RESEARCH
Original Research

Calcium Plus Vitamin D Supplementation and Joint Symptoms in Postmenopausal Women in the Women's Health Initiative Randomized Trial

Rowan T. Chlebowski, MD, PhD; Mary Pettinger, MS; Karen C. Johnson, MD, MPH; Robert Wallace, MD, MS; Catherine Womack, MD; Yasmin Mossavar-Rahmani, PhD, RD; Marcia Stefanick, PhD; Jean Wactawski-Wende, PhD; Laura Carbone, MD; Bing Lu, MD, DrPH; Charles Eaton, MD, MS; Brian Walitt, MD, MPH; Charles L. Kooperberg, PhD

ARTICLE INFORMATION

Article history:
Accepted 5 June 2013
Available online 15 August 2013

Keywords:
Calcium
Vitamin D
Joint symptoms

2212-2672/$36.00
http://dx.doi.org/10.1016/j.jand.2013.06.007

ABSTRACT

Background Low vitamin D intake and levels have been associated with increased joint symptoms in some observational studies but the findings are mixed and evidence from randomized trials sparse.

Objective To evaluate the influence of supplemental calcium and vitamin D on joint symptoms in the Women's Health Initiative randomized, placebo-controlled, clinical trial.

Design In post hoc analyses, the results of the Women's Health Initiative randomized clinical trial in which 36,282 postmenopausal women were randomized to receive calcium carbonate (1,000 mg as elemental calcium) with vitamin D-3 (400 IU) daily or placebo were examined in the 6% subgroup of 1,911 participants, oversampled for minorities, who had serial joint symptom assessment. Qualitative information on joint pain and joint swelling was collected by questionnaire before entry and 2 years after randomization. Logistic regression models were used to compare the occurrence and severity of joint symptoms across randomization groups.

Results At baseline, total calcium and vitamin D intakes from diet and supplements were similar in the two randomization groups. In addition, both joint pain (reported by 73%) and joint swelling (reported by 34%) were commonly reported and comparable in the supplement and placebo groups. Two years after randomization, no statistically significant differences between supplement and placebo groups were seen for joint pain frequency (74.6% compared with 75.1% [P=0.79] for supplement and placebo groups, respectively) or joint swelling frequency (34.6% compared with 32.4% [P=0.29], respectively) or in severity scores for either outcome. Subgroup analyses suggested study participants also using nonprotocol calcium supplements at study entry may have less joint pain with supplement group randomization (interaction P=0.02).

Conclusions Joint symptoms are relatively common in postmenopausal women. However, daily supplementation with 1,000 mg calcium carbonate and 400 IU vitamin D-3 in a randomized, placebo-controlled clinical trial setting did not reduce the self-reported frequency or severity of joint symptoms.
J Acad Nutr Diet. 2013;113:1302-1310.

SEVERE VITAMIN D DEFICIENCY CAN LEAD TO JOINT disorders[1] but reports on the influence of vitamin D intake and status on joint symptoms have been mixed. Both low vitamin D intake[2-4] and low 25-hydroxyvitamin D levels,[5-7] as measures of vitamin D status, have been associated with increased joint pain. However, vitamin D status has been associated with knee osteoarthritis in only some[2,5,7] but not all[4,8-10] observational study reports. In addition, reports from full-scale randomized trials are sparse.[11] To address this issue, in post hoc analyses we examined the influence of calcium and vitamin D supplementation (CaD) on joint symptoms in a randomly identified subgroup of postmenopausal women participating in the Women's Health Initiative (WHI) Calcium Plus Vitamin D Supplement randomized, placebo-controlled clinical trial.[12]

To take the Continuing Professional Education quiz for this article, log in to www.eatright.org, click the "myAcademy" link under your name at the top of the homepage, select "Journal Quiz" from the menu on your myAcademy page, click "Journal Article Quiz" on the next page, and then click the "Additional Journal CPE Articles" button to view a list of available quizzes, from which you may select the quiz for this article.

METHODS

The WHI program includes four clinical trials (two hormone therapy [HT] trials, a dietary modification [DM] trial, and a CaD trial) and an observational study. For the WHI clinical trials, postmenopausal women aged 50 to 79 years with life expectancy ≥3 years, no personal breast cancer history, and no other cancer within 10 years were eligible. The HT and DM trials had additional eligibility requirements largely based on medical history. Women participating in the WHI HT trials[13,14] or WHI DM[15] trial were invited to enroll in an additional randomized, placebo-controlled trial evaluating CaD at their first or second annual follow-up main trial visit.[16,17] For the CaD trial, additional exclusions included hypercalcemia, history of kidney stones, and current corticosteroid or calcitriol use. Personal use of calcium (no upper limit) and vitamin D was allowed during the study period. The upper limit for allowed personal vitamin D initially was 600 IU daily, which was subsequently increased to 1,000 IU daily during the study course.[17] Eligible women who entered the CaD trial were randomly assigned, in a double-blind fashion, to receive active supplement or placebo stratified according to clinical center and calcium and vitamin D supplement containing calcium carbonate (500 mg as elemental calcium) with vitamin D-3 (200 IU) or matching placebo was taken twice daily (all from GlaxoSmithKline Consumer Healthcare). Study pills were discontinued after development of kidney stones; hypercalcemia; kidney dialysis; and calcitriol use, which causes a greater hypercalcemia risk than other vitamin D compounds.

