenance of sleep on a five-point response scale ("no, not in past four weeks"; "yes, less than once a week"; "1-2 times a week"; "3 or 4 times a

week"; or "5 or more times a week"), and a fifth item assessed the quality of sleep, also using a five-point scale ("very sound or restful," "sound or restful," "average quality," "restless," or "very restless"). Scores range from 0 (worst) to 20 (best).

##### *Sexual Functioning*

Sexual functioning was assessed by a single item with a four-point response scale ("very unsatisfied," "a little unsatisfied," "somewhat satisfied," or "very satisfied"). Scores range from 1 (worst) to 4 (best).

##### *Cognitive Functioning*

Cognitive functioning was assessed in participants 65 years of age or older by the Modified Mini-Mental State Examination,<sup>27</sup> a scale used in the Cardiovascular Health Study.<sup>28</sup> This examination consists of 15 parts that contain 46 separately scored items. The functions tested included orientation to time, place, and person; short-term memory; reading; writing; naming; verbal fluency; praxis; and graphomotor skill. The overall score ranges from 0 (worst functioning) to 100 (best functioning).

##### *Menopausal Symptoms*

A checklist of symptoms used in previous research<sup>7</sup> was modified to assess symptoms associated with menopause, aging, and hormone use. Five items from this checklist, each with four response categories (none, mild, moderate, and severe) were summed to create a menopausal symptom score. Two items assessed the severity of vasomotor symptoms (hot flashes and night sweats), and three assessed emotional and mental symptoms (mood swings, forgetfulness, and difficulty concentrating). The overall score ranges from 0 (best) to 15 (worst).

#### STATISTICAL ANALYSIS

All primary analyses focused on changes in health-related quality of life from base line to year 1 in relation to study-group assignment. For each measure of health-related quality of life, we fit a linear model to test whether estrogen plus progestin had a significant treatment effect on the change in the score for health-related quality of life. Statistical significance of these 13 treatment effects was judged according to a Bonferroni-corrected alpha value ( $0.05 \div 13$ , or approximately 0.004). To examine whether a statistically significant effect of estrogen plus progestin was moderated by base-line variables, we fit a series of linear models. Each pair—a base-line variable and the corresponding interac-

**Table 1. Base-Line Characteristics of the 16,608 Women According to Study Group.\***

Characteristic	Estrogen-plus-Progestin Group (N=8506)	Placebo Group (N=8102)	P Value
Age group at screening — no. (%)			0.80
50–59 yr	2839 (33.4)	2683 (33.1)	
60–69 yr	3853 (45.3)	3657 (45.1)	
70–79 yr	1814 (21.3)	1762 (21.7)	
Race or ethnic group — no. (%)			0.33
Non-Hispanic white	7140 (83.9)	6805 (84.0)	
Non-Hispanic black	549 (6.5)	575 (7.1)	
Hispanic	472 (5.5)	416 (5.1)	
American Indian	26 (0.3)	30 (0.4)	
Asian or Pacific Islander	194 (2.3)	169 (2.1)	
Unknown or unspecified	125 (1.5)	107 (1.3)	
Educational level — no. (%)			0.19
Less than high school	202 (2.4)	177 (2.2)	
Some high school	373 (4.4)	362 (4.5)	
High-school diploma or GED	1614 (19.1)	1608 (20.0)	
School after high school	3356 (39.7)	3059 (38.0)	
College degree or higher	2915 (34.5)	2838 (35.3)	
Family annual household income — no. (%)			0.60
<\$10,000	451 (5.6)	406 (5.3)	
\$10,000 to \$19,999	1231 (15.3)	1117 (14.6)	
\$20,000 to \$34,999	2228 (27.7)	2088 (27.3)	
\$35,000 to \$49,999	1692 (21.0)	1637 (21.4)	
\$50,000 to \$74,999	1396 (17.3)	1377 (18.0)	
≥\$75,000	1051 (13.1)	1024 (13.4)	

tion between that variable and study-group assignment — was added one at a time followed by a test of the interaction, with one degree of freedom. Base-line characteristics included age, body-mass index (the weight in kilograms divided by the square of the height in meters), moderate or severe vasomotor symptoms, menopausal symptoms, sleep disturbance, previous use of hormone therapy, and history of cardiovascular disease. For exploratory purposes, the moderation of the effect of estrogen plus progestin was investigated for nonsignificant main effects. To avoid overly conservative results,

tests of significance for the two sets of interaction terms — those related to significant effects and those related to nonsignificant effects — used separate Bonferroni adjustments. We performed similar analyses including women with data available at year 3 (a randomly selected subgroup representing 8.6 percent of the entire study population, in which members of minority groups were oversampled) and including the subgroup of women who were 50 to 59 years of age. A post-hoc analysis was performed including women 50 to 54 years of age who reported moderate-to-severe night sweats or hot

