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Estrogen Alone and Joint Symptoms in the Women's Health Initiative Randomized Trial

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Abstract

Objectives—While joint symptoms are commonly reported after menopause, observational studies examining exogenous estrogen influence on joint symptoms provide mixed results. Against this background, estrogen alone effects on joint symptoms were examined in post hoc analyses in the Women's Health Initiative randomized, placebo-controlled clinical trial.

Methods—10,739 postmenopausal women with prior hysterectomy were randomized to receive daily oral conjugated equine estrogen (0.625 mg/d) or matching placebo. The frequency and severity of joint pain and joint swelling were assessed by questionnaire at entry and year 1 from all participants and in a random 9.9% subsample (n=1062) following years 3 and 6. Logistic regression models were used to compare frequency and severity of symptoms by randomization group. Sensitivity analyses evaluated adherence influence on symptoms.

Results—At baseline, joint pain and swelling were closely comparable in the randomization groups (about 77% with joint pain and 40% with joint swelling). After one year, joint pain

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frequency was significantly lower in the estrogen alone compared to the placebo group (76.3% vs 79.2%, P=0.001) as was joint pain severity and the difference in pain between randomization groups persisted through year 3. However, joint swelling frequency was higher in the estrogen alone group (42.1% vs 39.7%, P=0.02). Adherence adjusted analyses strengthen the estrogen association with reduced joint pain but attenuated the estrogen association with increased joint swelling.

Conclusions—The current findings suggest that estrogen alone use in postmenopausal women results in a modest but sustained reduction in the frequency of joint pain.

Keywords

Estrogen; joint pain; joint swelling; Women's Health Initiative; postmenopausal women; randomized clinical trial

Introduction

While joint symptoms are commonly reported by women after menopause, [1, 2] a determinant role for estrogen in the process is not established. [3, 4] While some observational studies examining relationships between exogenous estrogen use and joint symptoms report a favorable effect, [2, 5-8] negative studies have been reported [9-12] and no clear association has emerged. [3, 13]

The issue of hormonal influence on joint symptoms was examined previously in the WHI trial evaluating estrogen alone use in women with prior hysterectomy where analyses compared women with no joint pain to those with moderate or severe pain. At one year, compared to placebo, a marginal effect of estrogen alone on joint pain was seen (P<0.04). In analyses conducted in adherent women at the end of intervention, about 5% more women in the estrogen group were free of joint pain (P=0.001). [14] The current analyses in this WHI trial expands those observations. Joint symptoms are now evaluated for severity and serially assessed alone with joint swelling frequency and severity. The findings are presented for women assigned estrogen alone and compared to those assigned placebo at baseline and after one year (all participants) and after 3 and 6 years (in a randomly identified 9.9% subset with joint symptoms assessments) in both intent-to-treat analyses and analyses adjusted for adherence.

The study objective was to determine whether estrogen alone use favorably influences the incidence or severity of joint pain or joint swelling in postmenopausal women. The Women's Health Initiative randomized placebo-controlled clinical trial evaluating estrogen alone use in postmenopausal women with prior hysterectomy provides an opportunity to evaluate this association in a rigorous manner.

Methods

WHI estrogen alone trial

The study design and conduct of the WHI trial evaluating estrogen alone has been reported elsewhere. [15, 16] Postmenopausal women between 50-79 years old who had previous hysterectomy with life expectancy ≥ 3 years and no prior breast cancer were entered into the randomized, double-blind, placebo-controlled trial at 40 US clinical centers. Women using hormones at baseline required a three month washout period before study entry.

A total of 10,739 postmenopausal women were randomized using a permuted-blocked algorithm to receive daily oral conjugated equine estrogen (0.625 mg/d) or matching

placebo. The influence of estrogen alone on primary disease outcomes has been reported. [15-18] Women participating in the estrogen alone trial were invited to join an additional randomized, placebo-controlled trial evaluating daily calcium (1000 mg) plus vitamin D (400 IU) supplementation at their first or second annual follow-up visit. The influence of calcium plus vitamin D supplementation on major primary study endpoints has also been previously reported. [19-21] The influence of estrogen alone on joint symptoms is the focus of the current report.