Details of the eligibility and conduct of the HT and DM trials have been reported.[13-15] We now report on joint symptom outcomes in a subset of CaD trial participants. The participant flow through the WHI clinical trial to arrive at the study population with joint symptom assessment is outlined in Figure 1.

From the 36,282 CaD clinical trial participants, a 6% subsample of 2,185 participants for the current study was randomly identified from those who were randomized at their first annual visit for the main trial and who had information collected during follow-up on joint symptoms. The sampling was done on the entire clinical trial population (n=68,132) with sixfold higher odds of selection for nonwhite participants, and a sampling rate of 8.6% in the HT trials and 4.3% in the DM trial, resulting in a 6% overall sample. There was not a specific sampling target for the CaD trial because the women in that trial were also in a HT and/or DM trial.[16]

It was planned to assess joint symptoms at baseline and after 2 years in the identified subgroup. Among these 2,185 women, 242 had missing information on joint symptoms or for other variables at Year 2 and 32 (1.5%) died or dropped out resulting in a study population of 1,911.

Details of the eligibility and conduct of the CaD trial have also been reported.[12,17] The trial completed the planned intervention duration of mean 7 years of follow-up and calcium and vitamin D supplement effects on hip fracture as the primary study endpoint[17,18] and colorectal cancer[18] and breast cancer,[19,20] as secondary endpoints, have been published.

The described 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 were conducted at the WHI Clinical Coordinating Center.

Dietary supplement data was collected during in-person clinic visits. Women brought their supplement bottles to the baseline clinic visit and annually thereafter. A standardized interviewer-administered form was used to collect information on multivitamins and single supplements. Staff members directly transcribed the ingredients for each supplement and asked participants about frequency and duration of use. A validity study of these procedures found correlations with photocopied labels ranged from 0.8 to 1.0.[21,22] Prescription medication use was similarly determined by in-person review of medication containers. All reported medications were matched to the Master Drug Data Base (Medi-Span).

A self-assessment food frequency questionnaire (FFQ) specifically designed for WHI[23] was used to assess dietary intake during the previous 3 months at entry into the WHI HT or DM trials.[23] DM trial participants also had the FFQ administered at Year 1, coinciding with entry into the CaD trial. For non-DM participants, the baseline vitamin D intake at entry into the HT trials, which was 1 year before entry into the CaD trial, was used for baseline analyses. For DM participants, dietary vitamin D at baseline was correlated to Year 1 values (correlation coefficient $P<0.0001$). Total daily calcium intake at baseline was defined as the sum of the dietary intake (assessed with the use of a modified Block FFQ)[23] and the average daily self-reported intake of elemental calcium from supplements and from prescription medications during the previous 2 weeks. Total vitamin D intake was similarly determined reflecting not only dietary vitamin D intake (largely from fortified dairy products and fatty fish) but also vitamins D supplement use. Information on physical activity was collected by questionnaire regarding walking outside the house and recreational physical activity, including frequency, duration, and intensity. This information was used to generate metabolic equivalent values.[24] Measurements of height and weight were made in the clinic to permit body mass index (BMI) determinations.

Clinical outcomes were determined at annual clinic visits and semiannual contacts. Annual clinic visits included counting or weighing returned pills as an adherence measure. Joint pain and swelling was assessed by questionnaire collected at initial WHI clinical trial entry (1 year before the CaD trial randomization), 1 year after entry and again after 2 years of participation in the CaD study. Joint pain was assessed as yes/no; severity was assessed as none=0, mild=1, moderate=2, and severe=3. Joint swelling was assessed similarly.

Statistical Analyses

The analysis of joint symptoms utilized results from the 1,911 randomized participants with available baseline and follow-up information. χ^2 Tests were used to compare the baseline characteristics between randomization groups. The frequency and severity of joint symptoms (pain and swelling) were compared by randomization group (active vs placebo) and logistic regression models were used to compare the occurrence of any symptoms vs none, both unadjusted and adjusted for age and race/ethnicity. Similarly, the average symptom score, where none=0 and severe=3, was compared in unadjusted and adjusted linear regression models. The difference in scores between follow-up and baseline were computed and analyzed the same way.

