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Calcium plus Vitamin D Supplementation and Height Loss: Findings from the Women's Health Initiative Calcium plus Vitamin D Clinical Trial

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Statistical analysis: CA and AA.

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Abstract

Objective—The goal of this study was to determine the associations between calcium + vitamin D supplementation (vs. placebo) and height loss in 36,282 participants of the Women’s Health Initiative Calcium with Vitamin D trial.

Methods—Post-hoc analysis of data from a double-blind randomized controlled trial of 1000 mg of elemental calcium as calcium carbonate with 400 IU of vitamin D3 daily (CaD) or placebo in postmenopausal women at 40 U.S. clinical centers. Height was measured annually (mean follow-up 5.9 years) with a stadiometer.

Results—Average height loss was 1.28 mm/year among participants assigned to CaD versus 1.26 mm/year for women assigned to placebo ($p=0.35$). Effect modification of the CaD intervention was not observed by age, race/ethnicity, or baseline intake of calcium or vitamin D. Randomization to the CaD group did not reduce the risk of clinical height loss (loss of 1.5 inches [3.8 cm]: HR (95% CI) = 1.00 (0.81, 1.23). A strong association ($p<0.001$) was observed between age group and height loss. When we censored follow-up data in participants who became non-adherent to study pills, the results were similar to those of our primary analysis.

Conclusions—Compared with placebo, the CaD supplement used in this trial did not prevent height loss in healthy postmenopausal women.

Keywords

Height loss; Calcium; vitamin D; Women’s Health Initiative

INTRODUCTION

The etiology of postmenopausal height loss is not well understood. Height loss among women probably begins in midlife. The Baltimore Longitudinal Study of Aging, which performed serial measurements of height over 9 years in a cohort of men and women, documented that height loss begins at approximately age 30 and increases with age¹. On average, in women, height decreased 5 cm between ages 30 and 70 years, and by age 80, women had lost 8 cm of height¹. Age-related height loss is believed to be a result of decreasing height of inter-vertebral discs and joint cartilage, scoliosis, less pronounced foot arches, and postural changes² as well as osteoporotic vertebral fractures and weakness of the back muscles^{3–6}.

Clinical trials have not examined longitudinal associations between calcium plus vitamin D (CaD) supplementation and change in height among U.S. postmenopausal women. It is possible that CaD supplementation reduces height loss, particularly if it decreases vertebral fracture risk. However, whether CaD supplementation reduces vertebral fracture risk is controversial, with heterogeneity among clinical trial results^{7, 8}. It is also possible that CaD supplementation may decrease height loss by decreasing morphometric vertebral fractures, slowing bone mineral density loss, and/or by decreasing the frequency of falls⁹.

The goal of the current study was to determine the associations between calcium plus vitamin D supplementation (vs. placebo) and height loss in participants enrolled in the Women's Health Initiative (WHI) Calcium with Vitamin D trial. We prospectively measured participant height using a standard protocol and collected detailed data regarding osteoporosis risk factors in more than 36,000 postmenopausal women.

Methods

Participants

The WHI calcium and vitamin D (CaD) trial enrolled 36,282 postmenopausal women 50–79 years of age who were already participating in a WHI clinical trial (the WHI Dietary Modification trial and/or the WHI Hormone Therapy trial) at 40 U.S. clinical centers (Figure 1). Participants were randomly assigned in a double-blind fashion to receive 1000 mg of elemental calcium as calcium carbonate with 400 IU of vitamin D₃ daily or placebo. Women were permitted to take their own calcium supplements up to 1000 mg per day and their own vitamin D₃ supplements up to 1000 IU per day. Eligibility criteria and recruitment methods were described in detail previously^{10, 11}. Participants were followed until death, loss to follow-up, or study close-out (March 31, 2005) (Figure 1).

Between calendar years 1995 and 2000, 36,282 participants were enrolled in the WHI CaD trial. For the current study, we analyzed baseline (at the time of randomization into the CaD trial) and follow-up data from all participants of the CaD trial who underwent height measurement at one or more time points. We excluded data from eight participants (5 in the active therapy group, 3 in the placebo group) for whom information on measured height was not available at any time point (baseline or subsequent follow-up).