Table 1. (Continued.)			
Characteristic	Estrogen-plus-Progestin Group (N = 8506)	Placebo Group (N = 8102)	P Value
No. of years since menopause — no. (%)			0.46
<5	1315 (17.1)	1224 (16.3)	
5 to <10	1467 (19.1)	1488 (19.8)	
10 to <15	1611 (21.0)	1566 (20.9)	
≥15	3286 (42.8)	3231 (43.0)	
Duration of previous hormone use — no. (%)			0.30
0 yr	6277 (73.8)	6020 (74.3)	
<5 yr	1539 (18.1)	1470 (18.1)	
5 to <10 yr	427 (5.0)	356 (4.4)	
≥10 yr	263 (3.1)	255 (3.1)	
Moderate or severe vasomotor symptoms at base line — no. (%)			0.27
No	7341 (87.3)	7030 (87.8)	
Yes	1072 (12.7)	974 (12.2)	
History of cardiovascular disease — no. (%)†			0.17
No	8014 (95.2)	7582 (94.8)	
Yes	406 (4.8)	419 (5.2)	
Body-mass index	28.5±5.8	28.5±5.9	0.66
Sleep-disturbance score	13.4±4.5	13.4±4.4	0.70
Menopausal symptom score‡	2.3±2.2	2.3±2.1	0.22

\* Plus-minus values are means ±SD. Data on educational level were missing for 46 women in the estrogen-plus-progestin group and 58 women in the placebo group; data on family annual household income were missing for 457 women in the estrogen-plus-progestin group and 453 women in the placebo group; data on the number of years since menopause were missing for 827 women in the estrogen-plus-progestin group and 593 women in the placebo group; data on duration of previous hormone use were missing for 1 woman in the placebo group; data on moderate or severe vasomotor symptoms at base line were missing for 93 women in the estrogen-plus-progestin group and 98 women in the placebo group; data on history of cardiovascular disease were missing for 86 women in the estrogen-plus-progestin group and 101 women in the placebo group; data on body-mass index were missing for 36 women in the estrogen-plus-progestin group and 52 women in the placebo group; data on sleep disturbance were missing for 186 women in the estrogen-plus-progestin group and 193 women in the placebo group; and data on general symptoms were missing for 40 women in the estrogen-plus-progestin group and 36 women in the placebo group. GED denotes graduate-equivalency diploma.

† Data are for women with a history of myocardial infarction, stroke, congestive heart failure, angina, coronary-artery bypass grafting, or percutaneous transluminal coronary angioplasty.

‡ Data are for women reporting night sweats, hot flashes, mood swings, forgetfulness, or inability to concentrate.

flashes at base line. All analyses were based on the intention-to-treat principle and were performed with the use of SAS software, version 8.02.<sup>29</sup>

To assess the clinical significance of these findings, we determined the effect size and the smallest increment of change. The effect size was defined as

$$d = \frac{M_{\text{estrogen plus progestin}} - M_{\text{placebo}}}{S_{\text{placebo}}}$$

where M is the average difference in a quality-of-life measure, and S the standard deviation of the difference.<sup>30</sup> Effect sizes of 0.20 to 0.49 are gener-

**Table 2. Quality-of-Life Scores for 16,608 Women at Base Line and Year 1.\***

Quality-of-Life Measure	Estrogen-plus-Progestin Group		Placebo Group		Mean with Estrogen plus Progestin minus Mean with Placebo	
	No. of Women	Mean (±SD) Score	No. of Women	Mean (±SD) Score	Mean ±SE	P Value
<b>General health</b>						
Base line	8400	76.7±16.2	8003	76.5±16.4	0.2±0.3	0.44
Year 1	7722	76.7±16.9	7381	76.0±17.1	0.7±0.3	0.008
Change from base line to year 1	7637	-0.4±13.4	7305	-0.7±13.5	0.4±0.2	0.08
<b>Physical functioning</b>						
Base line	8324	82.8±18.6	7934	82.9±18.9	0.0±0.3	0.95
Year 1	7638	82.5±19.9	7287	81.8±20.4	0.8±0.3	0.02
Change from base line to year 1	7503	-0.6±13.6	7160	-1.4±13.6	0.8±0.2	<0.001†
<b>Role limitations due to physical problems</b>						
Base line	8407	77.7±32.9	8012	78.3±32.4	-0.6±0.5	0.28
Year 1	7735	77.2±34.3	7395	76.2±34.5	1.0±0.6	0.08
Change from base line to year 1	7658	-0.9±34.8	7327	-2.3±34.2	1.5±0.6	0.008
<b>Bodily pain</b>						
Base line	8446	77.3±21.8	8036	77.2±21.9	0.0±0.3	0.92
Year 1	7825	77.6±22.4	7487	75.6±23.1	2.0±0.4	<0.001†
Change from base line to year 1	7777	0.1±21.1	7432	-1.8±20.9	1.9±0.3	<0.001†
<b>Energy and fatigue</b>						
Base line	8391	64.8±18.8	7993	64.8±18.7	0.0±0.3	0.87
Year 1	7733	65.3±19.7	7379	64.9±19.6	0.4±0.3	0.26
Change from base line to year 1	7648	0.2±15.0	7293	0.0±15.3	0.2±0.2	0.31
<b>Social functioning</b>						
Base line	8430	91.5±16.5	8029	91.5±16.4	0.0±0.3	0.89
Year 1	7782	89.9±18.4	7459	90.0±18.4	-0.1±0.3	0.78
Change from base line to year 1	7720	-1.9±18.9	7397	-1.8±19.4	-0.1±0.3	0.76
<b>Role limitations due to emotional problems</b>						
Base line	8417	85.6±27.8	8023	85.3±28.1	0.3±0.4	0.45
Year 1	7720	85.3±28.9	7399	85.4±29.1	0.0±0.5	0.93
Change from base line to year 1	7650	-0.7±30.8	7335	-0.5±30.7	-0.2±0.5	0.68

ally regarded as small, 0.50 to 0.79 as medium, and 0.80 or more as large.<sup>31</sup> The smallest increment of change is the smallest benefit or harm to an individual person as measured by a particular instru-

ment. For example, on the physical-limitations scale of the RAND-36, possible scores were 0, 25, 50, 75, and 100, giving a smallest increment of change of 25. The smallest increment of change serves as a

Table 2. (Continued.)

