Postmenopausal hormone therapy and body composition—a substudy of the estrogen plus progestin trial of the Women’s Health Initiative1–3

Zhao Chen, Tamsen Bassford, Sylvan B Green, Jane A Cauley, Rebecca D Jackson, Andrea Z LaCroix, Meryl Leboff, Marcia L Stefanick, and Karen L Margolis

ABSTRACT

Background: It has been suggested that hormone therapy may help counter undesirable changes in body composition in older women. 

Objective: This study was designed to test whether estrogen plus progestin (E+P) therapy favorably affects age-related changes in body composition in postmenopausal women.

Design: The substudy was composed of 835 women from the estrogen plus progestin trial of the Women’s Health Initiative who were randomly assigned to receive either E+P therapy (n = 437) or placebo (n = 398). The women had a mean age of 63.1 y and, on average, were 13.8 y past menopause. More than 17% of the participants were from an ethnic minority. No significant differences in baseline body composition (measured with dual-energy X-ray absorptiometry) by intervention assignment were observed.

Results: After 3 y of intervention, the women who received active E+P therapy lost less lean soft tissue mass (−0.04 kg) than did the women who received placebo (−0.44 kg; P = 0.001). Additionally, the women in the E+P group had less upper-body fat distribution than did the women in the placebo group (change in ratio of trunk to leg fat mass: −0.025 for the E+P group and 0.004 for the placebo group; P = 0.003). A sensitivity analysis, which was conducted on the women who took ≥80% of the study medication during the intervention period, corroborated the findings from the intent-to-treat analysis.

Conclusions: A 3-y E+P intervention significantly reduced both the loss of lean soft tissue mass and the ratio of trunk to leg fat mass in postmenopausal women. However, the effect sizes were small, and whether these changes in body composition lead to significant health benefits remains to be confirmed. *Am J Clin Nutr* 2005; 82:651–6.

KEY WORDS Estrogen plus progestin, body composition, Women’s Health Initiative, dual-energy X-ray absorptiometry, postmenopausal women

INTRODUCTION

Older women may experience increases in body fat mass and redistribution of fat mass from the limbs to a more central or android location (1). These changes can increase the risk of diabetes and cardiovascular diseases in older women. Menopausal therapy may help counter these changes in body composition in postmenopausal women (1–3). Most of the previous studies investigating the effects of menopausal therapy on body composition were limited either to observational studies or to clinical trials with small sample sizes or short intervention periods. The techniques used for assessing body composition have varied widely across these studies; many studies have not used direct measurements of body composition but have instead relied on anthropometric measurements, such as body mass index (BMI) or hip and waist circumferences, as proxies for obesity, lean soft tissue mass, and body fat distribution. These limitations highlight the need for a better understanding of the relation between body composition and hormone therapy in postmenopausal women. The estrogen plus progestin (E+P) randomized controlled clinical trial of the Women’s Health Initiative (WHI) provides a unique opportunity to investigate the effect of hormone therapy on body composition. All the women in the WHI substudy underwent body-composition assessment by dual-energy X-ray absorptiometry (DXA) scans serially throughout the trial. Because of the advantages of the randomized controlled clinical trial, the present substudy had the unique ability to test whether the E+P intervention had positive effects on body composition, including preventing the loss of lean soft tissue mass, reducing the gain in body fat mass, and reducing the redistribution of fat from the limbs to a central or android location.

SUBJECTS AND METHODS

Subjects

Between 1993 and 1998, a total of 16 608 postmenopausal women who had not previously undergone a hysterectomy were recruited and enrolled into the WHI E+P trial at 40 WHI clinical sites in the United States. The clinical trial and its substudies were approved by the institutional review boards at each of the participating centers and by the WHI Data and Safety Monitoring Board. Participants provided written informed consent, which included consent for the substudies. The Women’s Health Initiative was funded by the US Department of Health and Human Services (the Women’s Health Initiative Program) and the National Heart, Lung, and Blood Institute, National Institutes of Health, and the National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases. The estrogen plus progestin trial investigators have a number of affiliations: University of Arizona, Tucson, AZ (ZC, TB, and SBG); the University of Pittsburgh, Pittsburgh, PA (JAC); the Ohio State University, Columbus, OH (RDJ); the Fred Hutchinson Cancer Research Center, Seattle, WA (AZL); the Brigham and Women’s Hospital, Harvard University, Boston, MA (ML); the Stanford University, Stanford, CA (MLS); and the University of Minnesota, Minneapolis, MN (KLM).