The WHI estrogen alone clinical trial had institutional review board approval from all participating institutions and written informed consent was obtained from all participants. Statistical analyses and data management was conducted at the WHI Clinical Coordinating Center.

Data Collection

At entry, information on demographics, family and medical history and lifestyle factors were obtained by self-reported questionnaires. Medication and supplement use was assessed by interviewer-administered questionnaire. A written protocol, central training of clinic staff and quality assurance visits by the WHI Coordinating Center ensured uniform data collection across centers.

Physical activity was assessed by questionnaire with information used to generate metabolic equivalent (MET) values. [22] Measurements of height and weight were made by clinical personnel to permit body mass index (BMI) determination. Total daily calcium and vitamin D intake were defined as the sum of the dietary intake (assessed with a modified Block food frequency questionnaire) [23] and the self-reported intake from supplement and prescription medication.

Joint symptoms were assessed by questionnaire at entry into the trial and at the first annual visit from all participants. Additionally, joint symptoms were assessed in a random 9.9% subsample of participants at years 3 and 6 after entry in the estrogen alone randomized clinical trial. The sampling was done on the entire clinical trial population (n=68,132) with a 6-fold higher odds at selection for non-White participants. Joint pain and joint symptoms were separately assessed and categorized by presence (yes/no) and severity (mild, moderate, severe) among those with each symptom. The joint pain and swelling severity scores were calculated as an average from: 0 (none), one (mild), two (moderate) and three (severe).

Information on other clinical outcomes was collected at annual clinic visits and semi-annual contacts. Annual clinic visits included counting or weighing returned pills as an adherence measure.

Patients entered between 1993-1998. The estrogen alone and placebo intervention ended on February 29, 2004 after 7.1 years mean follow-up. Thus, all presented data through year 3 and almost all data through year 6 reflect findings during active intervention. Of the 10,739 estrogen alone trial participants, 6,176 were randomized into the calcium and vitamin D supplement trial receiving either calcium carbonate (1,000 mg as elemental calcium) with vitamin D_3 (400 IU) or matching placebo daily.

Statistical Analysis

Analyses of joint symptoms utilized all available data at each time point. The frequency and severity of joint symptoms (pain and swelling) were compared by randomization group assignment (active vs placebo). A logistic regression model was used to compare the frequency of having any symptoms compared to having no symptoms in analyses both unadjusted and adjusted for age and race/ethnicity. Similarly, the average symptom score

where a response of “none” equals zero and “severe” equals 3 was compared in unadjusted and adjusted linear regression models incorporating age, BMI, and WHI calcium and vitamin D supplementation trial participation. Score differences between baseline and follow-up were computed the same way. To help place the joint score differences in clinical context regression models examined the year-to-year change in joint pain and swelling in the placebo group.

A sensitivity analyses examined estrogen influence in participants who were adherent to study medication use by censoring follow-up 6 months after a participant became non-adherent. Non-adherence was defined as using < 80% of study pills or initiating non-protocol hormone therapy.

All analyses were done with SAS version 9.1.3. All P-values are two-sided and P-values of 0.05 or less were regarded as significant. The WHI study is registered with clinicaltrialsgov, NCT000000611.

Results

Most baseline clinical and demographic characteristics were comparable in the two randomization groups including age, body mass index, non-steroidal anti-inflammatory drug (NSAID) use, physical activity, self-reported history of rheumatoid arthritis and previous hormonal exposure. In addition, total calcium and vitamin D intakes at baseline, reflecting both dietary intake and supplement use, were similar in the two randomization groups. Finally, participation in the WHI calcium and vitamin D supplementation trial was also balanced between the randomization groups (Table 1), the latter relevant for the year 3 and year 6 results.