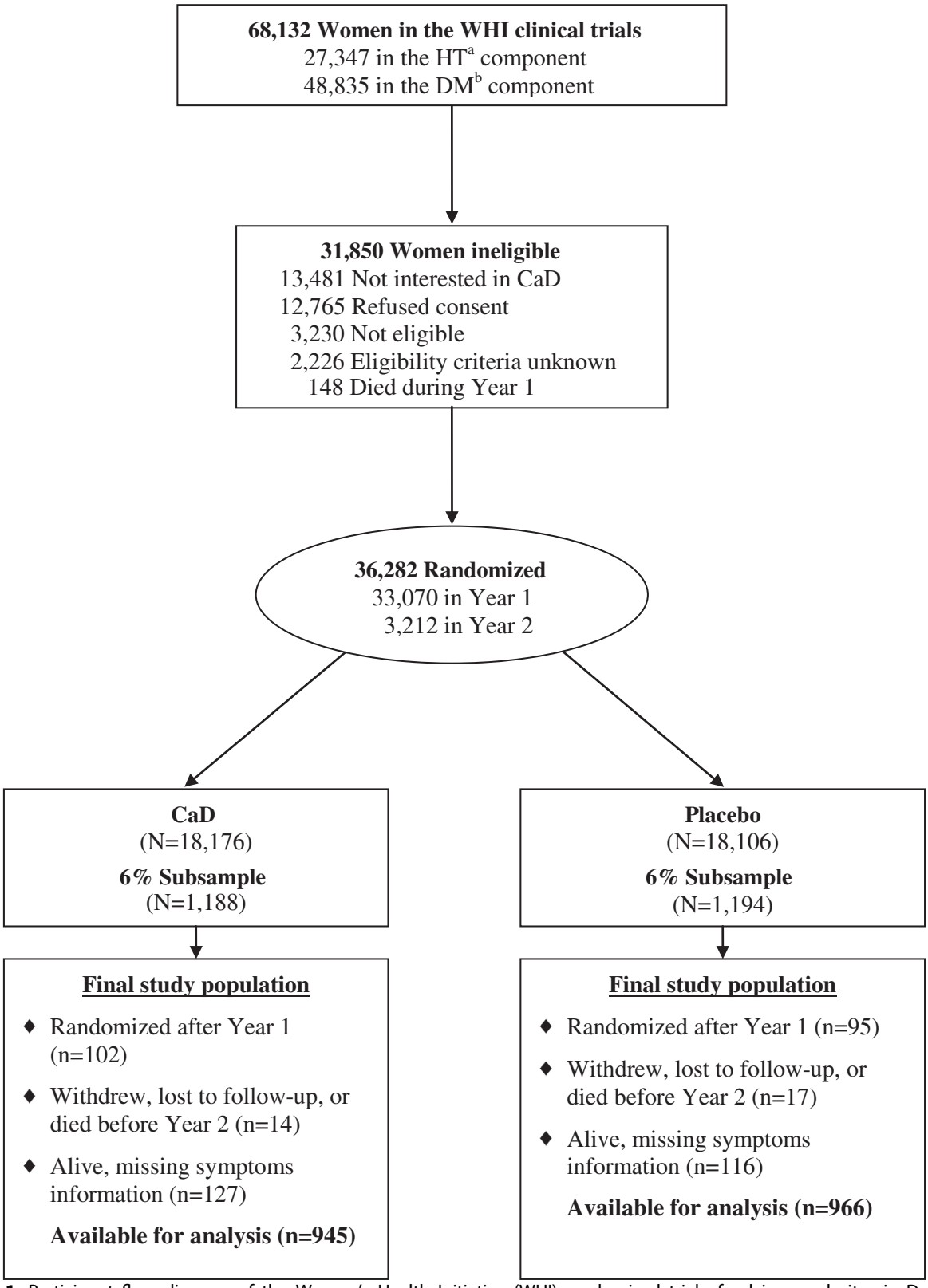

Figure 1. Participant flow diagram of the Women's Health Initiative (WHI) randomized trial of calcium and vitamin D supplementation (CaD) to illustrate the identification of the randomized subset included in current analysis examining CaD influence on joint symptoms. [a]HT=hormone therapy. [b]DM=dietary modification.

Table 1. Baseline characteristics of the sample of Women's Health Initiative participants studied for calcium and vitamin D (CaD) use and joint pain/swelling

	CaD (n=945)		Placebo (n=966)		
Characteristic	**n**	**%**	**n**	**%**	***P* value[a]**
Age at screening (y)					0.57
50-59	373	39.5	382	39.5	
60-69	431	45.6	424	43.9	
70-79	141	14.9	159	16.6	
Race/ethnicity					0.72
White	483	51.1	512	53.0	
Black	217	23.0	232	24.0	
Hispanic	128	13.5	118	12.2	
American Indian	21	2.2	22	2.3	
Asian/Pacific Islander	80	8.5	66	6.8	
Unknown	16	1.7	16	1.7	
Education					0.84
None—some high school	78	8.3	75	7.8	
High school diploma/GED[b]	181	19.3	174	18.1	
School after high school	352	37.6	376	39.1	
College degree or higher	326	34.8	336	35.0	
Body mass index					0.58
<25	218	23.2	242	25.2	
25-<30	322	34.3	325	33.9	
≥30	399	42.5	393	40.9	
Physical activity (METs[c]/wk)					0.23
None	189	21.2	179	19.5	
>0-3.5	164	18.4	138	15.1	
>3.5-8.0	186	20.9	207	22.6	
>8.0-16.5	177	19.9	201	21.9	
>16.5	174	19.6	192	20.9	
Alcohol use					0.66
Nondrinker	126	13.5	141	14.8	
Past drinker	193	20.7	203	21.3	
Current drinker	613	65.8	611	64.0	
Smoking					0.75
Never smoked	503	53.9	529	55.6	
Past smoker	350	37.5	342	36.0	
Current smoker	80	8.6	80	8.4	
NSAID[d] medication use					0.09
No	784	83.0	829	85.8	
Yes	161	17.0	137	14.2	