The institutional review boards of each participating institution approved the trial protocol and each participant provided written informed consent at the CaD trial randomization visit. The WHI study is registered with ClinicalTrials.gov, number NCT00000611.

Outcome measurement

Height was measured at baseline and annually by specially-trained staff at each clinical center using a wall-mounted stadiometer with careful attention to positioning. After removing their shoes, participants stood on a level, uncarpeted, hard surface to undergo height measurement. Height values were rounded up to the nearest tenth of a centimeter.

Implausible height measurements of < 4 feet were uncommon (0.10% of all height measurements) and set to missing.

For the majority of participants (83%), the last height measurement occurred at the 5th (19%), 6th (28%), 7th (21%), or 8th (15%) annual visit after CaD randomization, where differential follow-up was due to study design (i.e., staggered enrollment period).

Other measurements

At the time of randomization, dietary calcium and vitamin D intake were assessed with a modified Block food frequency questionnaire¹². Information regarding the use of

prescription medications was collected using an interviewer-administered survey. Baseline questionnaires were used to obtain information regarding age, race/ethnicity, education, smoking, alcohol consumption, time since menopause, parental and personal history of hip fracture, history of treated diabetes, history of bilateral oophorectomy, and physical activity^{13, 14}.

Adherence to study medication use was established by the weighing of returned pill bottles during annual clinic visits.

Statistical Analysis

Primary analyses were performed according to the intention-to-treat principle using all available follow-up data during the intervention period.

Mean height loss per year (95% confidence interval [CI]) was estimated from a linear mixed effects (LME) model. Mean heights were assumed to be equal between treatment groups at randomization, so the model included a common intercept, along with variables for time (years since randomization; linear), time x randomization group interaction, age at randomization as a covariate, along with a random intercept and random slope for time. To confirm that the LME model was reasonable, estimates for mean height (95% CI) were also computed from a classical repeated measures model with an unstructured variance-covariance matrix that did not assume a linear relationship with time; annual visits were coded categorically. In the aforementioned analyses, follow-up was restricted to eight years after CaD trial randomization. (Only 3% of participants underwent a 9th visit).

The incidence of clinical height loss, defined as ≥ 1.5 inches changes from time of randomization, was investigated with a Cox proportional hazards model that was stratified on age group and randomization into the dietary trial and hormone therapy trials. (Clinical guidelines state that historical height loss of 1.5 inches [3.8 cm] among postmenopausal women age 50 and older constitutes the need for further evaluation for vertebral fractures¹⁵.) The Grambsch and Therneau test did not suggest any evidence against the proportionality assumption (p-value = 0.65).

Subgroup analyses, designated *a priori*, were performed to investigate whether the effect of CaD on height loss was modified by age (5-year age groups), race/ethnicity (White, Black, Hispanic, other), total calcium intake (< 1200 , ≥ 1200 mg/day), total vitamin D intake (< 600 , ≥ 600 IU/day for women ≤ 70 years old; < 800 , ≥ 800 IU/day for women > 70 years old), use of calcium supplements at baseline, use of vitamin D supplements at baseline, use of menopausal hormone therapy (randomization into the active arm of the WHI hormone therapy trials or self-initiation of menopausal hormone therapy), and physical activity level (MET-hours/week above vs. below median). The cutpoints for total calcium and total vitamin D were based on Institute of Medicine recommendations¹⁶. Statistical significance was based on a test of interaction, and no adjustment for multiple testing was made; at most one interaction was expected to be significant by chance alone.

We also examined a range of height loss thresholds (0.5 inches to 3.0 inches) as individual outcomes of Cox regression models⁶.