By the termination of study drug intervention, after 7.1 years mean follow-up, 53.8% of participants had stopped study drugs with similar frequency noted between randomization groups. In addition, 5.7% percent of estrogen alone group women and 9.1% of placebo group women had started hormone therapy outside the trial. [15]

Joint pain and swelling at entry into the estrogen alone trial were closely comparable in the two randomization groups with about 77% of participants reporting some joint pain and about 40% reporting joint swelling. After one year, women randomized to estrogen alone compared to placebo had joint pain significantly less frequently, (76.3% vs 79.2%, respectively P=0.001) and had significantly lower joint pain scores (1.16 ± 0.87 vs 1.22 ± 0.88, mean ± SD, P<0.001, respectively). In contrast, joint swelling frequency was higher in the estrogen alone group (42.1% vs 39.7%, P=0.02) as was swelling severity score (0.58 vs 0.52, P<0.001).

Serial analyses of joint symptoms also found differences between randomization groups. At year 3 in the subset of participants with joint symptom assessment, women randomized to estrogen continued to have joint pain less frequently compared to women randomized to placebo (74.2% vs 79.8%, respectively, P=0.03). In addition, women in the estrogen alone group had no change in pain score from baseline (0.01 ± 0.81) while those in the placebo group had an increase in pain score (0.15 ± 0.94, P=0.01). Similar findings for joint pain continue through year 6 but did not achieve statistical significance. Joint swelling continued to be significantly higher through year 6 in the estrogen group (P=0.04) while the change in the joint swelling severity score from baseline was no longer statistically significant (P=0.31) (Table 2).

To put the joint pain score and joint swelling score differences in the estrogen compared to the placebo group at 1 year of 0.06 and 0.08, respectively, in clinical context, regression

models were used to assess year-to-year change in these parameters in the placebo group. The mean joint pain score increased by 0.0003 for a one year increase in age and the mean joint swelling score decreased by 0.001 for a one year increase in age.

The influence of adherence on joint symptom findings was examined by censoring joint symptoms reported six months after participants first became non-adherent (took < 80% of study drugs or started non-study hormone therapy). A stronger association between estrogen use and lower frequency of joint pain was seen, especially for findings after 1 and 3 years follow-up. At year 3, 72.5% of adherent women randomized to estrogen alone had joint pain compared to 81.7% of adherent women randomized to placebo (P=0.006) (Table 3). In contrast to joint pain where adherence adjusted analyses provided stronger incidence of favorable influence of estrogen alone, adherence adjusted analyses attenuated the estrogen effect on joint swelling. At year 3, the difference in joint swelling between estrogen alone and placebo group adherent participants was no longer statistically significant (P=0.31) (Table 3). Analyses in year 6 for both joint pain and joint swelling were hindered by limited number of adherent participants.

Discussion

In the present post hoc analyses in a randomized clinical trial setting, statistically significantly fewer women in the estrogen alone compared to the placebo group had joint pain after one and three years. In analyses adjusted for adherence, stronger favorable associations with estrogen use and reduced joint pain are seen. Thus, in a randomized clinical trial, estrogen alone use in postmenopausal women results in a modest but sustained and statistically significant reduction in joint pain. In contrast, joint swelling was more common in estrogen alone group participants but the findings were attenuated in adherence adjusted analyses.

The current report expands on prior findings in this trial [14] by including information on joint pain severity, joint swelling, joint symptom severity and adding serial and adherence analyses. The statistically significant reduction in joint pain frequency in intention-to-treat analyses after 1 year on study currently reported in the estrogen alone group included all participants while the prior analyses excluded women with mild joint pain. [14] To our review, no other randomized trial has described estrogen alone influence on joint symptoms. While the reduction in joint pain score with estrogen alone use were modest, they far exceeded the year-to-year increase in joint pain score seen in placebo group participants.

The apparent opposite effects of estrogen alone on joint pain (reduction) and joint swelling (increase) appears contradictory but may be related to the performance of the self-reported joint symptom measures. Self-reported joint pain has reasonable correlation with clinical and radiographic osteoarthritis measures. [24, 25] However, the relation between self-reported joint swelling and articular change has been questioned. [26] Importantly, analyses adjusted for adherence strengthened the estrogen alone association with reduced joint pain but attenuated the estrogen association with increased joint swelling.