(*continued on next page*)

Table 1. Baseline characteristics of the sample of Women's Health Initiative participants studied for calcium and vitamin D (CaD) use and joint pain/swelling (*continued*)

	CaD (n=945)		Placebo (n=966)		
Characteristic	**n**	**%**	**n**	**%**	***P* value[a]**
Total vitamin D[e] (IU)					
Mean	352.0		354.7		0.84
<200	394	43.1	380	40.6	0.70
200-<400	155	17.0	164	17.5	
400-<600	209	22.9	219	23.4	
≥600	156	17.1	174	18.6	
Multivitamin use[f]					0.17
No	626	66.2	611	63.3	
Yes	319	33.8	355	36.8	
Total calcium[e] (mg)					
Mean	1,035.5		1,070.2		0.21
<800	394	43.1	363	38.7	0.16
800-<1,200	217	23.7	238	25.4	
≥1,200	303	33.2	336	35.9	
Current hormone therapy[g]					0.92
None	477	50.6	489	50.8	
Estrogen	216	22.9	226	23.4	
Estrogen plus progestin	249	26.4	247	25.6	

[a]From χ^2 tests of independence for categorical variables, and *t* tests for continuous total vitamin D and total calcium intake.
[b]GED=general educational development.
[c]METs=metabolic equivalents.
[d]NASAID=nonsteroidal anti-inflammatory drug.
[e]Supplements+diet.
[f]With or without minerals.
[g]For women randomized to receive calcium and vitamin D at Year 1 of the clinical trial, who were in the 6% subsample, and had symptom information collected at CaD baseline and at CaD Year 2.

The influence of randomization to calcium and vitamin D supplementation or placebo on joint symptoms was examined in six subgroups (BMI, physical activity, nonprotocol calcium supplement use, nonprotocol vitamin D supplement use, race/ethnicity, and HT use [randomization to the intervention group for HT trial participants and current HT use for women not in HT trials]). In these analyses, odds ratios and 95% CIs for effect of CaD on joint pain are estimated from a logistic regression model adjusted for linear age and race/ethnicity. *P* values testing for interaction separately for each subgroup are from models, including terms for the main effects for CaD supplementation and the subgroup, plus their interaction. For testing, age and BMI (log-transformed) were modeled as linear terms; physical activity was coded 0 to 4, representing the five quintile categories of physical activity. Less than one statistically significant interaction test ($P<0.05$) would be expected based on chance alone.

All analyses were performed using SAS statistical software, version 9.1.3 (2007, SAS Institute Inc). All *P* values are two-sided and $P<0.05$ was regarded as significant. The WHI study is registered with clinicaltrials.gov, no. NCT000000611.

RESULTS

In the subgroup of 1,911 clinical trial participants with serial joint symptom assessment, demographic characteristics, health behaviors, and medical history were well balanced between randomization groups. Considering all participants, mean age at entry was 62 years with a mean BMI of 29. As a result of oversampling for minorities, nearly half of participants were nonwhite (Table 1).

At baseline, total calcium and vitamin D intakes, reflecting both dietary intake and supplement use, were similar in the two randomization groups with nonprotocol vitamin D supplement use ≥400 IU daily reported by 42% of the placebo group and 40% of the supplement group, respectively (Table 1). During the course of the study, nonprotocol calcium and vitamin D supplements were permitted and their use was similar between randomization groups. At 2 years, median nonprotocol calcium use was 40 mg/day and nonprotocol vitamin D supplement was being used by 48% of participants with mean dose of 199 IU and median dose of 0 IU/day. As a result, total vitamin D intake (diet plus nonprotocol supplement plus protocol supplement) was 773 IU,

mean and 724 IU, median in the supplement group and 367 IU, mean and 312 IU, median in the placebo group after 2 years. At that time, total calcium intake was 2,031 mg, mean and 1,877 mg, median in the supplement group and 1,041 mg, mean and 920 mg, median in the placebo group.

Adherence to the randomly assigned calcium and vitamin D supplement or placebo (defined as use of 80% or more of study medication) ranged from 60% to 63% during the first 3 years with an additional 13% to 21% taking at least half of their study pills with small difference between randomization groups.

