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Hormone therapy and physical function change among older women in the Women's Health Initiative: a randomized controlled trial

Yvonne L. Michael, ScD^{1,2}, Rachel Gold, PhD, MPH², JoAnn E. Manson, MD, DrPH³, Erin M. Keast, MPH⁴, Barbara B. Cochrane, RN, PhD⁵, Nancy F. Woods, RN, PhD⁵, Robert G. Brzyski, MD, PhD⁶, S. Gene McNeeley, MD⁷, and Robert B. Wallace, MD, MS⁸

¹ Department of Epidemiology, Drexel University School of Public Health, Philadelphia, PA

² The Center for Health Research, Kaiser Permanente Northwest, Portland, OR

³ Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston MA

⁴ Department of Public Health and Preventive Medicine, Oregon Health and Science University, Portland, OR

⁵ School of Nursing, University of Washington, Seattle, WA

⁶ School of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX

⁷ Michigan State University College of Osteopathic Medicine, Detroit, MI

⁸ Department of Epidemiology, University of Iowa, Iowa City, IA

Abstract

Objective—Although estrogen may be linked to biological pathways that maintain higher physical function, the evidence is derived mostly from observational epidemiology and therefore has numerous limitations. We examined whether hormone therapy affected physical function in women 65 to 79 years of age at enrollment.

Methods—This study involves an analysis of the Women's Health Initiative randomized controlled trials of hormone therapy in which 922 nondisabled women who had previous hysterectomies were randomized to receive estrogen therapy or a placebo and 1,458 nondisabled women with intact uteri were randomized to receive estrogen + progestin therapy or a placebo. Changes in physical function were analyzed for treatment effect, and subgroup differences were evaluated. All women completed performance-based measures of physical function (grip strength, chair stands, and timed walk) at baseline. These measures were repeated after 1, 3, and 6 years.

Results—Overall, participants' grip strength declined by 12.0%, chair stands declined by 3.5%, and walk pace slowed by 11.4% in the 6 years of follow-up (all *P* values <0.0001). Hormone therapy, as compared with placebo, was not associated with an increased or decreased risk of decline in physical function in either the intention-to-treat analyses or in analyses restricted to participants who were compliant in taking study pills.

Conclusions—Hormone therapy provided no overall protection against functional decline in nondisabled postmenopausal women 65 years or older in 6 years of follow-up. This study did not address the influence of hormone therapy for women of younger ages.

Keywords

Hormone therapy; Conjugated equine estrogens; Medroxyprogesterone; Postmenopausal women; Physical function

Impairments in physical function, such as decreased muscle strength and balance, increase sharply with age.¹ Declines in physical function are associated with increased risk of disability, especially among older women.^{2,3} Prior research suggests that estrogen depletion in women, related to hormonal transitions of menopause, causes physiological changes that damage the musculoskeletal system, thus causing subsequent decreases in function.^{4,5} The mechanisms by which estrogen influences muscle function remain unknown, but studies have established that estrogen and estrogen receptors in the skeletal muscle cells of women⁴ regulate carbohydrate and lipid metabolism. Moreover, recent data suggest that higher endogenous estrogen levels and lower sex hormone-binding globulin concentrations were associated with muscle strength in 75-year-old women. These parameters were associated with lower rates of fall-related limb fractures even after adjusting for bone mineral density.⁵

The literature on connections between hormone therapy (HT) and physical function is complex because of inconsistent use of definitions and measurement of physical function, different classifications of HT use, and study design effects. Results from cohort studies examining the role of HT on physical function are not consistent, with some studies reporting improved physical function associated with HT,⁶ some reporting decrements,⁷ and others reporting no association.⁸ In randomized controlled trials (RCTs) examining the effects of HT on physical function, results have also been inconclusive.^{9–12} However, these trials relied on self-reported physical function, rather than on objective measures,^{9–11} or failed to differentiate between unopposed estrogen and estrogen + progestin.¹²

Identification of factors that affect changes in physical function can provide information useful for forecasting disability burden and related outcomes. Furthermore, evidence regarding the association between HT and physical function could inform our understanding of the musculoskeletal impact of hormone depletion associated with the menopausal transition and help physicians counsel women about the effects of HT. This study investigated the association between HT and changes in performance-based measures of physical function as part of the Women's Health Initiative (WHI).