1 From the University of Arizona, Tucson, AZ (ZC, TB, and SBG); the University of Pittsburgh, Pittsburgh, PA (JAC); the Ohio State University, Columbus, OH (RDJ); the Fred Hutchinson Cancer Research Center, Seattle, WA (AZL); the Brigham and Women’s Hospital, Harvard University, Boston, MA (ML); the Stanford University, Stanford, CA (MLS); and the University of Minnesota, Minneapolis, MN (KLM).

2 Supported by the National Heart, Lung, and Blood Institute, US Department of Health and Human Services (the Women’s Health Initiative Program) and the National Institute of Arthritis, Musculoskeletal, and Skin Diseases (grant R01–AR049411 to ZC).

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centers in the United States. The inclusion criteria were as follows: age of 50-79 y, postmenopausal status, likelihood of residence in the area for 3 y, and provision of written informed consent. All the women were stratified by age and randomly allocated (block randomization by clinical center) into either the E+P group (0.625 mg conjugated equine estrogen combined with 2.5 mg medroxyprogesterone acetate per day) or the placebo group. Women who were taking estrogen therapy at the initial screening were asked to go through a 3-mo washout period before starting E+P therapy. The protocol and consent forms were approved by the review boards of all participating institutions. Details regarding inclusion and exclusion criteria, recruitment procedures, participant characteristics, randomization, blinding, and follow-up for the entire E+P cohort can be found in previously published articles (4, 5).

At 3 WHI clinical centers (Pittsburgh, PA; Birmingham, AL; and Tucson-Phoenix, AZ), body composition was assessed with the use of a DXA scanner at baseline and every 3 y thereafter. The participants who completed the baseline and year 3 DXA scan measurements were included in the substudy. The characteristics of the substudy participants differed from those of the entire WHI cohort in that recruitment was aimed at yielding maximum race-ethnicity and age diversity at the WHI clinical centers where DXA measurements were conducted.

**Body-composition measurements**

Body-composition measurements, which included measurements of lean soft tissue mass, fat mass, percentage of lean soft tissue mass, and percentage of fat mass, were assessed from whole-body DXA scans (QDR 2000, 2000+, or 4500W; Hologic Inc., Bedford, MA). Both regional and total body-composition measurements were generated from total-body DXA scans. The ratio of trunk to leg fat mass (trunk:leg fat mass), which indicates fat distribution, was calculated by dividing the fat mass of the trunk region by the fat mass of the leg region. The DXA scans were conducted at baseline and every 3 y during the intervention. Because the E+P trial stopped on 7 July 2002, when the mean follow-up time was 5.6 y, few participants had year 6 scans done before the trial ended. Therefore, the present substudy only examined changes in body composition between the measurements made at baseline and those made at year 3.

Standard protocols for positioning and analysis were used by technicians who were trained and certified by the DXA manufacturer and the WHI DXA coordination center at the University of California, San Francisco. The quality assurance program included monitoring of phantom scans; reviewing random samples of all scans and flagging scans with specific problems; controlling changes in hardware and software, which included in vitro and in vivo cross-calibration; and scanning of calibration phantoms across instruments and clinical sites.

**Other covariates**

Information on age, years since menopause, race and ethnicity, smoking history, recreational physical activities, use of menopausal hormone therapy, energy intake, and alcohol use were assessed with baseline questionnaires. Age at menopause was defined as the age at which the participant last reported any menstrual bleeding, had a bilateral oophorectomy, or began receiving menopausal hormone therapy. Caloric intake was assessed with the use of a validated food-frequency questionnaire, which was based on instruments that were previously used in large-scale dietary intervention trials (6, 7). Recreational physical activity was assessed by questions on the frequency and duration of several types of recreational activities, and metabolic equivalent task scores (defined as the ratio of work metabolic rate to a standard resting metabolic rate, with one metabolic equivalent task roughly equivalent to the resting metabolism while sitting quietly) were computed as the product of days per week, minutes per day, and metabolic equivalent task value for each activity (8). Physical function was measured with the use of the 10-item Medical Outcomes Study Scale (9); a higher score indicates better physical function. Weight was measured to the nearest 0.1 kg on a balance-beam scale while the participant wore indoor clothing and no shoes. Each participant’s height was measured to the nearest 0.1 cm with the use of a wall-mounted stadiometer. BMI was calculated as weight (in kg)/height2 (in m).