Joint pain and swelling at baseline entry into the CaD trial was closely comparable in the two randomization groups with more than 70% of supplement and placebo group participants reporting joint pain and about a third reporting joint swelling. Joint symptoms at baseline and after 2 years on CaD or placebo are shown by randomization group in Table 2. After 2 years, no statistically significant difference between supplement and placebo groups were seen for joint pain frequency (74.6% vs 75.1%, for supplement and placebo groups, respectively; P=0.79) or joint swelling frequency (34.6% vs 32.4%, respectively; P=0.29). The severity of joint pain or joint swelling also was similar in the supplement and placebo groups after 2 years (Table 2).

The potential for interaction with age, BMI, physical activity, nonprotocol calcium and vitamin D use, race/ethnicity, and HT on the association between joint pain and randomization group was examined (Figure 2). No interaction with age, BMI, race/ethnicity, or physical activity was seen. The CIs for all but white and black women are very wide and are essentially noninformative. There was a suggestion of a favorable effect of CaD on joint pain in hormone therapy users and women aged 70 to 79 years, but the interactions were not statistically significant (interaction P values 0.07 and 0.09, respectively). Participants who were also using nonprotocol calcium supplements at entry had less joint pain when randomized to the supplement compared to the placebo group (interaction P=0.02), whereas no significant interaction was seen with nonprotocol vitamin D supplement use at entry.

DISCUSSION

Joint symptoms were common in this population of postmenopausal women. However, in the setting of a

Table 2. Results of statistical tests[a] of joint pain/swelling by calcium and vitamin D (CaD) use of Women's Health Initiative participants (N=1,911)

	CaD Trial Baseline				CaD Trial Year 2			
	CaD		Placebo		CaD		Placebo	
	%	n	%	n	%	n	%	n
Numbers[b]		945		966		945		966
Joint pain								
None	26.3	247	28.1	270	25.4	239	24.9	239
Any	73.7	693	71.9	691	74.6	702	75.1	722
Severity								
Mild	65.4	453	64.8	448	61.7	433	63.2	456
Moderate	27.6	191	25.9	179	29.5	207	27.6	199
Severe	7.1	49	9.3	64	8.8	62	9.3	67
					Change in Score at Year 2			
Severity score (mean±SD[c])	1.04±0.82		1.04±0.86		0.06±0.84		0.09±0.82	
Joint swelling								
None	65.7	620	65.8	630	65.4	615	67.6	648
Any	34.3	324	34.2	328	34.6	326	32.4	310
Severity								
Mild	72.2	234	75.0	246	72.1	235	76.1	236
Moderate	23.2	75	20.4	67	21.8	71	18.7	58
Severe	4.6	15	4.6	15	6.1	20	5.2	16
					Change in Score at Year 2			
Severity score (mean±SD)	0.45±0.71		0.44±0.69		0.02±0.73		0.02±0.72	

[a]Statistical tests comparing CaD treatment randomization included P values from either a logistic regression model (none/any) or linear regression model (average) demonstrated no statistically significant difference comparing CaD to placebo use at baseline, after 2 years of intervention, or in the change from baseline to Year 2. Tests were performed both unadjusted and adjusted for age and race/ethnicity.

[b]For women randomized to CaD at Year 1 of the clinical trial, who were in the 6% subsample, and had symptom information collected at CaD baseline and at CaD Year 2.

[c]SD=standard deviation.