Quality-of-Life Measure	Estrogen-plus-Progestin Group		Placebo Group		Mean with Estrogen plus Progestin minus Mean with Placebo	
	No. of Women	Mean ( $\pm$ SD) Score	No. of Women	Mean ( $\pm$ SD) Score	Mean $\pm$ SE	P Value
<b>Mental health</b>						
Base line	8384	79.8 $\pm$ 14.1	7989	79.8 $\pm$ 13.9	-0.1 $\pm$ 0.2	0.77
Year 1	7731	80.6 $\pm$ 14.5	7370	80.7 $\pm$ 14.5	0.0 $\pm$ 0.2	0.84
Change from base line to year 1	7631	0.6 $\pm$ 12.1	7279	0.7 $\pm$ 12.4	0.0 $\pm$ 0.2	0.81
<b>Modified Mini-Mental State Examination<math>\ddagger</math></b>						
Base line	2672	95.0 $\pm$ 6.4	2730	95.2 $\pm$ 5.5	-0.2 $\pm$ 0.2	0.18
Year 1	2922	95.5 $\pm$ 5.5	2995	95.8 $\pm$ 4.7	-0.3 $\pm$ 0.1	0.05
Change from base line to year 1	2490	0.7 $\pm$ 6.0	2557	0.6 $\pm$ 4.9	0.1 $\pm$ 0.2	0.40
<b>Depression score</b>						
Base line	8242	-5.5 $\pm$ 1.8	7839	-5.5 $\pm$ 1.8	0.0 $\pm$ 0.0	0.21
Year 1	7591	-5.7 $\pm$ 1.8	7286	-5.7 $\pm$ 1.7	0.0 $\pm$ 0.0	0.41
Change from base line to year 1	7398	-0.1 $\pm$ 1.8	7083	-0.1 $\pm$ 1.8	0.0 $\pm$ 0.0	0.72
<b>Sleep disturbance</b>						
Base line	8320	13.4 $\pm$ 4.5	7909	13.3 $\pm$ 4.4	0.0 $\pm$ 0.1	0.70
Year 1	7642	13.9 $\pm$ 4.4	7307	13.5 $\pm$ 4.4	0.4 $\pm$ 0.1	<0.001 $\ddagger$
Change from base line to year 1	7497	0.5 $\pm$ 3.7	7146	0.1 $\pm$ 3.6	0.4 $\pm$ 0.1	<0.001 $\ddagger$
<b>Satisfaction with sex</b>						
Base line	6945	2.9 $\pm$ 1.1	6604	2.9 $\pm$ 1.1	0.0 $\pm$ 0.0	0.83
Year 1	6223	3.0 $\pm$ 1.1	5849	3.0 $\pm$ 1.1	0.0 $\pm$ 0.0	0.15
Change from base line to year 1	5656	0.0 $\pm$ 1.1	5379	0.0 $\pm$ 1.1	0.0 $\pm$ 0.0	0.48

\* Scales are described in the Methods section. For the depression score, higher scores indicate lower quality of life. For all other measures, higher scores indicate better quality of life. Details on scoring are shown in Appendix 2. Because of rounding, differences between groups may not equal the differences between the two means given.

$\ddagger$  The difference is statistically significant as determined according to the Bonferroni-corrected alpha ( $P < 0.005$ ).

$\ddagger$  Data are for women 65 years of age or older.

reference for use in the translation of the treatment effect in a group into the change that occurs in an individual person.

## RESULTS

### STUDY PARTICIPANTS

Overall, 8506 women were randomly assigned to the estrogen-plus-progestin group, and 8102 to the placebo group. The initial design of the WHI al-

lowed women with a uterus to be randomly assigned to estrogen alone, estrogen plus progestin, or placebo. Release of the data from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial<sup>32</sup> showing that estrogen alone enhanced the development of endometrial hyperplasia prompted the WHI to revise this protocol; randomization of women with a uterus was then limited to estrogen plus progestin or placebo. The 331 women randomly assigned to estrogen alone before that change in

protocol were unblinded and reassigned to estrogen plus progestin, resulting in the inclusion of 8506 women in the estrogen-plus-progestin group and 8102 in the placebo group.<sup>3</sup>