Waist and hip circumferences of the participants were measured with the use of measurement tapes at baseline and a year after the randomization for all the E+P participants from the 3 WHI centers where the DXA measurements were conducted. After the first annual visit, the WHI trial only collected waist and hip circumferences in a subcohort of E+P trial participants. In the present WHI substudy, the waist and hip circumference measurements as well as waist-to-hip ratios (WHRs) were repeated in year 3 for only 214 women in the E+P group and 198 women in the placebo group.

**Statistical analysis**

The analysis was performed on 835 women who had DXA scans done at both baseline and year 3. Because of the replacement of an older DXA machine with a new DXA model, 135 of the women from the Tucson WHI clinic (16% of the 835 women in the present substudy) had their baseline scans done with the QDR2000 model and their year 3 scans with the QDR4500W model. With the use of DXA calibration data from an independent group of 50 women who were scanned with both DXA machines on the same day, linear regression equations were developed for the total and regional body-composition assessments, which predicted QDR2000 values from QDR4500W measurements. These equations were used to correct the measurements from the participants who switched scanners. Three additional women who had different scanner models for their 2 evaluations were eliminated from the analysis because no correction was possible.

An intent-to-treat analysis was used for the primary comparisons between the E+P group and the placebo group. Because the effects of E+P therapy might have been adversely affected by a reduced adherence to the study medication, a sensitivity analysis was conducted in the participants who completed ≥80% of the intervention assignments. All analyses were conducted with JMP version 5 (SAS Institute, Cary, NC) for Macintosh computers. Descriptive statistics were used for baseline data, and t tests were used for comparisons of body-composition measurements between the 2 intervention groups. All P values were 2-tailed.

**RESULTS**

**Descriptive analysis of baseline covariates by intervention**

The baseline characteristics of the women by intervention group are shown in Table 1. In this subsample, 398 women were...
assigned to placebo and 437 were assigned to active E+P therapy. No statistically significant differences between the groups were found in age, years since menopause, dietary energy intake, total weekly expenditure on recreational activities, physical functional score, hormone use, smoking history, or alcohol consumption. A small but statistically significant difference in ethnicity by intervention group was observed (P = 0.03).

**Comparison of baseline body composition by intervention**

No significant differences in baseline body-composition measurements by intervention group were found (Table 2). The mean (±SD) weight was 74.98 ± 16.55 kg in the placebo group and 73.78 ± 15.01 kg in the E+P group; the mean (±SD) BMI was 28.64 ± 5.93 in the placebo group and 28.31 ± 5.51 in the E+P group; and the mean (±SD) trunk:leg fat mass was 1.295 ± 0.44 cm in the placebo group and 1.266 ± 0.41 cm in the E+P group. For both the placebo and E+P groups, ~44% of body weight was fat mass and ~53% was lean soft tissue mass.

**Effects of intervention on body composition**

The absolute changes in body-composition measurements were compared between the women who were assigned to placebo and the women who were assigned to E+P therapy (Table 3). The women in the placebo group had a greater loss of lean soft tissue mass (0.44 kg) than did the women in the E+P group (0.04 kg; P = 0.001). A small but statistically significant difference in the changes in trunk:leg fat mass was also observed (0.004 for the placebo group compared with −0.025 for the E+P group; P = 0.003). No significant intervention effect was found for changes in weight, BMI, fat mass, percentage of lean soft tissue mass, and the percentage of fat mass, although the increase in BMI was almost significantly different between the 2 groups (P = 0.07).