METHODS

Design overview

The WHI includes two randomized, placebo-controlled hormone trials: the estrogen + progestin therapy (EPT) trial in women with intact uteri and the estrogen therapy (ET) trial in women who had undergone prior hysterectomy. Follow-up contacts by telephone or clinic visit occurred every 6 months, with clinic visits required annually. Informed consent was obtained using forms approved by local institutional review boards.

Setting and participants

The eligibility criteria, recruitment procedures, and main study outcomes for the hormone trials have been published previously.^{13–15} Briefly, postmenopausal women aged 50 to 79 years were recruited between October 1993 and December 1998 at 40 US clinical centers and randomized to one of the HT trials.

Randomization and interventions

Women who had had a hysterectomy received either placebo or ET (0.625 mg/d conjugated equine estrogens supplied by Wyeth), and women who had not undergone a hysterectomy received either placebo or EPT (0.625 mg/d conjugated equine estrogens plus 2.5 mg/d medroxyprogesterone acetate in a combined tablet; Wyeth). Participants and clinic staff were blinded to the study pill assignments.

Outcomes and follow-up

As part of the WHI's overall goal to identify and prevent major causes of disability, performance-based measures of physical function were taken from a 25% subsample of WHI Clinical Trial participants aged 65 to 79 years. Physical function was measured at baseline and again at 1, 3, and 6 years by trained, certified clinical center staff blinded to treatment group. When obtained under standardized conditions, the performance-based measures of physical function included in the WHI are reliable, have strong predictive validity, and are somewhat sensitive to change.^{16–18}

Timed-walk and chair-stand tests provided information on gait and dynamic leg strength, respectively. Grip strength is a measure of upper extremity functional status and has been used as a general indicator of frailty. For each measure, the better of two trials was used in the analyses. Extreme and implausible function assessments were excluded from analyses. In the timed-walk test, a stopwatch was used to measure the number of seconds (to the nearest one-tenth second) from start to when the first foot completely crossed the end line of a 6-meter course. Participants used ambulatory aids as needed. Walk pace was calculated as meters per second. The chair-stand test counted the number of times a participant could stand up from a straight-back armless chair without using her arms. Grip strength was measured in the dominant arm using a hand-grip dynamometer (Jamar hand-grip dynamometer). Measurement was recorded to the nearest kilogram (rounding up) for both trials.

Statistical analyses

Primary analyses were performed on an intent-to-treat basis. Baseline characteristics were compared by randomized groups using χ^2 tests, or Fisher's exact test when subgroups contained fewer than five women. Analyses of the short-term effects of HT focused on changes in physical function from baseline to year 1 and long-term effects at years 3 and 6. For each of the three performance-based physical function measures, the effects of ET and EPT randomization assignment on physical function change score were assessed separately in linear models. Analyses were conducted in SAS 9.1 (SAS Institute Inc, Cary, NC) using PROC GLM. To account for the correlated structure of performance data across repeated measurements, a mixed-effect model was used to fit the 3-and 6-year longitudinal performance data as a function of follow-up time since baseline, using PROC MIXED.¹⁹ The results from the mixed-effect models did not differ from the results from the linear models; thus, we report only the results of the linear models. Sensitivity analyses were conducted to examine the effect of nonadherence by repeating these analyses among women who were at least 80% adherent during follow-up. Additional sensitivity analyses evaluated the potential influence of incident conditions by excluding women who experienced a health outcome that may impair physical performance and is also related to HT (stroke, myocardial infarction, breast cancer, hip or knee replacement, any fracture, and venous thromboembolism) before the follow-up function assessment. To evaluate the influence of stopping HT on function, models were stratified by current HT status.