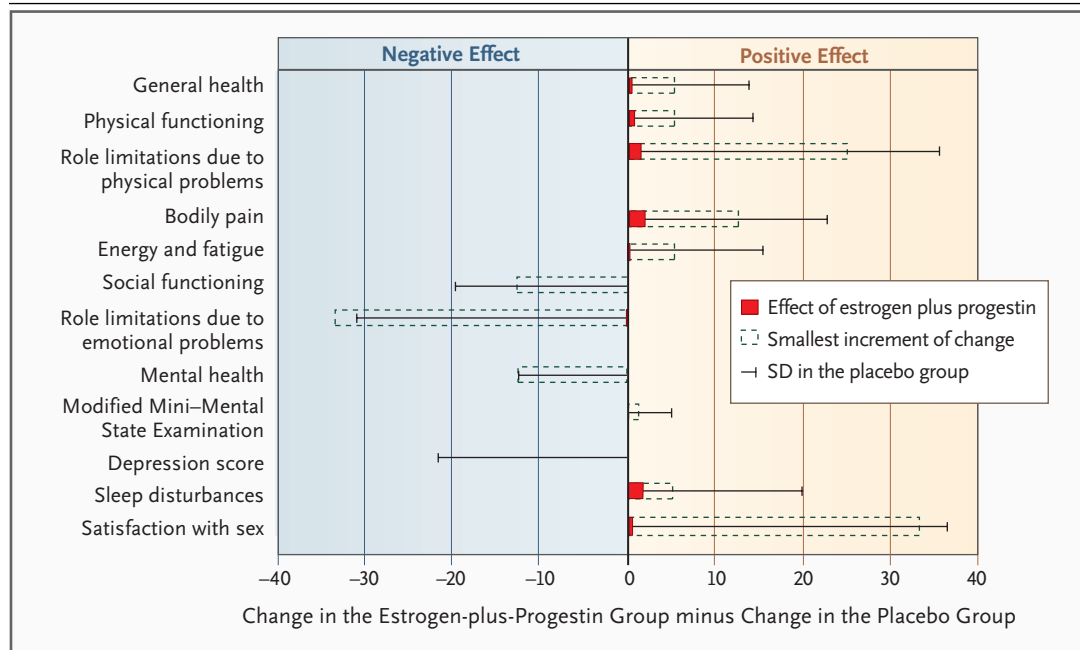
There were no significant differences between these groups at base line (Table 1). The mean age was 63.2 years; 84 percent of the women were white, 35 percent had a college education, 26 percent had some previous hormone use, and 12 percent had moderate-to-severe vasomotor symptoms at base line. Base-line scores on the RAND-36 (see Appendix 2) were similar to scores observed in other healthy populations.<sup>33</sup>

This analysis focused on changes in measures of health-related quality of life during the first year the women were taking the study drugs. At year 1, vital status was known for 99.9 percent of participants, including 0.2 percent who were deceased and 0.1 percent who were lost to follow-up. During the first year, 9.7 percent of the women in the estrogen-plus-progestin group and 6.6 percent of the women in the placebo group stopped taking the study pills

for various reasons. Overall, the rate of adherence to the study regimen (defined as the taking of at least 80 percent of the pills) was 74 percent in the estrogen-plus-progestin group and 81 percent in the placebo group at year 1.

**EFFECTS ON HEALTH-RELATED QUALITY OF LIFE**

When the change in measures of health-related quality of life between base line and year 1 was examined, few differences were observed between the estrogen-plus-progestin group and the placebo group (Table 2). There were small but statistically significant positive effects of estrogen plus progestin, relative to placebo, on physical functioning (P<0.001), bodily pain (P<0.001), and sleep disturbance (P<0.001). For example, the mean benefit in terms of physical functioning was 0.8 point on the 100-point scale. Figure 1 shows the mean differences in the change scores (the change in score from base line to year 1) in the context of the natural variation (SD) of the change scores in the placebo group, as well as the smallest increment of change possible



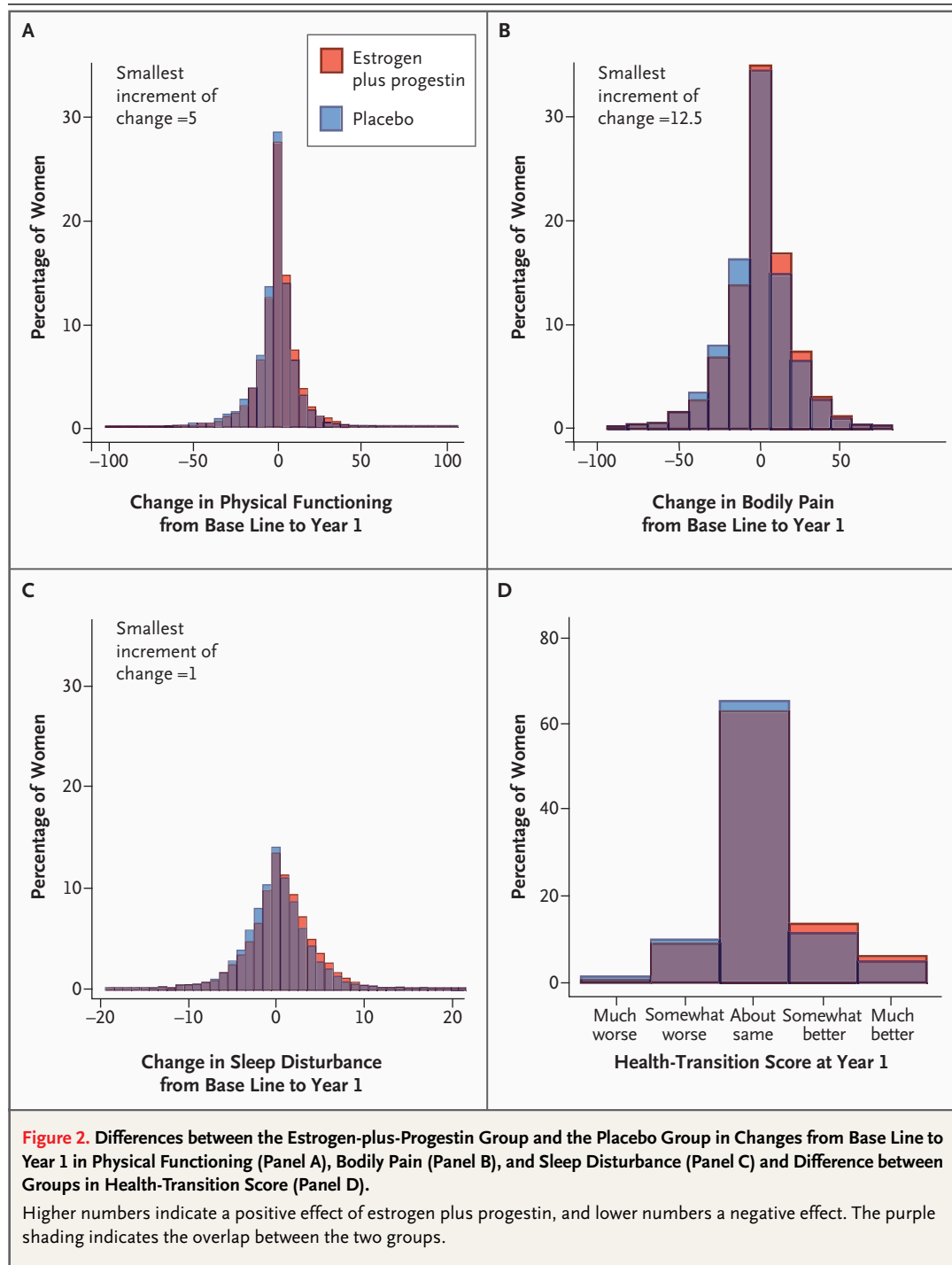
**Figure 1. Differences between the Estrogen-plus-Progestin Group and the Placebo Group in Changes in Quality-of-Life Scores from Base Line to Year 1.**