The absolute changes in waist circumference, hip circumference, and WHR from baseline to year 3 were examined in women who had year 3 measurements for these variables (214 women in the E+P group and 198 women in the placebo group). No significant differences by intervention group were observed for either the WHR measurements (x ± SEM: 0.008 ± 0.004 and 0.014 ± 0.004 for the E+P group and the placebo group, respectively; P = 0.30) or the waist circumference measurements (x ± SEM: 1.000 ± 0.42 and 0.37 ± 0.44 cm for the E+P group and

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**TABLE 1**

Baseline covariates by intervention group

<table>
<thead>
<tr>
<th></th>
<th>E+P group</th>
<th>Placebo group</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>62.9 ± 7.2 [437]</td>
<td>63.4 ± 7.2 [398]</td>
<td>0.31</td>
</tr>
<tr>
<td>Time since menopause (y)</td>
<td>13.7 ± 9.2 [327]</td>
<td>13.9 ± 8.5 [333]</td>
<td>0.77</td>
</tr>
<tr>
<td>Dietary energy intake (kcal)</td>
<td>1745 ± 713 [424]</td>
<td>1689 ± 697 [380]</td>
<td>0.26</td>
</tr>
<tr>
<td>Total weekly expenditure on recreational activities (MET)</td>
<td>10.8 ± 14.4 [304]</td>
<td>11.3 ± 13.8 [326]</td>
<td>0.66</td>
</tr>
<tr>
<td>Physical functioning score ≥90 (%)</td>
<td>38.7 [432]</td>
<td>35.1 [387]</td>
<td>0.30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity (%)</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
<th>American Indian</th>
<th>Asian or Pacific Islander</th>
<th>Other or unknown</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>83.1 [363]</td>
<td>8.2 [36]</td>
<td>6.6 [29]</td>
<td>0.7 [3]</td>
<td>0.7 [3]</td>
<td>0.7 [3]</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>Never</td>
<td>Past</td>
<td>Current</td>
<td>Never</td>
<td>Past</td>
<td>Current</td>
<td>P²</td>
</tr>
<tr>
<td></td>
<td>77.5 [338]</td>
<td>18.8 [82]</td>
<td>3.7 [16]</td>
<td>56.4 [246]</td>
<td>33.7 [147]</td>
<td>9.9 [43]</td>
<td>0.83</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td>No</td>
<td>Past</td>
<td>Current</td>
<td>No</td>
<td>Past</td>
<td>Current</td>
<td>P²</td>
</tr>
<tr>
<td></td>
<td>19.8 [86]</td>
<td>18.4 [80]</td>
<td>61.8 [268]</td>
<td>16.2 [64]</td>
<td>23.0 [91]</td>
<td>60.8 [240]</td>
<td>0.63</td>
</tr>
</tbody>
</table>

1 E+P, estrogen + progestin; MET, metabolic equivalent.
2 Comparison of intervention groups by t test for continuous variables, Pearson’s chi-square for categorical variables, and Cochran-Mantel-Haenszel chi-square for ordered categories (never, past, or current).
3 x ± SD; n in brackets (all such values).

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**TABLE 2**

Baseline body-composition measurements by intervention group

<table>
<thead>
<tr>
<th></th>
<th>E+P group (n = 437)</th>
<th>Placebo group (n = 398)</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)⁴</td>
<td>73.78 ± 15.01</td>
<td>74.98 ± 16.55</td>
<td>0.27</td>
</tr>
<tr>
<td>BMI (kg/m²)⁴</td>
<td>28.31 ± 5.51</td>
<td>28.64 ± 5.93</td>
<td>0.41</td>
</tr>
<tr>
<td>Lean soft tissue mass (kg)</td>
<td>37.91 ± 5.22</td>
<td>38.49 ± 5.59</td>
<td>0.12</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>32.69 ± 11.1</td>
<td>33.02 ± 11.39</td>
<td>0.68</td>
</tr>
<tr>
<td>Trunk:leg fat ratio</td>
<td>1.266 ± 0.401</td>
<td>1.295 ± 0.442</td>
<td>0.3</td>
</tr>
<tr>
<td>Lean soft tissue mass (%)</td>
<td>53.21 ± 6.85</td>
<td>53.39 ± 6.99</td>
<td>0.71</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>43.98 ± 7.16</td>
<td>43.82 ± 7.24</td>
<td>0.76</td>
</tr>
</tbody>
</table>