Unadjusted models were run first, followed by models adjusted for clinic, randomization into the calcium/vitamin D and dietary modification arms of the WHI, and baseline

characteristics that significantly differed ($P < 0.05$) between the intervention and control groups within each treatment arm. Linear modeling assumes complete information (ie, no missing data) for the covariates in an analysis. Because the amount of missing data on each confounding factor was small, participants with missing covariate data were excluded from the adjusted models.

To examine whether there were any important subgroup effects, a series of two-way interaction terms (treatment $\times$ baseline characteristic) were evaluated in the adjusted models. Twenty-nine interaction terms were added separately to test the interaction significance (see Table 1 for list of baseline characteristics). Because one to two interaction terms at each time point would be significant because of chance alone, a stratified adjusted model was run to evaluate the effect of HT by level of baseline characteristic only if the interaction term was significant ($P < 0.05$) at two or more time points. Women self-reported their race/ethnicity as American Indian or Alaskan Native; Asian or Pacific Islander; black or African American; Hispanic/Latino; white (not of Hispanic origin); or other. Because of the low frequency of nonwhite selections, race/ethnicity was collapsed into white and nonwhite for this analysis.

Clinical significance

The clinical significance of the results was determined by calculating the effect size and smallest increment of change. Effect size was defined as

$$D = \frac{M_{\text{intervention}} - M_{\text{placebo}}}{S_{\text{placebo}}}$$

where M is the average change in function score and S is the standard deviation of the change.²⁰ Effect size was interpreted as large, effect size of 0.80 or greater; medium, 0.50 to 0.79; or small, 0.20 to 0.49. The smallest increment of change was determined using measurements of functional assessments.¹⁰ For example, grip-strength measurements were rounded up for a smallest increment of change of 1 kg.

Power

Power was assessed in terms of the study's ability to detect a clinically significant change in function given the available number of observations. Effect size was used as an indicator of clinical significance as described above. Low ends of the ranges were used as cutoffs to not overestimate power. Effect size was calculated in Excel using PROC MEAN output for treatment and control groups. PROC GLMPower in SAS 9.1 (SAS Institute Inc) was used to calculate power.

RESULTS

The WHI study population included in these analyses is described in Fig. 1. A total of 5,310 women were in the ET group and 5,429 women were in the placebo group for the ET trial, whereas 8,506 women were in the EPT group and 8,102 women were in the placebo group in the EPT trial. For the analyses presented here, participants younger than 65 years ($n = 15,101$) or disabled at baseline ($n = 1,721$) were excluded. Of the 3,858 women remaining in the ET trial, 922 (23%) women were randomly selected to participate in the physical function subsample and completed all baseline assessments; of the 6,087 women remaining in the EPT trial, 1,458 (24%) were randomly selected to participate in the physical function subsample and completed all baseline assessments (Fig. 1), for a total of 2,380 women in the

subsample. During 6 years of follow-up, 1,365 (57.4%) of the 2,380 women completed physical function assessments at all three time points and 2,289 (96.2%) women completed these assessments at least once during follow-up. After 6 years, participants' grip strength declined by 12.0%, chair-stand ability declined by 3.5%, and walk pace slowed by 11.4% from baseline.

Baseline characteristics among participants in the physical function subsample by treatment arm and randomization status are shown in Table 1. In the ET arm, baseline grip strength, years since menopause, and experience of hot flashes or night sweats differed between the intervention and control groups. In the EPT arm, there were no significant differences between the control and intervention groups.