Secondary analyses were conducted to test whether results differed in analyses limited to data from women who were adherent to study pills. Follow-up was censored when participants took less than 80% of study pills according to weight of returned pill bottles during clinic visits^{11, 17}. To maintain balance of participant characteristics and produce a fair comparison between randomization groups, regression models included the inverse of a participant's estimated adherence probability as a weighting factor. Weights were time-dependent and estimated from a Cox model that allowed the baseline hazard to vary by randomization group and age group, and included race/ethnicity, marital status, smoking status, calcium supplement use at Year 1, vitamin D supplement use at Year 1, WHI Dietary Modification Trial randomization group and WHI Hormone Therapy trial randomization group as predictor variables, which have previously been found to be significantly associated with CaD adherence¹⁸. Interactions between CaD randomization group and predictor variables were initially included in our Cox model, but later dropped, and not used to estimate weights, because they were not significant predictors of adherence.

All analyses were performed with SAS version 9.4 and figures were drawn with R 3.1. All p-values are two-sided and p-values < 0.05 were regarded as statistically significant.

Results

CaD trial participants were predominantly White (83%) and their average (standard deviation [SD]) age and height at the time of screening were 62.4 (6.9) years and 162.0 (6.5) cm. Baseline characteristics were balanced between the two randomization groups (Table 1).

The mean (SD) of time elapsed between a participant's last height measurement and their baseline measurement was 5.9 (1.9) years, where the 25th percentile, median, and 75th percentile were 5.0, 6.0, 7.0 years.

Histograms of heights at each visit were approximately normal (not shown), without any suggestion of skew or heavy tails, and consistent with a normal distribution. For example, at randomization the observed skewness and kurtosis of height were near zero; -0.002 and 0.4, respectively. Mean height loss was similar between randomization groups during the trial. Participants assigned to the CaD group lost an average height of 1.28 mm per year versus 1.26 mm per year in the placebo group ($p=0.35$; Figure 2, Figure 3). Effect modification of the CaD intervention was not observed by age group ($p_{\text{interaction}} = 0.49$; Figure 4), race/ethnicity ($p_{\text{interaction}} = 0.55$), total calcium intake ($p_{\text{interaction}} = 0.11$), use of calcium supplements at baseline ($p_{\text{interaction}} = 0.53$), total vitamin D intake ($p_{\text{interaction}} = 0.77$), use of vitamin D supplements at baseline ($p_{\text{interaction}} = 0.42$), WHI hormone trial randomization group ($p_{\text{interaction}} = 0.31$), use of menopausal hormone therapy at baseline ($p_{\text{interaction}} = 0.85$), or physical activity (above vs. below median $p_{\text{interaction}} = 0.89$) (Table 2).

Figure 4 demonstrates the variation by age in the natural trajectory of height loss during the 8-year follow-up period. Specifically, after adjustment for race/ethnicity, the average (95% CI) annual change in height was -0.70 (-0.79, -0.62), -0.94 (-1.00, -0.89), -1.11 (-1.16, -1.06), -1.44 (-1.49, -1.38), -1.81 (-1.88, -1.74) and -2.23 (-2.33, -2.12) mm per year for participants aged <55, 55-60, 60-65, 65-70, 70-75 and 75 years old, respectively.

When clinical height loss (defined as height loss of ≥ 1.5 inches [3.8 cm]) was the outcome of Cox proportional hazards models, randomization to the CaD group did not reduce the risk of clinical height loss. An overall effect of HR (95% CI) = 1.00 (0.81, 1.23) was observed, and there was no suggestion of effect modification by any of the prespecified characteristics (Table 3).

When we varied the definition of substantial height loss over the range of thresholds (0.5 inches to 3.0 inches [1.25 cm to 7.5 cm]), associations between CaD trial randomization group and substantial height loss were not statistically significant (Table 4). Confidence intervals for the upper range of thresholds were wider corresponding to the lower number of substantial height loss “events”.

In sensitivity analyses in which we censored follow-up after a participant became non-adherent (took $< 80\%$ of study pills based on collection weight or reported that she stopped taking study pills), the resulting summary statistics were similar to those of our primary analysis. Specifically, accounting for adherence changed the mean difference of height loss (95% CI) from -0.03 (-0.08 , 0.03) to 0.002 (-0.08 , 0.09) mm per year, and the p-value changed from 0.35 to 0.97. Similarly, accounting for adherence changed the HR (95% CI) for clinical height loss from 1.00 (0.81, 1.23) to 1.05 (0.75, 1.48), and the p-value changed from 0.99 to 0.72.