1 All values are x ± SD. E+P, estrogen + progestin.
2 t test.
3 n = 397 in the placebo group.
4 n = 436 in the E+P group and 396 in the placebo group.
Sensitivity analysis on body-composition outcomes

The sensitivity analysis included a total of 511 women (256 in the E+P group and 253 in the placebo group). The results from this analysis (Table 4) showed significant intervention effects of E+P therapy on changes in lean soft tissue mass (P < 0.001) and changes in the trunk:leg fat mass (P < 0.001) and thus support the findings of the intent-to-treat analysis. The sensitivity analysis suggested an increase (0.11 kg) in lean soft tissue mass and thus support the findings of the intent-to-treat analysis. The absolute changes (Δ) in body-composition measurements between baseline and year 3 by intervention group are shown in Table 3.

**DISCUSSION**

Our study suggests that E+P therapy can attenuate undesirable changes in body composition in postmenopausal women. The results from both the intent-to-treat analysis and the sensitivity analysis support the hypothesis that E+P therapy may help maintain lean soft tissue mass and reduce upper-body fat distribution in apparently healthy postmenopausal women. The sensitivity analysis also suggested that E+P therapy had a beneficial effect on BMI and the percentage of body fat. However, because of the exploratory nature of the sensitivity analysis, the following discussion is primarily based on the results of the intent-to-treat analysis.

Most of the previous studies on the effects of E+P therapy on body weight or body composition were limited by small sample sizes. The sample size in the Postmenopausal Estrogen-Progestin Intervention (PEPI) trial (10) was comparable with our WHI substudy sample. In the PEPI trial, 875 women aged 45−65 y were randomly assigned to 4 hormone therapy regimens or to placebo. In that trial, the women who were assigned to E+P therapy had significantly smaller increases in waist and hip circumferences than did the women who were assigned to receive placebo. Although the WHR was reduced by hormone treatment in the PEPI trial, which suggested a reduction in central adiposity, the result was not statistically significant. In addition, the

**TABLE 3**

Absolute changes (Δ) in body-composition measurements between baseline and year 3 by intervention group

<table>
<thead>
<tr>
<th></th>
<th>E+P group (n = 437)</th>
<th>Placebo group (n = 398)</th>
<th>Difference (95% CI)</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔWeight (kg)</td>
<td>0.59</td>
<td>0.10</td>
<td>0.49 (−0.48, 1.46)</td>
<td>0.32</td>
</tr>
<tr>
<td>ΔBMI (kg/m²)</td>
<td>0.43</td>
<td>0.14</td>
<td>0.29 (−0.02, 0.60)</td>
<td>0.07</td>
</tr>
<tr>
<td>ΔLean soft tissue mass (kg)</td>
<td>−0.04</td>
<td>−0.44</td>
<td>0.40 (0.16, 0.64)</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔFat mass (kg)</td>
<td>0.29</td>
<td>0.36</td>
<td>−0.07 (−0.63, 0.49)</td>
<td>0.81</td>
</tr>
<tr>
<td>ΔTrunk:leg fat ratio</td>
<td>−0.025</td>
<td>0.004</td>
<td>−0.029 (−0.047, −0.010)</td>
<td>0.003</td>
</tr>
<tr>
<td>ΔPercentage lean soft tissue mass</td>
<td>−0.16</td>
<td>−0.47</td>
<td>0.31 (−0.14, 0.76)</td>
<td>0.18</td>
</tr>
<tr>
<td>ΔPercentage fat mass</td>
<td>0.04</td>
<td>0.44</td>
<td>−0.40 (−0.85, 0.06)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

1. E+P, estrogen + progestin.
2. t test.
3. n = 432 in the E+P group and 390 in the placebo group.
4. n = 430 in the E+P group and 388 in the placebo group.