Scales are described in the Methods section. Depression scores, scores for sleep disturbance, and scores for satisfaction with sex were rescaled from 0 (worst) to 100 (best). P<0.001 for the comparisons of physical functioning, bodily pain, and sleep disturbance between groups. The smallest increment of change is the smallest possible change in score for an individual woman. The depression score does not have a smallest increment of change because it is a continuous variable.

on each scale, all of which reinforces the small size of the statistically significant effects of estrogen plus progestin. The sizes of the effect of estrogen plus progestin on physical functioning, bodily pain, and sleep disturbance were 0.06, 0.09, and 0.11, re-

spectively (with 0.2 generally considered the threshold for even a small effect<sup>31</sup>).

Figure 2 shows the pattern of changes in individual women from base line to year 1 for the three measures that were significantly associated with the



**Table 3. Changes in Quality-of-Life Scores from Base Line to Year 1 and from Base Line to Year 3 for a Subgroup of 1511 Women.\***

Quality-of-Life Measure	Estrogen-plus-Progestin Group		Placebo Group		Mean with Estrogen plus Progestin minus Mean with Placebo	
	No. of Women	Mean ( $\pm$ SD) Score	No. of Women	Mean ( $\pm$ SD) Score	Mean $\pm$ SE	P Value
<b>General health</b>						
Base line	765	75.5 $\pm$ 16.2	718	75.0 $\pm$ 16.6	0.5 $\pm$ 0.9	0.55
Change from base line to year 1	681	0.2 $\pm$ 13.8	642	-0.9 $\pm$ 14.3	1.2 $\pm$ 0.8	0.14
Change from base line to year 3	652	-2.2 $\pm$ 15.9	620	-2.1 $\pm$ 14.7	-0.1 $\pm$ 0.9	0.95
<b>Physical functioning</b>						
Base line	754	82.1 $\pm$ 19.9	714	81.1 $\pm$ 20.4	1.0 $\pm$ 1.1	0.34
Change from base line to year 1	660	0.6 $\pm$ 15.1	630	-1.0 $\pm$ 15.1	1.6 $\pm$ 0.8	0.06
Change from base line to year 3	636	-3.2 $\pm$ 16.9	612	-1.9 $\pm$ 15.5	-1.3 $\pm$ 0.9	0.15
<b>Role limitations due to physical problems</b>						
Base line	764	76.5 $\pm$ 34.6	724	77.2 $\pm$ 33.0	-0.8 $\pm$ 1.8	0.66
Change from base line to year 1	677	1.3 $\pm$ 36.7	651	-1.6 $\pm$ 34.8	2.9 $\pm$ 2.0	0.14
Change from base line to year 3	643	-2.9 $\pm$ 38.5	626	-2.8 $\pm$ 37.0	0.0 $\pm$ 2.1	0.98
<b>Bodily pain</b>						
Base line	768	75.6 $\pm$ 23.6	727	77.1 $\pm$ 22.1	-1.5 $\pm$ 1.2	0.20
Change from base line to year 1	696	1.5 $\pm$ 22.4	659	-1.7 $\pm$ 22.2	3.2 $\pm$ 1.2	0.008
Change from base line to year 3	659	-1.7 $\pm$ 22.9	633	-3.3 $\pm$ 22.2	1.6 $\pm$ 1.3	0.20
<b>Energy and fatigue</b>						
Base line	755	65.8 $\pm$ 17.7	717	64.3 $\pm$ 18.9	1.5 $\pm$ 1.0	0.11
Change from base line to year 1	671	0.4 $\pm$ 15.8	641	-0.7 $\pm$ 16.4	1.1 $\pm$ 0.9	0.21
Change from base line to year 3	631	-0.6 $\pm$ 16.8	610	-0.3 $\pm$ 15.6	-0.3 $\pm$ 0.9	0.76
<b>Social functioning</b>						
Base line	767	90.2 $\pm$ 17.5	721	90.7 $\pm$ 16.9	-0.5 $\pm$ 0.9	0.56
Change from base line to year 1	689	-1.7 $\pm$ 20.0	650	-2.9 $\pm$ 19.6	1.2 $\pm$ 1.1	0.25
Change from base line to year 3	658	-1.6 $\pm$ 20.5	627	-2.1 $\pm$ 20.1	0.5 $\pm$ 1.1	0.67
<b>Role limitations due to emotional problems</b>						
Base line	762	86.0 $\pm$ 28.4	722	83.8 $\pm$ 29.6	2.2 $\pm$ 1.5	0.15
Change from base line to year 1	676	-1.0 $\pm$ 29.5	648	-1.5 $\pm$ 34.3	0.6 $\pm$ 1.8	0.75
Change from base line to year 3	650	-2.5 $\pm$ 31.0	629	-0.8 $\pm$ 34.4	-1.6 $\pm$ 1.8	0.38