Supportive findings for a favorable influence of estrogen alone use on joint pain come from other prior analyses in this WHI randomized trial. [27, 28] Women with prior hysterectomy randomized to estrogen alone had fewer cases of rheumatoid arthritis (25 cases of 5,076 vs 37 cases of 5,195, for estrogen alone vs placebo, respectively) but the difference was not statistically significant (HR 0.69, 95% CI 0.41-1.14, P=0.149). [27] Estrogen alone users in the trial were also found to have significantly fewer hip and knee joint replacements (222 cases of 5,076 vs 269 cases of 5,195 for estrogen alone vs placebo, respectively, HR 0.84, 95% CI 0.70-1.00, P=0.05. [28] Given that arthroplasty due to osteoarthritis is generally indicated

when pain can no longer be managed with pain medications, the findings support an association between estrogen alone use and lower frequency of joint symptoms.

In contrast to the findings in the WHI estrogen alone trial, in the WHI estrogen plus progestin trial in women with an intact uterus, there was no association seen between combined hormone therapy use and arthroplasty frequency seen. [28] This difference between the two WHI hormone trials reinforces the message that current findings are based on one regimen, conjugated equine estrogen, 0.625 mg/d alone in women with prior hysterectomy, and the results cannot be extrapolated to other hormone regimens or treatment durations.

Biological plausibility for an estrogen and joint pain association is provided by clinical studies of estradiol and its metabolites and osteoarthritis risk. In a study of 842 pre and peri-menopausal women, women with radiographically defined osteoarthritis had estradiol concentrations in the lowest tertile (OR 1.88, 95% CI 1.07-3.51) compared to women without osteoarthritis. [29] More recently, significantly lower free estradiol levels were seen in both premenopausal and postmenopausal women with osteoarthritis compared to levels in healthy women.[30]

Findings from observational studies examining relationships among joint problems including arthritis and menopausal hormone therapy have been mixed and their heterogeneity with respect to outcome measures and study populations have precluded pooling. [3] Nonetheless, in a recent review, while insufficient information to support strong conclusions was acknowledged, nonetheless, evidence was felt supportive of an effect of endogenous and exogenous estrogen on joint health. [31] While further study is warranted, the current results, seen in a randomized clinical trial setting, support a moderate effect of exogenous estrogen in mitigating joint pain. Any consideration of estrogen use for this purpose must incorporate available information on the identified risks and benefits of menopausal hormone therapy including the admonition to use the lowest dose for the shortest duration consistent with the intended therapeutic goal. [15, 16]

Likely mechanisms mediating estrogen influence on joint pain include reduction in inflammation markers and reduction in cartilage turnover, as potential contributors to arthritis risk [32, 33] seen in both preclinical [34] and clinical settings. [35, 36] In addition, if future studies could confirm associations among cartilage turnover, joint pain and estrogen levels, a clinical model for more rapidly identifying potential intervention strategies for joint problems could result. Finally, both preclinical and clinical studies suggest estrogens may modulate pain processing pathways. [1]

The current findings are of most relevance to women with limiting climacteric symptoms near the beginning of menopause who have had a prior hysterectomy and are considering estrogen alone use. Recent follow-up [16, 18] and subgroup analyses [37] from this WHI randomized trial evaluating estrogen alone indicate a favorable benefit/risk balance for estrogen use for about 5 years. [16] A modest, favorable effect on joint symptoms represents one additional factor for women contemplating estrogen alone use in this setting to consider.

These findings also may inform understanding of aromatase inhibitor-associated joint symptoms. Aromatase inhibitors substantially lower circulatory estrogen levels [38] and increase arthralgias. [39-41] The effect of exogenous estrogen to reduce joint pain frequency supports the concept that such arthralgias, at least in part, may be influenced by circulatory estrogen levels. Given the uncertainty regarding the potential influence of exogenous hormones on breast cancer recurrence, [42, 43] estrogen alone should not be used to treat joint symptoms arising from aromatase inhibitor use in women with resected breast cancer.

Study strengths include the size of the large well characterized, ethnically diverse study population, serial joint symptom determination within the context of a randomized clinical trial using a quantitative instrument which was prospectively applied. However, joint symptoms were not primary study endpoints and the findings emerge from post hoc analyses. In addition, the joint pain and joint swelling scales used have not been compared to other instruments or formally validated.

Conclusion

Current study findings suggest that estrogen alone use in postmenopausal women with prior hysterectomy results in a modest but sustained and statistically significant reduction in joint pain.