Average changes in function assessments by treatment arm are provided graphically in Fig. 2. The effects of ET and EPT on function change were not significant in short- or long-term models of any functional test (Tables 2 and 3). Adjustment for characteristics that differed at baseline did not affect the significance of the effects. Among the most adherent participants in the EPT arm, the chair-stand ability of the intervention group declined by an average of 0.41 more than that of the control group at year 6 (-1.52 vs -1.11 stands, respectively; $P = 0.04$). Although statistically significant, this difference indicates a small clinical effect. Results were unchanged in models that excluded women with incident conditions and stratified by active intervention status (data not shown).

The association between EPT use and physical function seemed to vary according to race at year 6 ($P < 0.01$). Among nonwhite women, women randomized to EPT retained 3.60 kg more grip strength than that of women randomized to placebo after 6 years of follow-up ($P = 0.04$). This difference is clinically significant ($D = 1.03$). Evaluating the effect on specific racial/ethnic categories (ie, Asian/Pacific Islander, African American, and Hispanic) failed to produce significant results, probably because of the very small sample sizes (26–38 women). There was no evidence that the association between unopposed estrogen and physical function varied by race.

DISCUSSION

Analyses of WHI data from RCTs comparing estrogen alone and estrogen + progestin with placebo in women 65 to 79 years of age at enrollment showed no evidence of treatment effects on measures of physical function. Analyses of women who were highly adherent ($\geq 80\%$) to the treatment did not alter the primary results. The results remained unchanged after excluding women with incident conditions associated with HT during follow-up. Stopping HT did not result in a change in function in this population. The observed improved grip strength associated with EPT in nonwhite women in this study should be interpreted cautiously given that effect modification by race was not proposed a priori and there is no known mechanism for the observed association. This study did not address the influence of HT for women of younger ages.

The overall results are similar to the results from the only other clinical trial that directly assessed the relation between HT and change in performance-based measures of physical function among older women.¹² That trial also reported no clinically meaningful associations. However, Greenspan et al¹² were not able to differentiate between EPT and ET and did not collect follow-up data after cessation of HT. In a recent trial of EPT and exercise training for 1 year among 51 women aged 50 to 57 years, significant changes were seen in the improving condition of the skeletal muscle and in preventing attenuation in women during the early postmenopausal phase; these changes likely exerted a positive effect on muscle performance.²¹ We are unable to examine whether HT produces differential effects

depending on when it is administered in relation to the menopausal transition with respect to physical functioning because of the nature of our cohort and because very few women were past users of HT (Table 1). However, a recent analysis of the WHI randomized HT trials found no evidence of a beneficial effect of initiation of HT close to menopause for a wide variety of health outcomes, including coronary heart disease, total cancer, hip fracture, total mortality, and a summary global index.²²

Randomized trials that assessed the relation between HT and change in self-reported physical function reported conflicting results. The Heart and Estrogen/Progestin Replacement Study reported a significantly faster decline in self-reported physical function scores among 2,763 women assigned to EPT therapy after 3 years.¹¹ In contrast, the WHI found no association between HT and self-reported physical function after 3 years.^{9,10} Performance-based measures of physical function are generally preferable to self-reported measures because of their high reliability and strong predictive value.²³

The current study excludes participants without function measures at follow-up visits. However, the percentage of participants with incomplete follow-up did not significantly differ between the treatment (41.9%) and control (43.4%) groups ($P = 0.48$). In general, women with incomplete follow-up were older and had lower physical function at baseline. The difference in age was small (0.4 y) but significant ($P < 0.01$). Baseline grip strength did not differ by follow-up ($P = 0.85$), but baseline chair stands and walk pace did ($P < 0.0001$ for both). Women with incomplete follow-up performed 0.3 fewer chair stands and 0.1 meter/second slower walk pace at baseline compared with women with complete follow-up. Although the population included in these analyses may have been healthier than the general population, follow-up did not differ by treatment/control status and does not explain our null findings. However, if a younger and healthier population is less likely to experience functional decline, this study may have had a decreased ability to detect function change. In addition, most (91.0%) women with incomplete follow-up completed at least one follow-up assessment and were included in the analysis to some extent.