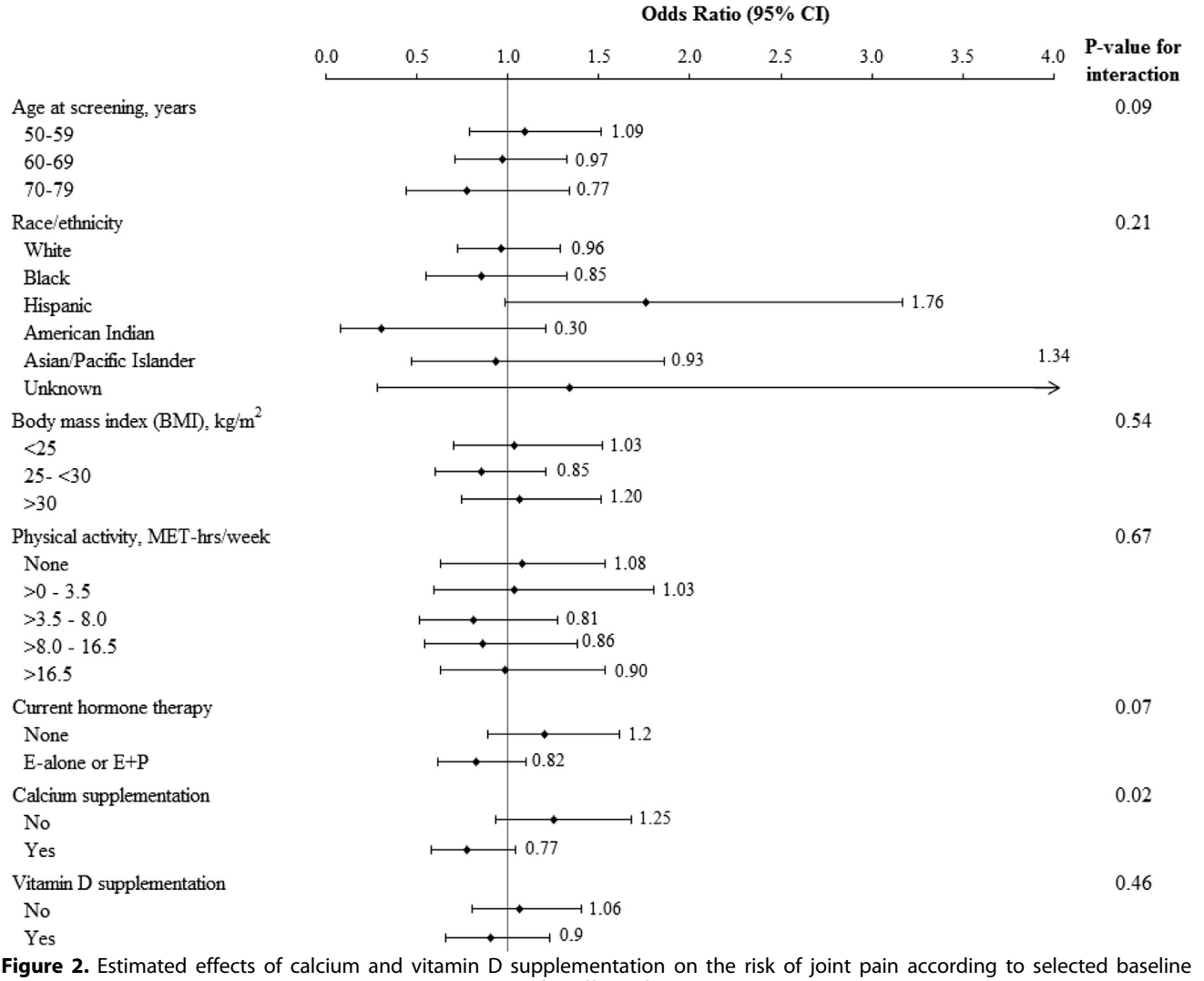

Figure 2. Estimated effects of calcium and vitamin D supplementation on the risk of joint pain according to selected baseline characteristics. In these analysis, odds ratios and 95% CIs for effect of calcium and vitamin D supplementation on joint pain are estimated from a logistic regression model adjusted for linear age and race/ethnicity. *P* values testing for interaction separately for each subgroup are from models including terms for the main effects for calcium and vitamin D supplementation and the subgroup, plus their interaction. For testing, age and body mass index (log-transformed) were modeled as linear terms; physical activity was coded zero to four representing the five categories of physical activity. Current hormone therapy reflects use at baseline if randomized to the dietary modification trial only or randomized to active vs placebo if randomized to one of the hormone therapy trials. Calcium supplementation and vitamin D supplementation reflects nonprotocol use at study entry. E-alone=estrogen alone. E+P=estrogen plus progestin.

randomized, placebo-controlled, clinical trial, calcium (1,000 mg/day as elemental calcium) plus vitamin D supplementation (400 IU/day of D-3) did not reduce the frequency or severity of joint symptoms of postmenopausal women compared with placebo. Thus, women using CaD at this dose should not anticipate joint symptom relief.

Severe vitamin D deficiency can result in osteomalacia characterized by proximal muscle weakness and bone loss[1] but reports on the association between vitamin D intake and/or levels with joint symptoms have been mixed. Whereas some observational studies suggest a threshold of 25-hydroxyvitamin D levels above 36 ng/mL (89.86 nmol/L) are needed for lower osteoarthritis risk,[2,7] others find no association.[4,8-10] In previously reported analyses in WHI clinical trial participants, women with low serum 25-hydroxyvitamin D levels did have statistically significantly higher joint pain scores compared with women with higher 25-hydroxyvitamin D levels but the threshold (seen in the lowest quintile) was a much lower 12 ng/mL[6] (29.95 nmol/L) than found in some prior studies.[2,7] The inconsistent observational study findings[25-27] support the need for randomized clinical trials to definitively address this issue.

Only one other full-scale, randomized clinical trial has addressed the issue of joint pain and vitamin D supplementation but studied a different population with a different intervention. McAlindon and colleagues[11] entered 146 men and women with symptomatic osteoarthritis of the knee with serial cartilage volume loss documented by magnetic

resonance imaging. Participants were randomized to a higher dose, vitamin D–only intervention (2,000 IU/day daily oral vitamin D-3 with escalation to target 25-hydroxyvitamin D serum levels >36 ng/mL [89.86 nmol/L]) or placebo. After 2 years, no reduction in knee pain or cartilage volume loss was seen with the supplementation.[11] As one possible explanation for the null findings, the authors suggested that the severity of the structural damage might have been too severe to expect reversal. Two smaller randomized trials, entering between 50 and 60 participants, also evaluated higher-dose vitamin D regimens (50,000 IU vitamin D-2 weekly for 3 or 4 months) but reported no significant influence on musculoskeletal pain.[28,29]

In our study, we addressed, for the first time in a full-scale, randomized clinical trial setting, the clinically relevant question regarding whether postmenopausal women using calcium and vitamin D supplements in currently recommended dosages would experience any favorable effect on joint pain or swelling, common symptoms in postmenopausal women.