Discussion

In this cohort of generally healthy postmenopausal women, CaD supplementation versus placebo did not decrease height loss over an average follow-up of 5.9 years. There was no evidence that the associations between treatment group and height loss varied by age, race/ethnicity, total calcium intake, or total vitamin D intake. In the sensitivity analysis accounting for adherence to study pills, the results were similar to those of the main analysis, with no evidence of an effect of randomization to CaD in decreasing height loss.

To our knowledge, previously-published results of clinical trials have not specifically focused on longitudinal associations between CaD supplementation and change in height among U.S. postmenopausal women.

We believe that our findings reflect the multifactorial nature of age-related height loss. In addition to osteoporotic vertebral fractures¹⁹, weakness of the back muscles^{3–6}, decreasing height of inter-vertebral discs and joint cartilage, less pronounced foot arches, and postural changes² are believed to contribute to height loss. All types of vertebral deformity may be associated with height loss²⁰. The multiple causative factors, not all of which would be amenable to an influence of CaD supplementation, may have obscured our ability to detect protective effects of calcium with vitamin D on height loss, if such effect exists. We also note that although height loss has been associated with adverse health consequences in longitudinal studies, including increased risk of falls, decreased grip strength, decrease walking speed, increased fracture incidence, and increased risk of death^{19, 21–32}, it is not clear that interventions to prevent height loss can prevent those adverse health outcomes.

The use of CaD supplements is widespread. In the National Health and Nutrition Examination Survey 2005–2006 of the U.S. population, among women aged between 51 and 70 years, 40% reported using vitamin D supplements and 67% reported using calcium supplements³³. A protective effect of CaD supplementation against height loss would potentially impact large numbers of postmenopausal women. However, our results do not support this strategy. Previous studies from the WHI CaD trial data did not find evidence of protective effects of CaD supplementation against decline in physical functioning³⁴, hip fracture risk¹¹, vertebral fracture risk¹¹, or risk of death^{35, 36}, although there was a lower hip fracture risk among women aged 60 years and older who were assigned to CaD versus placebo¹¹.

In both treatment groups, we observed strong associations between age and height loss, with older women experiencing the largest magnitudes of annual decrease in height. Compared with the Baltimore Longitudinal Study of Aging (BLSA), height loss by age group was less rapid in the current study¹. For example, among the 71 women aged 60 to 69, and the 78 women aged 70–79 years of age in the BLAS study, mean height loss was 0.223 and 0.290 cm/year, respectively. In contrast, height loss was 0.223 cm/year among more than 2600 WHI participants age 75 or older. One reason may be that the data collection in the previous study occurred from 1978 to 1993 with an average of five height measurements over 9 years of follow-up, whereas our data collection occurred from 1995 to 2005, and may reflect changes in lifestyle and nutrition.

Our study has potential limitations. First, it is possible that results would have shown CaD supplementation to be protective against height loss if the trial participants had been selected on the basis of having low calcium or vitamin D intake. Participants were allowed to take multivitamins as well as calcium and vitamin D up to 1000 mg/day of supplemental calcium and up to 1000 IU/d of supplemental vitamin D during the trial. In the current study, average total baseline intake from dietary sources and supplements was 1150 mg/day for calcium and 365 IU/day for vitamin D. Although participants were permitted to use bisphosphonates selective estrogen receptor modulators, the prevalence of use of these medications was low at baseline (<2%). Participants of the WHI Dietary Modification trial were permitted to take selective estrogen receptor modulators and menopausal hormone therapy. Second, participants were healthy postmenopausal women living in the community and predominantly free of disability. Results cannot be generalized to the institutionalized elderly. Third, WHI did not assess morphometric vertebral fractures (which would have required serial vertebral x-rays in all participants). It remains possible that CaD supplementation may decrease morphometric vertebral fractures, although we found no association between CaD and clinical vertebral fractures. Despite the large sample size of this study, overall mean height loss was low and few women experienced clinical height loss. Finally, although we used a wall-mounted stadiometer with a standardized protocol for height measurements, height was measured only once for each participant, so there may have been some measurement error. However, this type of error would likely bias the findings towards the null, and the large sample size suggests that the overall effect of such an error would be small.