This study had adequate power (≥ 0.80) to detect very small differences in functional change (difference, ≥ 0.22). In the ET trial, the 6-year analysis had adequate power to assess a difference of 1.31-kg change in grip strength, 0.47 change in chair stands, and 0.07-meter/second change in walk pace (a difference of 0.38 s in the 6-meter timed walk) between the treatment and control groups. The EPT trial had power to detect differences of 1.04 kg, 0.36 stand, and 0.06 meter/second, respectively.

Negative confounding is a possible explanation for finding that follow-up status did not vary by study arm. Significant differences between the EPT group and placebo group in the current study were observed for three measured variables: experience of hot flashes, years since menopause, and baseline grip strength. Although we were able to adjust our analyses for these factors, it is possible that other unmeasured and unknown risk factors for decline in physical function were imbalanced between the study arms. Simulation studies demonstrate that bias in the exposure effect estimate increases as the amount of residual and unmeasured confounding increases.²⁴ In the current analysis, adjustment for characteristics that differed at baseline did not affect significance of effects, suggesting that the likelihood that unmeasured confounding completely explains the null results of this study was small.

Our finding that, on average, physical function in our study sample declined over time should be interpreted in light of other studies. In a study that followed a population-based sample of 5,178 community-dwelling women for more than 10 years, walking speed decreased by 17% (SD, 24%) and time to complete five chair stands increased by 22% (SD, 44%; both P values < 0.0001).⁷ In a study of short-term changes in walking speed, chair-

stand ability, and grip strength among 1,002 community-dwelling women with some disability at baseline, Onder et al³ reported an 11.2% decline in mean chair-stand ability after 1 year (21.1% by year 3), a 1-year decline of 5.2% in mean walking speed (16.2% by year 3), and a 1-year decline of 1% in mean grip strength (6.8% by year 3). In this study, decline in grip strength is comparable with that in the study of Onder et al. Short-term decline in walk pace is comparable, although long-term decline may be slower in the WHI sample. Decline in chair stands was notably slower in the WHI's sample than in the other two studies, in both the long and the short terms. This is consistent with the fact that, in general, RCTs enroll healthier participants than community studies do.

CONCLUSIONS

In conclusion, hormone treatment provided no overall protection against functional decline in nondisabled postmenopausal women 65 years or older in 6 years of follow-up. Possible race differences in the influence of HT on change in function should be explored in future research.