The vitamin D-3 dosage of 400 IU/day used in the WHI trial followed the Institute of Medicine recommendations that were available during the course of the trial.[30] The Institute of Medicine recently updated their guideline and increased their recommended dietary allowance for vitamin D intake moderately to 600 IU/day for those aged ≤70 years and 800 IU/day for those aged 71 years and older.[31] However, because about half of the WHI study participants were taking additional nonprotocol vitamin D,[19] many women in the supplement group had substantially greater vitamin D intakes. Based on the first comprehensive study of dose response to vitamin D supplementation in postmenopausal women in a recently reported randomized trial, Gallagher and colleagues[32] concluded that a vitamin D-3 dosage of 600 IU/day would be sufficient to meet the nutrition requirements of nearly all (97.5%) healthy persons. Because the mean total vitamin D dose in the WHI supplement randomization group was 773 IU/day, including diet and protocol and nonprotocol supplement use, we found no influence of the currently recommended vitamin D intake on joint symptoms in supplement group participants in this trial. Although the influence of higher-dose supplementation with calcium and vitamin D on joint symptoms are not known, current evidence does not support dosages exceeding the recent Institute of Medicine recommendation at this time.[31]

The statistically significant, positive interaction that was seen between baseline nonprotocol calcium use and joint pain benefit from protocol CaD was an unexpected finding. This result could reflect the play of chance or self-selection bias, especially because calcium has not historically been linked to joint symptoms. Alternatively, one could speculate that a calcium threshold level is required for vitamin D to favorably influence joint symptoms. In any case, the calcium result seen in a subgroup analyses clearly requires further study.

Study strengths include the size of the well characterized study population; the inclusion, by design, of a substantial minority population; joint symptom information collected within the context of a randomized clinical trial of calcium and vitamin D supplement use; and serial joint symptom assessment using a quantitative instrument that was prospectively applied. Study limitations include the fact that joint symptoms were not prospectively identified study endpoints and, although randomly identified, only a subset of participants in the trial was included. Also, the joint symptom scale used has not been compared with other instruments or been formally validated. Although joint symptoms in postmenopausal women have a range of etiologies (commonly osteoarthritis but also rheumatoid arthritis and other autoimmune diseases as well as fibromyalgia and other causes), a quantitative, prospective serial assessment of the presence and severity of joint pain and swelling provides clinically relevant outcome information. Allowing nonprotocol calcium and vitamin D use is another limitation. However, the difference in intakes between groups was sufficient to increase bone mineral density overall and decrease hip fracture in older participants and in adherent participants in the active intervention group.[15] The influence of taking calcium and vitamin D supplements individually on joint symptoms cannot be determined because both were provided combined in a single pill in this trial.

The findings from the current WHI randomized, placebo-controlled clinical trial evaluating CaD do not support use of calcium and vitamin D for joint symptom reduction at the dosage examined. These findings do not speak against current recommendations for vitamin D intakes for bone health and fracture risk reduction.

References

1. Holick MF. Vitamin D deficiency: What a pain it is. *Mayo Clin Proc*. 2003;78(12):1457-1459.
2. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med*. 1996;125(5):353-359.
3. Bergink AP, Uitterlinden AG, Van Leeuwen JP, et al. Vitamin D status, bone mineral density, and the development of radiographic osteoarthritis of the knee: The Rotterdam Study. *J Clin Rheumatol*. 2009;15(5):230-237.
4. Muraki S, Dennison E, Jameson K, et al. Association of vitamin D status with knee pain and radiographic knee osteoarthritis. *Osteoarthritis Cartilage*. 2001;19(11):1301-1306.
5. Heidari B, Heidari P, Hajian-Tilaki K. Association between serum vitamin D deficiently and knee osteoarthritis. *Int Orthop*. 2011;35(11):1627-1631.
6. Chlebowski RT, Johnson KC, Lane D, et al. 25-Hydroxyvitamin D, vitamin D intake, and joint symptoms in postmenopausal women. *Maturitas*. 2010;68(1):73-78.
7. Lane NE, Gore LR, Cummings SR, et al. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: A longitudinal study. Study of Osteoporotic Fractures Research Group. *Arthritis Rheum*. 1999;42(5):854-860.
8. Felson DT, Niv J, Clancy M, et al. Low levels of vitamin D and worsening of knee osteoarthritis: Results of two longitudinal studies. *Arthritis Rheum*. 2007;56(1):129-136.
9. Konstari S, Paananen M, Heliovaara M, et al. Association of 25-hydroxyvtiamin D with the incidence of knee and hip osteoarthritis: A 22-year follow-up study. *Scand J Rheumatol*. 2012;41(2):124-131.
10. Al-Jarallah KF, Shehab D, Al-Awadhi A, et al. Are 25(OH) D levels related to the severity of knee osteoarthritis and function? *Med Princ Pract*. 2012;21(1):74-78.
11. McAlindon T, LaValley M, Schneider E, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: A randomized controlled trial. *JAMA*. 2013;309(2):155-162.
12. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative Study Design. *Ann Epidemiol*. 2003;13(9 suppl):S5-S17.

13. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.
14. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701-1712.
15. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295(6):629-642.
16. Jackson RD, LaCroix AZ, Cauley JA, McGowan J. The Women's Health Initiative calcium-vitamin D trial: Overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(suppl 9):S98-S106.
17. Jackson RD, LaCroix AZ, Gass M, et al. Calcium and vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354(7):669-683.
18. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354(7):684-696.
19. Chlebowski RT, Johnson KC, Kooperberg C, et al. Calcium plus vitamin D supplementation and the risk of breast cancer. *J Natl Cancer Inst*. 2008;100(22):1604-1616.
20. Chlebowski RT. Vitamin D and breast cancer: interpreting current evidence. *Breast Cancer Res*. 2011;13(4):217-224.
21. Patterson RE, Kristal AR, Levy L, McLerran D, White E. Validity of methods used to assess vitamin and mineral supplement use. *Am J Epidemiol*. 1998;148(7):643-649.
22. Patterson RE, Levy L, Tinker L, Kristal AR. Evaluation of a simplified vitamin supplement inventory developed for the Women's Health Initiative. *Public Health Nutr*. 1999;2(3):273-276.
23. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol*. 1999;9(3):178-187.
24. McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women. *JAMA*. 2003;290(10):1331-1336.
25. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc*. 2003;78(12):1463-1470.
26. Singh S, Howell A, Cuzick J. Wolfson Institute of Preventive Medicine. Vit D levels among patients with arthralgia: Results from IBIS-II breast cancer prevention study [abstract 1068]. San Antonio Breast Cancer Symposium, Fort Sam Houston, TX, December 14-17, 2006.
27. Hicks GE, Shardell M, Miller RR, et al. Associations between vitamin D status and pain in older adults: The Invecchiare in Chianti study. *J Am Geriatr Soc*. 2008;56(5):785-791.
28. Warner AE, Arnspiger SA. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. *J Clin Rheumatol*. 2008;14(1):12-16.
29. Rastelli AL, Taylor ME, Gao F, et al. Vitamin D and aromatase inhibitor-induced musculoskelatal symptoms (AIMSS): A phase II, double-blind, placebo-controlled, randomized trial. *Breast Cancer Res Treat*. 2011;129(1):107-116.
30. Institute of Medicine, Food and Nutrition Board. Chapter 7: Vitamin D. In: *Dietary Reference Intakes for Calcium, Phosphorus Magnesium, Vitamin D and Fluoride*. Washington, DC: National Academies Press; 1997.
31. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *J Clin Endocrinol Metab*. 2011;96(1):53-58.
32. Gallagher JC, Sai A, Templin T, Smith L. Dose response to vitamin D supplementation in postmenopausal women. *Ann Intern Med*. 2012;156(9):425-437.

AUTHOR INFORMATION

R. T. Chlebowski is a professor of medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA. M. Pettinger is a senior statistician and C. L. Kooperberg is an affiliate professor, Fred Hutchinson Cancer Research Center, Seattle, WA. K. C. Johnson is a professor and interim chair, University of Tennessee Health Science Center, Department of Preventive Medicine, Memphis. R. Wallace is a professor, University of Iowa College of Public Health, Iowa City. C. Womack is an associate professor of medicine and L. Carbone is a professor of medicine, Veterans Affairs Medical Center, Memphis, and University of Tennesee Health Science Center, Memphis. Y. Mossavar-Rahmani is an associate professor of clinical epidemiology and population health, Albert Einstein College of Medicine, Bronx, NY. M. Stefanick is a professor of medicine, Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA. J. Wactawski-Wende is a professor and associate chair, The State University of New York, Buffalo. B. Lu is an assistant professor, Brigham and Women's Hospital, Harvard Medical School, Boston, MA. C. Eaton is a professor of family medicine and epidemiology, Brown University, Providence, RI. B. Walitt is an associate professor of medicine, Georgetown University Medical Center, Washington, DC.

Address correspondence to: Rowan T. Chlebowski, MD, PhD, Division of Medical Oncology and Hematology, Harbor-UCLA Medical Center, 1124 W Carson St, Building J-3, Torrance, CA 90502. E-mail: rowanchlebowski@gmail.com

STATEMENT OF POTENTIAL CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

FUNDING/SUPPORT

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services, through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221.

ACKNOWLEDGEMENTS

The WHI Project Office at the National Heart, Lung, and Blood Institute (NHLBI), the Sponsor, reviewed and approved the final manuscript but had no other role in the preparation of this report. Decisions concerning study design, data collection and analysis, interpretation of the results, the preparation of the manuscript, or the decision to submit the manuscript for publication resided with committees composed of WHI investigators that included NHLBI representatives.