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TABLE 1
Descriptive characteristics of participants at baseline by randomization assignment

	Conjugated equine estrogens alone (n = 5,310)	Placebo (n = 5,429)
Age at screening		
50-59 y	1,637 (30.8)	1,673 (30.8)
60-69 y	2,387 (45.0)	2,465 (45.4)
70-79 y	1,286 (24.2)	1,291 (23.8)
Race/ethnicity		
White	4,007 (75.5)	4,075 (75.1)
Black	782 (14.7)	835 (15.4)
Hispanic	322 (6.1)	333 (6.1)
American Indian	41 (0.8)	34 (0.6)
Asian/Pacific Islander	86 (1.6)	78 (1.4)
Unknown	72 (1.4)	74 (1.4)
Education		
None to some high school	535 (10.2)	518 (9.6)
High school diploma/GED	1,233 (23.5)	1,188 (22.1)
School after high school	2,271 (43.2)	2,350 (43.7)
College degree or higher	1,216 (23.1)	1,327 (24.7)
Age at menarche		
≤11 y	1,215 (23.0)	1,280 (23.7)
12-13 y	2,805 (53.1)	2,853 (52.8)
≥14 y	1,259 (23.8)	1,274 (23.6)
Body mass index		
<25 kg/m^2	1,110 (21.0)	1,096 (20.3)
25-29.9 kg/m^2	1,795 (34.0)	1,912 (35.5)
≥30 kg/m^2	2,376 (45.0)	2,383 (44.2)
Physical activity		
0 MET/wk	1,081 (22.2)	1,043 (21.3)
1-3.5 MET/wk	887 (18.2)	930 (19.0)
3.6-8.0 MET/wk	983 (20.1)	983 (20.0)
8.1-16.5 MET/wk	981 (20.1)	945 (19.3)
>16.5 MET/wk	948 (19.4)	1,003 (20.5)
Alcohol use		
Nondrinker	718 (13.7)	737 (13.7)
Past drinker	1,277 (24.3)	1,270 (23.6)
<1 drink/mo	767 (14.6)	766 (14.2)
<1 drink/wk	1,001 (19.1)	1,049 (19.5)

	Conjugated equine estrogens alone (n = 5,310)	Placebo (n = 5,429)
1-6 drinks/wk	1,027 (19.6)	1,091 (20.2)
≥7 drinks/wk	457 (8.7)	475 (8.8)
Smoking		
Never smoked	2,723 (51.9)	2,705 (50.4)
Past smoker	1,986 (37.8)	2,089 (38.9)
Current smoker	542 (10.3)	571 (10.6)
Self-reported history of rheumatoid arthritis		
No	4,679 (93.5)	4,784 (94.0)
Yes	327 (6.5)	304 (6.0)
Nonsteroidal anti-inflammatory drug use		
No	4,987 (93.9)	5,100 (93.9)
Yes	323 (6.1)	329 (6.1)
Daily total calcium (supplements + diet), mean (SD), mg	983.5 (643.5)	994.0 (652.2)
Daily total calcium (supplements + diet)		
<800 mg	2,420 (47.7)	2,469 (47.7)
800-1,199 mg	1,190 (23.4)	1,229 (23.8)
≥1,200 mg	1,466 (28.9)	1,476 (28.5)
Daily vitamin D (supplements + diet), mean (SD), IU	354.5 (257.4)	355.1 (256.6)
Daily vitamin D (supplements + diet)		
<200 IU	1,953 (38.5)	1,969 (38.1)
200-399 IU	1,190 (23.4)	1,212 (23.4)
400-599 IU	1,018 (20.1)	1,090 (21.1)
≥600 IU	915 (18.0)	903 (17.5)
CaD trial participation		
None	2,236 (42.1)	2,327 (42.9)
CaD randomization	1,531 (28.8)	1,540 (28.4)
Placebo randomization	1,543 (29.1)	1,562 (28.8)
Estrogen-alone use		
Nonuser	2,872 (54.1)	2,891 (53.3)
<5 y	1,317 (24.8)	1,368 (25.2)
≥5 y	1,121 (21.1)	1,170 (21.6)
Estrogen plus progestin		
Nonuser	5,093 (95.9)	5,178 (95.4)
<5 y	144 (2.7)	158 (2.9)
≥5 y	73 (1.4)	93 (1.7)

Data are presented as n (%), unless stated otherwise.