**TABLE 4**

Sensitivity analysis on body-composition outcomes

<table>
<thead>
<tr>
<th></th>
<th>E+P group (n = 255)</th>
<th>Placebo group (n = 256)</th>
<th>Difference (95% CI)</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔWeight (kg)</td>
<td>0.93</td>
<td>0.09</td>
<td>0.84 (−0.58, 2.25)</td>
<td>0.25</td>
</tr>
<tr>
<td>ΔBMI (kg/m²)</td>
<td>0.56</td>
<td>0.04</td>
<td>0.52 (0.09, 0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>ΔLean soft tissue mass (kg)</td>
<td>0.11</td>
<td>−0.45</td>
<td>0.56 (0.26, 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔFat mass (kg)</td>
<td>0.32</td>
<td>0.46</td>
<td>−0.14 (−0.85, 0.56)</td>
<td>0.69</td>
</tr>
<tr>
<td>ΔTrunk:leg fat ratio</td>
<td>−0.031</td>
<td>0.016</td>
<td>−0.048 (−0.069, −0.026)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔPercentage lean soft tissue mass</td>
<td>−0.18</td>
<td>−0.52</td>
<td>0.34 (−0.21, 0.89)</td>
<td>0.23</td>
</tr>
<tr>
<td>ΔPercentage fat mass</td>
<td>0</td>
<td>0.56</td>
<td>−0.56 (−1.12, 0.00)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

1. E+P, estrogen + progestin. Values are absolute changes from baseline to year 3 in women who had taken ≥80% of the study medication.
2. t test.
3. n = 252 in the E+P group and 253 in the placebo group.
4. n = 252 in the E+P group and 251 in the placebo group.
PEPI trial found significantly less weight gain in the hormone treatment groups than in the placebo group, whereas we observed a greater, although not statistically significant, weight gain in the intervention group than in the placebo group. The weight-reduction effect of hormone therapy was also suggested by the Danish Osteoporosis Prevention Study (DOPS), which was a 5-y randomized controlled clinical trial conducted in early postmenopausal women aged 45–58 y. The hormone intervention in DOPS included 2 mg estradiol plus 1 mg nonrethisterone acetate for women with an intact uterus or 2 mg estradiol for women who had undergone a hysterectomy. DOPS results indicated that the reduced weight gain with hormone therapy was due almost entirely to a reduced gain in fat weight (11). In contrast, the greater weight gain observed in the present substudy in the women who were assigned to the E+P therapy resulted primarily from an increase in lean body mass. The WHI participants were older than the PEPI and the DOPS participants, and it is possible that E+P therapy may affect fat gain and lean mass loss differently in younger postmenopausal women than in older postmenopausal women. In addition, differences in other characteristics of the study participants (such as smoking history and different baseline body weights) and in the techniques for the assessment of body composition and fat distribution may explain some of the different results.

It has been suggested that menopause contributes to a change in body fat distribution, irrespective of aging and obesity (12). Although reductions in body fat gain or in android distribution with hormone therapy were not reported by all the studies (13), several intervention studies support the notion that estrogen therapy may attenuate the accumulation of central fat in postmenopausal women (1, 2, 14, 15). At least one prospective observational study has indicated that continuous daily E+P therapy neither prevents nor increases early postmenopausal weight gain and fat accumulation; however, the study also showed that E+P therapy may minimize the shift from gynoid to android fat distribution (16). Another prospective study also found that menopausal hormone therapy significantly reduced fat mass accumulation in women, especially in the trunk region (3). One cross-sectional study reported that waist circumferences were significantly smaller in long-term estrogen users than in nonusers who were similar in age, years since menopause, and BMI (17). Research on twins has provided additional evidence of reduced total and central body fat with estrogen therapy (18).

It has been suggested that the beneficial effects of hormone therapy on changes in body fat mass and fat distribution are likely mediated through an increase in insulin sensitivity (19). A recent report from a subcohort of the WHI E+P intervention trial, which excluded women who reported a diagnosis of diabetes at baseline, found that E+P intervention reduced the incidence of diabetes. This reduction possibly resulted from a decrease in insulin resistance because the modified homeostasis assessment was lower in the intervention arm than in the placebo arm, but the treatment effect was not statistically significant ($P = 0.08$) (20).