Table 3. (Continued.)

Quality-of-Life Measure	Estrogen-plus-Progestin Group		Placebo Group		Mean with Estrogen plus Progestin minus Mean with Placebo	
	No. of Women	Mean ( $\pm$ SD) Score	No. of Women	Mean ( $\pm$ SD) Score	Mean $\pm$ SE	P Value
<b>Mental health</b>						
Base line	754	80.1 $\pm$ 13.4	725	79.8 $\pm$ 13.6	0.3 $\pm$ 0.7	0.66
Change from base line to year 1	667	0.4 $\pm$ 12.4	646	-0.2 $\pm$ 13.3	0.6 $\pm$ 0.7	0.41
Change from base line to year 3	635	1.3 $\pm$ 13.5	619	0.3 $\pm$ 13.9	1.0 $\pm$ 0.8	0.20
<b>Modified Mini-Mental State Examination<sup>†</sup></b>						
Base line	224	93.9 $\pm$ 8.5	233	94.5 $\pm$ 4.6	-0.6 $\pm$ 0.6	0.35
Change from base line to year 1	213	0.8 $\pm$ 7.7	217	0.8 $\pm$ 3.6	0.0 $\pm$ 0.6	0.99
Change from base line to year 3	199	1.3 $\pm$ 7.7	200	1.2 $\pm$ 4.1	0.2 $\pm$ 0.6	0.79
<b>Depression score</b>						
Base line	740	-5.5 $\pm$ 1.8	702	-5.5 $\pm$ 1.9	-0.1 $\pm$ 0.1	0.43
Change from base line to year 1	652	-0.1 $\pm$ 1.6	632	-0.0 $\pm$ 1.9	-0.1 $\pm$ 0.1	0.53
Change from base line to year 3	619	-0.2 $\pm$ 1.8	594	-0.2 $\pm$ 2.0	0.0 $\pm$ 0.1	0.94
<b>Sleep disturbance</b>						
Base line	756	13.5 $\pm$ 4.4	722	13.5 $\pm$ 4.6	0.0 $\pm$ 0.2	0.99
Change from base line to year 1	668	0.4 $\pm$ 3.9	637	0.0 $\pm$ 3.7	0.4 $\pm$ 0.2	0.07
Change from base line to year 3	635	0.4 $\pm$ 4.4	618	0.1 $\pm$ 4.0	0.3 $\pm$ 0.2	0.20
<b>Satisfaction with sex</b>						
Base line	615	3.0 $\pm$ 1.1	588	2.9 $\pm$ 1.0	0.1 $\pm$ 0.1	0.18
Change from base line to year 1	488	0.1 $\pm$ 1.1	456	0.1 $\pm$ 1.2	0.0 $\pm$ 0.1	0.99
Change from base line to year 3	449	0.0 $\pm$ 1.3	431	0.0 $\pm$ 1.2	0.0 $\pm$ 0.1	0.71

\* Scales are described in the Methods section. For the depression score, higher scores indicate lower quality of life. For all other measures, higher scores indicate better quality of life. Details on scoring are shown in Appendix 2. Because of rounding, differences between groups may not equal the differences between the two means given.

<sup>†</sup> Data are for women 65 years of age or older.

use of estrogen plus progestin and for the health-transition question, for which there was a nonsignificant association. The majority of women had little or no change, representing either benefit or harm, in these measures of health-related quality of life (the distributions are roughly symmetrical, with a distinct mode at zero). The RAND-36 health-transition item has a modal response of "about the same," with little difference between the distributions of responses in the estrogen-plus-progestin group and the placebo group.

#### ANALYSES AT YEAR 3

Assessments were repeated at year 3 (in 775 women in the estrogen-plus-progestin group and 736 in the placebo group). As is apparent from Table 3, the changes from base line to year 1 in this subgroup were similar to those in the full study population, with small positive effects in women assigned to estrogen plus progestin only for physical functioning ( $P=0.06$ ), bodily pain ( $P=0.008$ ), and sleep disturbance ( $P=0.07$ ). Differences between the groups were not significant at year 3.

**OTHER SUBGROUP ANALYSES**

Further analyses were performed to explore whether there were subgroups of women for whom estrogen plus progestin had more substantial effects on health-related quality of life. There were no significant interactions between study-group assignment and the following base-line characteristics: age, race or ethnic group, body-mass index, menopausal symptoms (night sweats or hot flashes, mood swings, forgetfulness, or inability to concentrate), sleep disturbances, previous use of any type of hormone therapy, and history of cardiovascular disease.