Our findings should not be interpreted as discouraging adherence to guidelines recommendations regarding CaD supplementation. The U.S. Preventive Services Task Force recommends vitamin D supplementation to prevent falls among community-dwelling adults aged 65 or older who are at increased risk for falls ³⁷.

Strengths of this study include the placebo comparison group, the availability of detailed information regarding important covariates, a large number of participants, and longitudinal standardized objective height measurements. The latter have advantages over self-reported height loss, which can be over-reported ³⁸.

Conclusion

In conclusion, the use of CaD supplements is widespread, but the CaD preparation and doses that were tested in this large clinical trial did not prevent height loss.

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Figure 1.
Participant flow diagram for the WHI Calcium and vitamin D trial.

Figure 2.

Linear estimates of mean height (solid lines; 95%CI, dotted lines) during the CaD trial by randomization group; estimates are from a liner mixed effects (LME) model. Mean (95%CI; bow ties) by visit are also shown to confirm that the LME trajectories are reasonable.

Figure 3.

Differences (CaD minus placebo) of mean height by randomization group. The blue dots (bow ties) are the differences of mean (95% CI) height at each visit from the repeated measures model, and the solid (dotted) red lines are the differences from the linear mixed effects model. The dashed reference lines are at ± 0.1 cm.

Mean height in the CaD trial by age

P-value for 1-df test for trend of CaD x age interaction = 0.49

Figure 4.

Linear estimates of mean height (solid lines; 95% CI, dotted lines) during the CaD trial by randomization group and age groups.

Table 1

Characteristics of Participants in the Calcium with Vitamin D Trial at the Time of the WHI Screening According to Randomization Group (N=36,274)

	Active (N=18171)		Placebo (N=18103)	
	N	%	N	%
Age group (years)				
50–54	2591	14.3	2561	14.1
55–59	4133	22.7	4135	22.8
60–64	4518	24.9	4499	24.9
65–69	3756	20.7	3743	20.7
70–74	2303	12.7	2335	12.9
75–79	870	4.8	830	4.6
Race/ethnicity				
White	15048	82.8	15101	83.4
Black	1678	9.2	1635	9.0
Hispanic	785	4.3	717	4.0
American Indian	77	0.4	72	0.4
Asian/Pacific Islander	370	2.0	351	1.9
Unknown	213	1.2	227	1.3
Body-mass index (kg/m ²)				
<25	4742	26.2	4834	26.8
25 – <30	6475	35.8	6486	36.0
30	6869	38.0	6690	37.1
Education				
High school/GED or less	4284	23.7	4290	23.8
School after high school	7217	40.0	7155	39.8
College degree or higher	6554	36.3	6544	36.4
Smoking status				
Never	9324	51.9	9428	52.6
Past	7254	40.3	7130	39.8
Current	1402	7.8	1356	7.6
Alcohol consumption				
Non/past drinker	5054	28.0	5099	28.4
< 7 drinks/week	11063	61.4	10976	61.1
7 drinks/week	1906	10.6	1899	10.6
Time since menopause				
< 10 years	5753	34.4	5740	34.4
10 – <20 years	6202	37.1	6167	37.0
20 years	4746	28.4	4771	28.6