Our finding regarding lean body mass loss is consistent with results from a short-term (two 12-wk periods) crossover study in postmenopausal women aged 55 ± 3 y ($\pm$ SD) that used 3 cycles of E+P intervention (Trisquens Forte: Novo Nordisk, Bagsvaerd, Denmark) (2). Their results suggested a significant increase in lean body mass and a reduction in abdominal fat and in the percentage of fat mass in the women who were receiving menopausal hormone therapy. In contrast, a significant reduction in lean soft tissue mass and a significant gain in both total body fat and percentage of fat mass were observed in women who were assigned to receive placebo; however, overall weight changes did not differ in the women before and after the crossover. With the use of urinary creatinine excretion rates as indicators of muscle mass, another study showed that 1 y of E+P therapy was associated with an increase in muscle mass without a change in body weight compared with placebo (21). However, in a randomized trial in postmenopausal women, Aloia et al (13) found no reduction in the loss of lean body mass (measured by using dual-photon absorptiometry) after women received menopausal hormone therapy. No relation between the use of estrogen and lean body mass was observed in cross-sectional studies (22, 23), which may reflect a prescription bias because physicians were more likely to prescribe estrogen to leaner women or to women with menopausal symptoms. Obviously, data related to the effect of hormone therapy on lean body mass are scarce, and more research with direct measurements on lean tissue mass is needed.

The mechanism by which E+P therapy maintains lean body mass is not well understood. Androgens increase lean soft tissue mass in postmenopausal women, but a drop in bioactive-free testosterone was found to be associated with hormone therapy (24). In a cross-sectional study, estrogen users had lower insulin-like growth factor I concentrations than did nonusers (25). However, a 10-mo hormone intervention (2 mg estradiol-valerate and 10 mg dydrogesterone) increased the release of growth hormone and various growth factors (26), which play important roles in muscle growth and development. This finding suggests that the maintenance of lean body mass via E+P therapy may be mediated by growth hormone and growth factors instead of androgens; however, more direct evidence of whether these factors link E+P therapy and body composition is needed.

Maintaining lean body mass in older age may be beneficial for better balance and, in turn, for reducing the number of falls. Central body fat distribution has been linked with insulin resistance. Results from the WHI trial showed that E+P intervention reduced both the risk of fracture (27) and the incidence of diabetes (20). Whether the reductions in the incidence rates of fractures and diabetes were partially mediated through E+P therapy—induced changes in body composition deserves additional investigation.

The major strengths of the present substudy were the relatively large sample size, the randomized and placebo-controlled design, the longer duration of follow-up, and the use of DXA scans (a state-of-the-art technique in assessing body composition) in ambulatory, multiethnic, postmenopausal women. If we had only used weight or BMI as a proxy for body-composition measurements, then a stable body weight or BMI would have masked the gain in fat mass in women who were assigned to the placebo group because a loss in lean tissue mass would cancel out a gain in fat. Similarly, BMI and weight measurements would have suggested that E+P therapy increases adiposity, but, in fact, the women who received E+P therapy gained more weight than did the women who received placebo only because of an increase in lean body mass and not because of an increase in body fat mass.

The present substudy included a subsample of women from the WHI E+P intervention trial from the 3 WHI centers where DXA measurements were conducted. Because the block randomization was done by clinical center, the randomization was well preserved, as indicated by the lack of significant differences in baseline body-composition measurements by intervention group.
in the subsample. The mean BMI and mean age in the subsample were similar to the mean BMI and mean age of the entire WHI E+P cohort by intervention assignments at baseline (4). Although the subsample differed slightly from the entire E+P cohort in race and ethnicity composition, hormone use, and smoking history, the findings from this study would probably be similar if the analyses were done on the entire WHI E+P cohort. In the present substudy, body-composition data were available for only 2 time points: baseline and year 3. This prevented us from assessing any trends in the changes in body composition and also limited the investigation to the effects of E+P therapy on body composition for only the first 3 y of intervention. The effect sizes of E+P therapy on body composition might be larger for the entire average 5.6-y intervention period.

In conclusion, we found that E+P intervention maintains lean body mass and reduces upper-body fat distribution in postmenopausal women. However, the effect sizes observed in this study were small, and the clinical implications of these changes in body composition remain to be investigated.

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ZC developed the manuscript and all other authors contributed to the writing of the manuscript. TB provided the resources and participated in the study design. SBG conducted the statistical analyses and helped to interpret the results. JAC contributed to the data collection. RDJ and ML contributed to the study design. AZL contributed to the study design and to the analysis plan. MLS contributed to the interpretation of the study results. KLM contributed to the study design, the analysis plan, and the interpretation of the study results. None of the authors had any conflicts of interest.

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