MET, metabolic equivalent; CaD, calcium and vitamin D.

TABLE 2

Joint symptoms at baseline and follow-up by randomization assignment in the estrogen-alone trial

	Baseline			Year 1			Year 3			Year 6		
	CEE	Placebo	*P*	CEE	Placebo	*P*	CEE	Placebo	*P*	CEE	Placebo	*P*
Joint pain												
n	5,248	5,377		4,780	4,893		523	539		465	477	
None, n (%)	1,196 (22.8)	1,249 (23.2)	0.59	1,135 (23.7)	1,018 (20.8)	<0.001	135 (25.8)	109 (20.2)	0.03	97 (20.9)	80 (16.8)	0.11
Any, n (%)	4,052 (77.2)	4,128 (76.8)		3,645 (76.3)	3,875 (79.2)		388 (74.2)	430 (79.8)		368 (79.1)	397 (83.2)	
Severity, n (%)												
Mild	2,381 (45.4)	2,435 (45.3)	0.82	2,139 (44.8)	2,236 (45.7)	0.001	197 (37.7)	217 (40.3)	0.19	189 (40.7)	203 (42.6)	0.38
Moderate	1,235 (23.5)	1,271 (23.6)		1,136 (23.8)	1,191 (24.3)		136 (26.0)	150 (27.8)		124 (26.7)	141 (29.6)	
Severe	436 (8.3)	422 (7.9)		370 (7.7)	448 (9.2)		55 (10.5)	63 (11.7)		55 (11.8)	53 (11.1)	
Severity score, mean (SD)	1.17 (0.87)	1.16 (0.87)	0.46	1.16 (0.87)	1.22 (0.88)	<0.001	1.21 (0.95)	1.31 (0.92)	0.09	1.29 (0.93)	1.35 (0.89)	0.35
Change in score from baseline, mean (SD)				−0.00 (0.79)	0.06 (0.80)	<0.001	0.01 (0.81)	0.15 (0.94)	0.01	0.09 (0.90)	0.18 (0.95)	0.16
Joint swelling												
n	5,254	5,378		4,788	4,890		521	537		468	473	
None, n (%)	3,136 (59.7)	3,283 (61.0)	0.15	2,772 (57.9)	2,949 (60.3)	0.02	299 (57.4)	341 (63.5)	0.04	244 (52.1)	282 (59.6)	0.02
Any, n (%)	2,118 (49.3)	1,562 (29.0)		2,016 (42.1)	1,941 (39.7)		222 (42.6)	196 (36.5)		224 (47.9)	191 (40.4)	
Severity, n (%)												

	Baseline			Year 1			Year 3			Year 6		
	CEE	**Placebo**	***P***	**CEE**	**Placebo**	***P***	**CEE**	**Placebo**	***P***	**CEE**	**Placebo**	***P***
Mild	1,535 (29.2)	1,562 (29.0)	0.14	1,399 (29.2)	1,431 (29.3)	0.001	151 (29.0)	130 (24.2)	0.23	153 (32.7)	129 (27.3)	0.15
Moderate	481 (9.2)	427 (7.9)		483 (10.1)	408 (8.3)		51 (9.8)	48 (8.9)		54 (11.5)	47 (9.9)	
Severe	102 (1.9)	106 (2.0)		134 (2.8)	102 (2.1)		20 (3.8)	18 (3.4)		11 (3.6)	15 (3.2)	
Severity score, mean (SD)	0.53 (0.74)	0.51 (0.73)	0.08	0.58 (0.78)	0.52 (0.74)	<0.001	0.60 (0.82)	0.52 (0.79)	0.11	0.67 (0.82)	0.57 (0.80)	0.06
Change in score from baseline, mean (SD)				0.06 (0.75)	0.02 (0.70)	0.03	0.10 (0.81)	0.05 (0.80)	0.31	0.17 (0.79)	0.09 (0.89)	0.13

Statistical tests comparing hormone therapy randomization: unadjusted *P* values from either a logistic regression model (none, any) or a linear regression model (average).