	Active (N=18171)		Placebo (N=18103)	
	N	%	N	%
Menopausal hormone therapy use status				
Never used	8786	48.4	8625	47.7
Past user	3238	17.8	3149	17.4
Current user	6132	33.8	6317	34.9
Menopausal hormone therapy use status *				
Never used	5813	32.0	5689	31.4
Past user	3003	16.5	2931	16.2
Current user	9355	51.5	9483	52.4
Bilateral oophorectomy	3303	18.6	3392	19.2
Calcium supplement use	9748	53.6	9821	54.3
Vitamin D supplement use	8554	47.1	8610	47.6
SERM use	23	0.1	24	0.1
Bisphosphonate use	292	1.6	298	1.6
Treated diabetes (pills or injections)	792	4.4	789	4.4
Parent broke hip	2215	15.7	2179	15.5
History of fracture age 55+	1948	14.8	1968	15.0
CEE * trial				
Placebo	1540	50.1	1562	50.3
Active	1531	49.9	1543	49.7
Not randomized	15100	83.1	14998	82.8
CEE + MPA † trial				
Placebo	2475	49.7	2394	48.6
Active	2506	50.3	2535	51.4
Not randomized	13190	72.6	13174	72.8
Low fat diet trial				
Comparison	7825	62.1	7736	61.3
Intervention	4766	37.9	4878	38.7
Not randomized	5580	30.7	5489	30.3
	Mean	(SD)	Mean	(SD)
Age	62.4	(7.0)	62.4	(6.9)
Body-mass index (kg/m ²)	29.1	(5.9)	29.0	(5.9)
Total energy expenditure/week from physical activity, MET-hours [‡]	10.7	(12.7)	10.6	(12.4)
Total Calcium intake (mg)	1148.6	(654.2)	1154.2	(657.9)

	Active (N=18171)		Placebo (N=18103)	
	N	%	N	%
Total Vitamin D intake (IU)	365.3	(265.5)	367.9	(266.0)
Height (cm)	162.0	(6.5)	162.1	(6.5)

* Values include use of personal menopausal hormone therapy in the Observational Study as well as menopausal hormone therapy during year 1 of the Hormone Therapy Trials.

* CEE denotes conjugated equine estrogens

[†] MPA denotes medroxyprogesterone acetate

[‡] MET denotes metabolic equivalent of task

Table 2

Mean height loss* (mm per year; 95%CI) by CaD trial randomization group and selected subgroups

	Active (N=18171)			Placebo (N=18103)			Difference [†]	
	N	Mean	(95% CI)	N	Mean	(95% CI)	Mean	(95% CI) p [‡]
Main effect	18171	-1.28	(-1.32, -1.25)	18103	-1.26	(-1.30, -1.22)	-0.03	(-0.08, 0.03) 0.35
Age[§] (years)								0.49
<55	1683	-0.69	(-0.80, -0.57)	1690	-0.72	(-0.83, -0.60)	0.03	(-0.13, 0.19)
55-59	3909	-1.00	(-1.07, -0.92)	3866	-0.89	(-0.96, -0.81)	-0.11	(-0.22, 0.00)
60-64	4425	-1.14	(-1.22, -1.06)	4386	-1.08	(-1.16, -1.00)	-0.06	(-0.17, 0.05)
65-69	3983	-1.41	(-1.49, -1.33)	4040	-1.46	(-1.54, -1.38)	0.05	(-0.06, 0.16)
70-74	2813	-1.78	(-1.88, -1.68)	2803	-1.84	(-1.94, -1.74)	0.06	(-0.08, 0.20)
75	1358	-2.30	(-2.45, -2.15)	1318	-2.15	(-2.30, -2.00)	-0.15	(-0.36, 0.06)
Race/ethnicity								0.55
White	15048	-1.33	(-1.37, -1.29)	15101	-1.31	(-1.35, -1.27)	-0.02	(-0.07, 0.04)
Black	1678	-1.11	(-1.24, -0.98)	1635	-0.97	(-1.10, -0.84)	-0.14	(-0.32, 0.05)
Hispanic	785	-0.98	(-1.17, -0.79)	717	-1.05	(-1.24, -0.85)	0.07	(-0.20, 0.34)
Other	660	-1.03	(-1.24, -0.83)	650	-0.95	(-1.16, -0.75)	-0.08	(-0.37, 0.21)
Total calcium intake (mg/day)^{**}								0.11
< 1200	10815	-1.26	(-1.31, -1.21)	10657	-1.21	(-1.26, -1.16)	-0.06	(-0.13, 0.01)
1200	7002	-1.31	(-1.38, -1.25)	7093	-1.35	(-1.41, -1.29)	0.03	(-0.05, 0.12)
Calcium supplement use^{††}								0.53
No	8423	-1.26	(-1.31, -1.20)	8282	-1.21	(-1.27, -1.16)	-0.04	(-0.12, 0.03)
Yes	9748	-1.31	(-1.36, -1.26)	9821	-1.30	(-1.35, -1.25)	-0.01	(-0.08, 0.06)
Total vitamin D intake (IU/day)^{‡‡}								0.77
<600	14897	-1.29	(-1.33, -1.24)	14869	-1.27	(-1.31, -1.23)	-0.02	(-0.08, 0.04)
600	2920	-1.27	(-1.37, -1.18)	2881	-1.23	(-1.33, -1.14)	-0.04	(-0.17, 0.09)
Vitamin D supplement use^{§§}								0.42
No	9617	-1.26	(-1.31, -1.21)	9493	-1.21	(-1.27, -1.16)	-0.05	(-0.12, 0.03)
Yes	8554	-1.31	(-1.37, -1.26)	8610	-1.31	(-1.37, -1.26)	-0.00	(-0.08, 0.08)