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Short list of WHI investigators: *Program office.* National Heart, Lung, and Blood Institute, Bethesda, MD: Elizabeth Nabel, Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller. *Clinical coordinating center.* Fred Hutchinson Cancer Research Center, Seattle, WA: Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg, Ruth E. Patterson, and Anne McTiernan; Medical Research Labs, Highland Heights, KY: Evan Stein; and University of California at San Francisco, San Francisco, CA: Steven Cummings. *Clinical centers.* Albert Einstein College of Medicine, Bronx, NY: Sylvia Wassertheil-Smoller; Baylor College of Medicine, Houston, TX: Aleksandar Rajkovic; Brigham and Women's Hospital, Harvard Medical School, Boston, MA: JoAnn E. Manson; Brown University, Providence, RI: Charles B. Eaton; Emory University, Atlanta, GA: Lawrence Phillips; Fred Hutchinson Cancer Research Center, Seattle, WA: Shirley Beresford; George Washington University Medical Center, Washington, DC: Lisa Martin; Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA: Rowan Chlebowski; Kaiser Permanente Center for Health Research, Portland, OR: Yvonne Michael; Kaiser Permanente Division of Research, Oakland, CA: Bette Caan; Medical College of Wisconsin, Milwaukee, WI: Jane Morley Kotchen; MedStar Research Institute/Howard University, Washington, DC: Barbara V. Howard; Northwestern University, Chicago/Evanston, IL: Linda Van Horn; Rush Medical Center, Chicago, IL: Henry Black; Stanford Prevention Research Center, Stanford, CA: Marcia L. Stefanick; State University of New York at Stony Brook, Stony Brook, NY: Dorothy Lane; The Ohio State University, Columbus, OH: Rebecca Jackson; University of Alabama at Birmingham, Birmingham, AL: Cora E. Lewis; University of Arizona, Tucson/Phoenix, AZ: Cynthia A. Thomson; University at Buffalo, Buffalo, NY: Jean Wactawski-Wende; University of California at Davis, Sacramento, CA: John Robbins; University of California at Irvine, Irvine, CA: F. Allan Hubbell; University of California at Los Angeles, Los Angeles, CA: Lauren Nathan; University of California at San Diego, LaJolla/Chula Vista, CA: Robert D. Langer; University of Cincinnati, Cincinnati, OH: Margery Gass; University of Florida, Gainesville/Jacksonville, FL: Marian Limacher; University of Hawaii, Honolulu, HI: J. David Curb; University of Iowa, Iowa City/Davenport, IA: Robert Wallace; University of Massachusetts/Fallon Clinic, Worcester, MA: Judith Ockene; University of Medicine and Dentistry of New Jersey, Newark, NJ: Norman Lasser; University of Miami, Miami, FL: Mary Jo O'Sullivan; University of Minnesota, Minneapolis, MN: Karen Margolis; University of Nevada, Reno, NV: Robert Brunner; University of North Carolina, Chapel Hill, NC: Gerardo Heiss; University of Pittsburgh, Pittsburgh, PA: Lewis Kuller; University of Tennessee Health Science Center, Memphis, TN: Karen C. Johnson; University of Texas Health Science Center, San Antonio, TX: Robert Brzyski; University of Wisconsin, Madison, WI: Gloria E. Sarto; Wake Forest University School of Medicine, Winston-Salem, NC: Mara Vitollins; and Wayne State University School of Medicine/Hutzel Hospital, Detroit, MI: Michael Simon.

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FIG. 1.
Screening and enrollment of the Women's Health Initiative Clinical Trial functional status subsample.

FIG. 2.
Average change in function by year.

TABLE 1

Baseline characteristics by randomization

	Estrogen therapy				Estrogen + progestin therapy			
	Intervention (n = 454)		Control (n = 468)		Intervention (n = 743)		Control (n = 715)	
	n	%	n	%	n	%	n	%
Age group at screening								
65–69 y	217	47.8	227	48.5	366	49.3	352	49.2
70–79 y	237	52.2	241	51.5	377	50.7	363	50.8
Body mass index								
Normal or underweight (<25 kg/m ²)	111	24.4	101	21.6	261	35.1	258	36.1
Overweight or obese (≥25 kg/m ²)	341	75.1	360	76.9	476	64.1	452	63.2
Hot flashes or night sweats								
No	147	32.4	187	40.0 ^a	293	39.4	283	39.6
Yes	297	65.4	272	58.1	434	58.4	411	57.5
Years since menopause								
<20 y ago	72	15.9	107	22.9 ^a	361	48.6	370	51.7
≥20 y ago	318	70.0	295	63.0	357	48.0	329	46.0
Bilateral oophorectomy								
No	241	53.1	241	51.5	735	98.9	707	98.9
Yes	175	38.5	186	39.7	3	0.4	2	0.3
Unopposed estrogen duration								
None	250	55.1	249	53.2	626	84.3	613	85.7
<5 y	135	29.7	145	31.0	102	13.7	87	12.2
≥5 y	69	15.2	74	15.8	15	2.0	15	2.1
Unopposed estrogen use status								
Never used	250	55.1	249	53.2	627	84.4	613	85.7
Past user	162	35.7	169	36.1	115	15.5	98	13.7
Current user	42	9.3	50	10.7	1	0.1	3	0.4
Estrogen + progestin duration								
None	446	98.2	456	97.4	666	89.6	630	88.1
<5 y	7	1.5	10	2.1	65	8.7	72	10.1