CEE, conjugated equine estrogens.

TABLE 3

Joint symptoms at baseline and follow-up by randomization assignment among adherent women in the estrogen-alone trial

	Baseline			Year 1			Year 3			Year 6		
	CEE	Placebo	*P*	CEE	Placebo	*P*	CEE	Placebo	*P*	CEE	Placebo	*P*
Joint pain												
n	5,248	5,377		4,125	4,314		298	312		155	183	
None, n (%)	1,196 (22.8)	1,249 (23.2)	0.59	997 (24.2)	905 (21.0)	<0.001	82 (27.5)	57 (18.3)	0.006	38 (24.5)	30 (16.4)	0.06
Any, n (%)	4,052 (77.2)	4,128 (76.8)		3,128 (75.8)	3,409 (79.0)		216 (72.5)	255 (81.7)		117 (75.5)	153 (83.6)	
Severity, n (%)												
Mild	2,381 (45.4)	2,435 (45.3)	0.82	1,877 (45.5)	1,970 (45.7)	<0.001	119 (39.9)	134 (43.0)	0.05	74 (47.7)	94 (51.4)	0.29
Moderate	1,235 (23.5)	1,271 (23.6)		945 (22.9)	1,047 (24.3)		71 (23.8)	86 (27.6)		31 (20.0)	45 (24.6)	
Severe	436 (8.3)	422 (7.9)		306 (7.4)	392 (9.1)		26 (8.7)	35 (11.2)		12 (7.7)	14 (7.7)	
Severity score, mean (SD)	1.17 (0.87)	1.16 (0.87)	0.46	1.14 (0.87)	1.21 (0.88)	<0.001	1.14 (0.92)	1.32 (0.90)	0.02	1.11 (0.86)	1.24 (0.82)	0.17
Change in score from baseline, mean (SD)				−0.01 (0.78)	0.06 (0.79)	<0.001	0.01 (0.74)	0.13 (0.96)	0.08	0.12 (0.81)	0.12 (0.87)	0.98
Joint swelling												
n	5,254	5,378		4,134	4,307		299	301		156	171	
None, n (%)	3,136 (59.7)	3,283 (61.0)	0.15	2,403 (58.1)	2,613 (60.7)	0.02	175 (58.5)	194 (62.6)	0.31	92 (59.0)	113 (62.4)	0.52
Any, n (%)	2,118 (49.3)	1,562 (29.0)		1,731 (41.9)	1,694 (39.3)		124 (41.5)	116 937.4)		64 (41.0)	68 (37.6)	
Severity, n (%)												

	Baseline			Year 1			Year 3			Year 6		
	CEE	Placebo	*P*	CEE	Placebo	*P*	CEE	Placebo	*P*	CEE	Placebo	*P*
Mild	1,535 (29.2)	1,562 (29.0)	0.14	1,217 (29.4)	1,257 (29.2)	0.007	99 (33.1)	80 (25.8)	0.16	48 (30.8)	40 (22.1)	0.23
Moderate	481 (9.2)	427 (7.9)		409 (9.9)	350 (8.1)		21 (7.0)	28 (9.0)		22 (12.2)	13 (8.3)	
Severe	102 (1.9)	106 (2.0)		105 92.5)	87 (2.0)		4 (1.3)	8 (2.6)		6 (3.3)	3 (1.9)	
Severity score, mean (SD)	0.53 (0.74)	0.51 (0.73)	0.08	0.57 (0.77)	0.52 (0.73)	0.001	0.51 (0.69)	0.52 (0.77)	0.94	0.53 (0.73)	0.56 (0.83)	0.71
Change in score from baseline, mean (SD)				0.05 (0.74)	0.02 (0.69)	0.06	0.08 (0.72)	0.05 (0.76)	0.70	0.18 (0.69)	0.16 (0.83)	0.76

Participants were excluded if they became nonadherent (using <80% of study pills or initiating nonprotocol hormone therapy) before the follow-up visit.

CEE, conjugated equine estrogens.