Two subgroups are of special interest in this report: the youngest women who were closest to menopause at entry into the trial and were most likely to have menopausal symptoms and the group of women who reported moderate-to-severe vasomotor symptoms (hot flashes or night sweats) at base line and therefore might have had greater improvements in quality of life because of the relief of symptoms by estrogen plus progestin. Limiting the analysis to women who were 50 to 59 years old produced no substantial difference in the findings. We examined the effects of estrogen plus progestin on the relief of symptoms among all women who reported moderate-to-severe vasomotor symptoms at base line (1072 women in the estrogen-plus-progestin group and 974 women in the placebo group). At the one year follow-up, 76.7 percent of the women in the estrogen-plus-progestin group had improvement in the severity of hot flashes, as compared with 51.7 percent of the women in the placebo group ( $P < 0.001$ ); 71.0 percent of the women in the estrogen-plus-progestin group had improvement in the severity of night sweats, as compared with 52.8 percent of the women in the placebo group ( $P < 0.001$ ).

As shown in Table 4, an analysis restricted to women 50 to 54 years of age who reported moderate-to-severe vasomotor symptoms at base line showed positive effects of estrogen plus progestin on sleep disturbance but no statistically significant improvements in any other health-related quality-of-life outcome at the nominal 0.05 level of significance. Thus, despite relief of symptoms by estrogen plus progestin, effects on the health-related quality of life of women 50 to 54 years of age with menopausal symptoms were similar to those observed among all women in the trial.

**DISCUSSION**

The WHI is a large randomized trial of combined hormone treatment in ethnically and geographically diverse postmenopausal women. Estrogen plus progestin had no clinically meaningful benefits on health-related quality of life or other psychosocial outcomes. Assignment to estrogen plus progestin was associated with a small but statistically significant benefit in terms of sleep disturbance, physical functioning, and bodily pain after one year. However, these differences did not represent meaningful effects according to accepted criteria for clinical effectiveness.

There were no significant effects of estrogen plus progestin on general health, limitations (either physical or emotional) on usual role-related activities, vitality, social functioning, mental health, depressive symptoms, or sexual satisfaction. The effect of estrogen plus progestin use did not vary, even among the youngest women closest to menopause or among women who reported hot flashes, night sweats, sleep disturbances, or emotional or mental symptoms at base line.

It has been postulated that positive effects of estrogen plus progestin on health-related quality of life may be masked or delayed during the first year, when some women have bothersome side effects such as bleeding and breast pain. Our results provide no evidence that long-term use of estrogen plus progestin has a more positive effect on health-related quality of life than short-term use. However, it is possible that differences were not significant at three years because of the smaller sample and poorer adherence to assigned therapy.

Sleep disturbance is a common and distressing symptom in postmenopausal women that may be slightly alleviated with the use of estrogen plus progestin. Anecdotal reports suggest that women are motivated to continue long-term use of estrogen plus progestin because they have difficulty sleeping. Our results indicate that, for individual women, the magnitude of the benefit in terms of sleep disturbance was small and would not outweigh the previously discussed risks associated with taking estrogen plus progestin. Although sleep disturbances were reduced, the subgroup of women with sleep disturbances did not benefit more than other women in terms of the effects of estrogen plus progestin on other measures of quality of life.

Analysis of data for the large number of women in the WHI can easily produce statistically signifi-

**Table 4. Changes in Quality-of-Life Scores from Base Line to Year 1 among 574 Women 50 to 54 Years of Age with Moderate-to-Severe Vasomotor Symptoms at Base Line.\***

Quality-of-Life Measure	Estrogen-plus-Progestin Group		Placebo Group		Mean with Estrogen plus Progestin minus Mean with Placebo	
	No. of Women	Mean ( $\pm$ SD) Score	No. of Women	Mean ( $\pm$ SD) Score	Mean $\pm$ SE	P Value
General health	269	0.0 $\pm$ 13.6	223	-0.9 $\pm$ 14.7	1.0 $\pm$ 1.3	0.45
Physical functioning	261	-0.4 $\pm$ 15.1	221	-1.5 $\pm$ 13.9	1.2 $\pm$ 1.3	0.38
Role limitations due to physical problems	269	-0.9 $\pm$ 37.9	225	0.9 $\pm$ 28.1	-1.8 $\pm$ 3.1	0.54
Bodily pain	271	-0.5 $\pm$ 21.7	228	-1.8 $\pm$ 20.8	1.3 $\pm$ 1.9	0.50
Energy and fatigue	267	0.6 $\pm$ 18.5	221	1.7 $\pm$ 19.0	-1.1 $\pm$ 1.7	0.53
Social functioning	269	-3.8 $\pm$ 23.3	227	0.2 $\pm$ 22.7	-4.0 $\pm$ 2.1	0.06
Role limitations due to emotional problems	267	-2.6 $\pm$ 37.0	223	2.5 $\pm$ 39.4	-5.2 $\pm$ 3.5	0.14
Mental health	267	0.3 $\pm$ 15.9	225	-0.3 $\pm$ 15.2	0.6 $\pm$ 1.4	0.68
Depression score	255	-0.1 $\pm$ 2.4	213	-0.4 $\pm$ 2.3	0.3 $\pm$ 0.2	0.23
Sleep disturbance	260	1.8 $\pm$ 4.8	216	0.8 $\pm$ 4.6	1.0 $\pm$ 0.4	0.02
Satisfaction with sex	221	0.1 $\pm$ 1.2	201	-0.2 $\pm$ 1.3	0.2 $\pm$ 0.1	0.06