	Estrogen therapy				Estrogen + progestin therapy			
	Intervention (n = 454)		Control (n = 468)		Intervention (n = 743)		Control (n = 715)	
	n	%	n	%	n	%	n	%
>5 y	1	0.2	2	0.4	12	1.6	13	1.8
Estrogen + progestin use status								
Never used	446	98.2	456	97.4	666	89.6	630	88.1
Past user	6	1.3	10	2.1	54	7.3	55	7.7
Current user	2	0.4	2	0.4	23	3.1	30	4.2
Ethnicity								
White (non-Hispanic)	380	83.7	400	85.5	670	90.2	634	88.7
Nonwhite	73	16.1	68	14.5	73	9.8	79	11.0
Education								
≤High school	151	33.3	145	31.0	178	24.0	182	25.5
>High school	299	65.9	322	68.8	564	75.9	530	74.1
Family income								
<\$20,000	127	28.0	132	28.2	158	21.3	142	19.9
≥\$20,000	288	63.4	308	65.8	548	73.8	535	74.8
Baseline grip strength								
Below median (<25 kg)	245	54.0	287	61.3 ^a	409	55.0	378	52.9
Above median (≥25 kg)	209	46.0	181	38.7	334	45.0	337	47.1
Baseline chair stands								
Below median (<7 stands)	204	44.9	214	45.7	321	43.2	295	41.3
Above median (≥7 stands)	250	55.1	254	54.3	422	56.8	420	58.7
Baseline walking pace								
Below median (<1.2 meter/s)	238	52.4	231	49.4	346	46.6	362	50.6
Above median (≥1.2 meter/s)	216	47.6	237	50.6	397	53.4	353	49.4

Columns may not add to 100% because of missing values.

^aDifferences between intervention and control groups significant, $P < 0.05$ by χ^2 or Fisher's exact test.

Change in function from baseline to years 1, 3, and 6 in the estrogen therapy arm

Estrogen therapy											
Intervention group				Placebo group				Difference (intervention-placebo)			
No. of participants		Mean	SD	No. of participants		Mean	SD	Mean		SE	P
Grip strength, kg											
Baseline	385	24.07	0.17	396	24.18	0.16		-0.11	0.18		0.536
Year 1	342	-0.29	0.38	354	-0.72	0.36		0.43	0.40		0.285
Year 3	324	-1.74	0.44	336	-1.82	0.41		0.09	0.46		0.854
Year 6	288	-2.74	0.44	296	-2.85	0.42		0.11	0.48		0.810
Chair stands, no.											
Baseline	385	6.77	0.12	396	6.66	0.11		0.11	0.12		0.355
Year 1	330	0.17	0.12	345	0.08	0.11		0.09	0.13		0.489
Year 3	310	-0.12	0.13	317	-0.34	0.12		0.22	0.13		0.100
Year 6	267	-0.24	0.17	270	-0.37	0.16		0.13	0.18		0.471
Walking pace, meter/s											
Baseline	385	1.14	0.02	396	1.17	0.02		-0.03	0.02		0.137
Year 1	342	-0.01	0.02	353	-0.04	0.02		0.03	0.02		0.158
Year 3	317	-0.09	0.03	333	-0.13	0.02		0.04	0.03		0.149
Year 6	282	-0.14	0.03	292	-0.16	0.02		0.02	0.03		0.382

Estrogen therapy models adjusted for clinic, randomization into the calcium/vitamin D and dietary modification arms, baseline grip strength, age at menopause, and experience of hot flashes or night sweats.

TABLE 3

Estrogen + progestin therapy models adjusted for clinic and randomization into the calcium/vitamin D and dietary modification arms.