		Active (N=18171)			Placebo (N=18103)			Difference [†]	
		N	Mean	(95% CI)	N	Mean	(95% CI)	Mean	(95% CI)
HT ^{***} randomization group									
	Placebo	4015	-1.46	(-1.56, -1.35)	3956	-1.47	(-1.58, -1.37)	0.02	(-0.13, 0.17)
	Active	4037	-1.28	(-1.39, -1.18)	4078	-1.20	(-1.30, -1.09)	-0.09	(-0.23, 0.06)
HT use at CaD randomization ^{†††}									
	Never used	5813	-1.45	(-1.53, -1.37)	5689	-1.43	(-1.51, -1.35)	-0.02	(-0.13, 0.09)
	Past user	3003	-1.33	(-1.44, -1.23)	2931	-1.35	(-1.45, -1.24)	0.02	(-0.14, 0.17)
	Current user	9355	-1.19	(-1.25, -1.13)	9483	-1.16	(-1.22, -1.10)	-0.03	(-0.12, 0.05)
Physical activity (MET-hr/wk)									
	<= 6.75	8312	-1.28	(-1.33, -1.22)	8310	-1.23	(-1.29, -1.17)	-0.04	(-0.13, 0.04)
	> 6.75	8230	-1.28	(-1.33, -1.22)	8135	-1.24	(-1.30, -1.18)	-0.04	(-0.12, 0.04)

* From a linear mixed effects model that included a common intercept, along with variables for time (years since randomization; linear), time x randomization group interaction, age at randomization as a covariate, along with a random intercept and random slope for time. Analysis includes up to eight annual visits following randomization to the CaD trial.

[†] Height loss in active (CaD) group minus height in placebo group

[‡] P value for interaction test

[§] Age at CaD trial randomization.

^{**} Baseline intake from dietary and supplement sources.

^{††} Refers to use of calcium supplements at baseline.

^{†††} Baseline intake from dietary and supplement sources. For participants > 70 years old, the threshold < 800 (800) IU/day was used to categorize participants that did not (did) meet institute of medicine recommendations.

^{§§} Refers to use of vitamin D supplements at baseline.

^{***} Women's Health Initiative Hormone therapy trials. Height measurements that occurred after the Women's Health Initiative Hormone therapy trials were stopped have been censored and follow-up is through year 6 after CaD trial randomization.

^{††††} Refers to use of personal menopausal hormone therapy at baseline or use during year 1 of the Women's Health Initiative Hormone Therapy trials.