\* Scales are described in the Methods section. For the depression score, higher scores indicate lower quality of life. For all other measures, higher scores indicate better quality of life. Details on scoring are shown in Appendix 2. Because of rounding, differences between groups may not equal the differences between the two means given.

cant results even when the differences may not be clinically significant. The calculated effect sizes and graphic representations of the three statistically significant effects on measures of health-related quality of life argue for caution in the interpretation of the significance of these findings. Moreover, in spite of the large number of comparisons made, few differences that were even nominally significant were found.

Previous trials have found few, marginal, and inconsistent effects of postmenopausal hormones on cognitive, emotional, and physical measures of quality of life. In the Heart and Estrogen/Progestin Replacement Study (HERS) comparing estrogen plus progestin with placebo, the effect of estrogen plus progestin on health-related quality of life depended on the presence or absence of menopausal symptoms at entry into the study<sup>11</sup>—a pattern that was not observed in the WHI. The PEPI Trial,<sup>7</sup> which randomly assigned women to receive placebo, estrogen alone, estrogen with cyclic progestin,

or estrogen with daily progestin, showed no significant differences among groups in measures of psychosocial and cognitive functioning.

As others have done in randomized trials of hormone therapy,<sup>7,11</sup> we studied postmenopausal women who were willing to be randomly assigned to estrogen plus progestin or placebo. Approximately 20 percent of postmenopausal women seek medical treatment for vasomotor or other menopausal symptoms that affect their quality of life.<sup>34</sup> Our data may not be applicable to these women, because women who believed they needed hormone therapy were unlikely to agree to undergo randomization.

A potential limitation of the data on cognitive functioning is that the Modified Mini-Mental State Examination may have been too crude a measure to be responsive to change over a one-year period. Alternatively, the average score on this measure may indicate the presence of a ceiling effect. The WHI Memory Study, an ancillary study of the WHI, was

designed specifically to detect cognitive decline and dementia among participants in the hormone trial who were 65 years of age or older. The results of this study should provide a comprehensive evaluation of cognitive changes over the course of the study in this subgroup. Another limitation is the lack of a validated multi-item measure of sexual functioning.

There may be effects of estrogen plus progestin on health-related quality of life that were not measured in the present study. For example, anecdotal reports by women suggest an effect on perceptions of youthfulness and attractiveness, and benefits in terms of skin tone have been attributed to hormone use.<sup>35</sup> Clinicians report that many women speak of generalized benefits, as indicated by such statements as “I just feel so much better.” There is a sizable placebo effect associated with hormone use<sup>11,36</sup> that may contribute to the perceived improvements in health-related quality of life report-

ed by some women. These and other potential effects should be investigated in future research.

Estrogen plus progestin did not have a clinically meaningful effect on any aspect of health-related quality of life assessed in the WHI trial of estrogen plus progestin. The statistically significant effects observed for physical function, bodily pain, and sleep disturbance were small and appeared to be restricted to the first year of use. For most women, these small benefits do not outweigh the risks of heart attack, stroke, blood clots, and breast cancer associated with combined hormone therapy.

Supported by the National Heart, Lung, and Blood Institute, Department of Health and Human Services.

Drs. Shumaker and LaCroix report having served as paid consultants to Pfizer. Dr. Shumaker reports having served as a paid lecturer for Wyeth–Ayerst and Pfizer. Drs. Hays, Brunner, and Shumaker report having received grant support from Wyeth–Ayerst. Dr. Shumaker reports having received grant support from Pfizer. Dr. Brzyski reports having received grant support from Berlex.

#### APPENDIX 1.

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**Appendix 2. Distribution of Base-Line Quality-of-Life Scores among 16,608 Women.\***

Score	Role Limitations Due to Physical Problems			Role Limitations Due to Emotional Problems			Mental Health	Mini-Mental State Examination	Depression Score	Sleep Disturbance	Satisfaction with Sex	
	General Health	Physical Functioning	Physical Problems	Bodily Pain	Energy and Fatigue	Social Functioning						
Mean ( $\pm$ SD)	76.6 $\pm$ 16.3	82.9 $\pm$ 18.7	78.0 $\pm$ 32.6	77.3 $\pm$ 21.8	64.8 $\pm$ 18.8	91.5 $\pm$ 16.4	85.4 $\pm$ 28.0	79.8 $\pm$ 14.0	95.2 $\pm$ 4.4	-5.5 $\pm$ 1.8	13.4 $\pm$ 4.5	2.9 $\pm$ 1.1
Maximum	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	2.9	20.0	4.0
75th percentile	90.0	95.0	100.0	87.5	80.0	100.0	100.0	88.0	98.0	-5.2	17.0	4.0
Median	80.0	90.0	100.0	87.5	70.0	100.0	100.0	84.0	96.0	-6.4	14.0	3.0
25th percentile	65.0	75.0	75.0	62.5	55.0	87.5	66.7	72.0	93.0	-6.5	10.0	2.0
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-7.9	0.0	1.0

\* Scales are described in the Methods section. For the depression score, higher scores indicate lower quality of life. For all other measures, higher scores indicate better quality of life.

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