Table 3Risk* of clinical height loss (≥ 1.5 inches) by CaD trial randomization group and selected subgroups

	Active (N=18171) N (%)	Placebo (N=18103) N (%)	HR (95% CI)	P-Value [†]
Main effect	185 (0.17%)	180 (0.17%)	1.00 (0.81, 1.23)	0.99
Age[‡] (years)				0.81
<55	8 (0.07%)	9 (0.09%)	0.88 (0.34, 2.29)	
55–59	26 (0.11%)	26 (0.11%)	0.96 (0.56, 1.66)	
60–64	33 (0.13%)	29 (0.11%)	1.14 (0.69, 1.87)	
65–69	42 (0.18%)	43 (0.18%)	0.95 (0.62, 1.46)	
70–74	44 (0.28%)	46 (0.29%)	0.90 (0.59, 1.37)	
75	32 (0.45%)	27 (0.38%)	1.19 (0.71, 2.00)	
Race/ethnicity				0.87
White	159 (0.18%)	150 (0.17%)	1.03 (0.82, 1.29)	
Black	16 (0.17%)	20 (0.22%)	0.90 (0.45, 1.77)	
Hispanic	6 (0.14%)	6 (0.15%)	0.63 (0.18, 2.18)	
Other	4 (0.11%)	4 (0.11%)	1.10 (0.27, 4.50)	
Total calcium intake (mg/day)[§]				0.88
< 1200	105 (0.17%)	103 (0.17%)	0.96 (0.73, 1.26)	
1200	73 (0.18%)	74 (0.18%)	0.99 (0.71, 1.38)	
Calcium supplement use^{**}				0.70
No	81 (0.16%)	78 (0.16%)	0.95 (0.69, 1.30)	
Yes	104 (0.18%)	102 (0.18%)	1.03 (0.78, 1.36)	
Total vitamin D intake (IU/day)^{††}				0.52
<600	154 (0.18%)	156 (0.18%)	0.96 (0.77, 1.20)	
600	24 (0.14%)	21 (0.12%)	1.19 (0.65, 2.17)	
Vitamin D supplement use^{‡‡}				0.51
No	98 (0.17%)	86 (0.15%)	1.08 (0.80, 1.45)	
Yes	87 (0.18%)	94 (0.19%)	0.94 (0.70, 1.26)	
HT^{§§} randomization group				0.96
Placebo	22 (0.11%)	17 (0.09%)	1.25 (0.66, 2.36)	
Active	27 (0.14%)	21 (0.11%)	1.28 (0.72, 2.27)	
HT use at CaD randomization^{***}				0.47
Never used	40 (0.15%)	38 (0.14%)	1.02 (0.66, 1.60)	
Past user	14 (0.09%)	18 (0.12%)	0.76 (0.37, 1.53)	
Current user	59 (0.12%)	54 (0.11%)	1.10 (0.76, 1.59)	
Physical activity (MET-hr/wk)				0.60
6.75	86 (0.18%)	88 (0.19%)	0.97 (0.72, 1.31)	
> 6.75	75 (0.16%)	70 (0.15%)	1.10 (0.79, 1.52)	

* From a Cox proportional hazards model that was stratified on age group and randomization into the dietary trial and hormone therapy trials.

[†] P value for interaction test.

[‡] Age at CaD randomization.

[§] Baseline intake from dietary and supplement sources.

^{**} Refers to use of calcium supplements at baseline.

^{††} Baseline intake from dietary and supplement sources. For participants > 70 years old, the threshold < 800 (= 800) IU/day was used to categorize participants that did not (did) meet institute of medicine recommendations.

^{‡‡} Refers to use of vitamin D supplements at baseline.

^{§§} Women's Health Initiative Hormone therapy trials. Events and corresponding event times, that occurred after the Women's Health Initiative Hormone therapy trials were stopped, have been censored.

^{***} Refers to use of personal menopausal hormone therapy at baseline or use during year 1 of the Women's Health Initiative Hormone Therapy trials.

Table 4

Risk of substantial height loss by CaD trial randomization group over a range of height loss thresholds

Threshold (inches)	HR(95%CI)	P
0.5	0.98 (0.94, 1.02)	0.29
1.0	1.00 (0.90, 1.12)	0.93
1.5	1.00 (0.81, 1.23)	0.99
2.0	0.94 (0.67, 1.32)	0.72
2.5	0.84 (0.54, 1.31)	0.43
3.0	0.72 (0.43, 1.22)	0.22