

# Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements<sup>1-3</sup>

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## ABSTRACT

**Background:** The Women's Health Initiative (WHI) randomized clinical trial (RCT) of calcium plus vitamin D (CaD) supplements found a 17% excess in urinary tract stone incidence in the supplemented group. This study evaluated whether this risk is modified by participant characteristics.

**Objective:** We examined the correlates of urinary tract stone occurrence in the CaD arm of the WHI trial.

**Design:** We analyzed an RCT involving 36,282 postmenopausal women aged 50–79 y from 40 WHI centers: 18,176 women received 500 mg calcium carbonate plus 200 IU vitamin D<sub>3</sub> twice daily (1000 mg and 400 IU daily, respectively), and 18,106 women received a matching placebo for an average of 7.0 y. The incidence of urinary tract stones was determined.

**Results:** The incidence of self-reported clinically diagnosed urinary tract stones was more common in the active CaD medication group than in the placebo group (hazard ratio: 1.17; 95% CI: 1.02, 1.34): 449 women in the CaD group and 381 women in the placebo group reported a stone during the trial. The rates of self-reported stones did not differ between various demographic, anthropomorphic, dietary, and other hypothesized risk factors according to randomization assignment. Neither the total calcium intake nor the use of calcium supplements at baseline was associated with the risk of stones. In sensitivity analyses that censored participants who were below 80% adherence, the findings were similar.

**Conclusions:** Daily supplementation with CaD for 7 y was associated with an increase in the number of self-reported urinary tract stones. These findings have implications for CaD supplement use. This trial was registered with the WHI at [clinicaltrials.gov](http://clinicaltrials.gov) as NCT00000611. *Am J Clin Nutr* 2011;94:270–7.

## INTRODUCTION

Calcium plus vitamin D (CaD) dietary supplements have been recommended for the prevention of osteoporotic fractures in postmenopausal women (1), and millions are using supplements to improve bone health. However, little is known about the long-term adverse effects of such supplements. Because supplemental CaD may alter calcium and vitamin D metabolism and calcium absorption and excretion, the possibility of altered rates of urolithiasis is an important clinical issue, particularly given the preventive nature of such supplement use. In the Women's Health Initiative (WHI) CaD supplementation trial in >36,000 women, urinary tract stones were reported to be 17% more common in those in the active supplementation group (hazard ratio: 1.17;

95% CI: 1.02, 1.34) (2). This, to our knowledge, is the first report of this adverse effect in a large-scale, randomized trial of CaD supplements. In this report, we explored the demographic, dietary, and clinical correlates of and risk factors for urinary tract stone occurrence in this trial to better understand whether specific participant characteristics may have modified the occurrence of this important clinical event.

## SUBJECTS AND METHODS

### Study population, eligibility, and consent

The design, execution, and outcomes of the WHI CaD supplementation trial and the other WHI intervention trials have been described in detail (3–8); subject progress through the trial is shown in **Figure 1**. Briefly, between 1993 and 1998, postmenopausal women aged 50–79 y were enrolled in the WHI randomized clinical trials designed to assess the risks and benefits of hormone therapy (HT) and dietary modification (DM). One year later, participants enrolled in the HT and/or DM trials were invited to enroll in the CaD supplementation trial. This trial was designed to determine whether supplementation would prevent hip fracture (the primary outcome), other fractures, or colorectal cancer (designated secondary outcomes). Exclusion

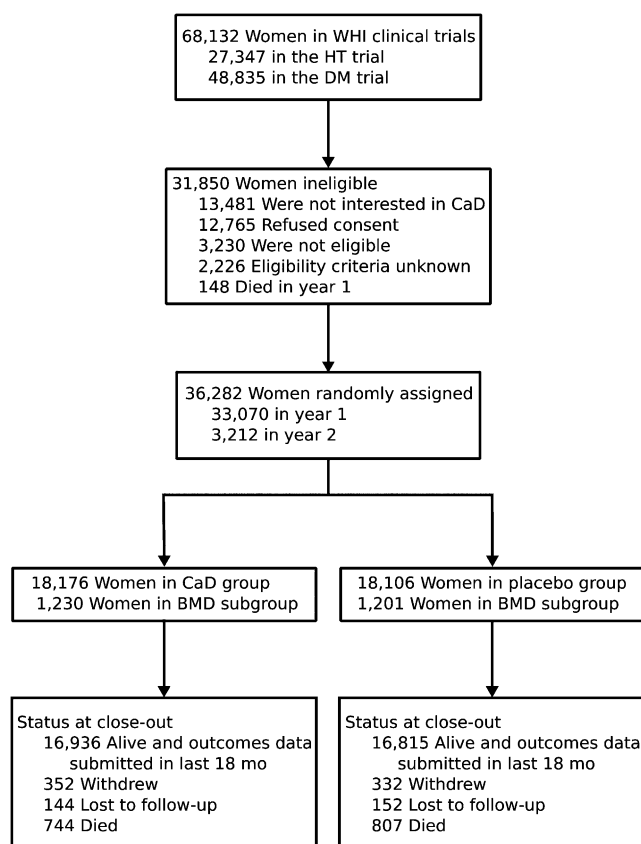
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**FIGURE 1.** Progress of subjects through the phases of the Women's Health Initiative (WHI) Calcium plus Vitamin D (CaD) Supplementation Study. HT, hormone therapy; DM, dietary modification; BMD, bone mineral density.

criteria for enrollment in the HT and DM trials were related to competing risks, safety, adherence, and retention. Additional exclusion criteria for the CaD trial included a predicted survival of  $<3$  y, a history of hypercalcemia or urinary tract stones, current use of corticosteroids, use of calcitriol or  $\geq 600$  IU supplemental vitamin D. Although excluded by protocol design, later review of CaD trial intake forms showed that 161 participants in the active CaD arm and 172 in the placebo arm had a self-reported history of urinary tract stones; we conducted intention-to-treat analyses and did not exclude these individuals. The protocol and consent forms were approved by the institutional review board at each participating institution. All women provided written informed consent. Baseline clinical, demographic, anthropomorphic, and dietary information was collected by using self-administered forms supplemented by in-person and telephone interviews, by using common WHI protocols and questionnaires (3).

#### Randomization, blinding, intervention, and monitoring

A permuted-block algorithm was used for randomization, with participants stratified according to clinical center and age. Of the 36,282 participants who enrolled in the CaD trial, 18,176 were randomly assigned to the active arm and received a total daily dose of 1000 mg elemental Ca (calcium carbonate) and 400 IU vitamin D. Each dose contained 500 mg elemental Ca as calcium carbonate combined with 200 IU vitamin D<sub>3</sub> and were to be

taken twice daily with meals, as either a chewable or (after 1997) a swallowable tablet. The remaining 18,106 participants were randomly assigned to receive an identical-appearing placebo tablet to be taken twice daily. Both active and placebo pills were provided by GlaxoSmithKline (Philadelphia, PA). An independent data and safety monitoring board reviewed the trial data semiannually. Closeout visits occurred as planned between 1 October 2004 and 31 March 2005, with final outcomes assessed before the treatment assignment was revealed. Participants were followed for a mean ( $\pm$ SD) time of  $7.0 \pm 1.4$  y.

#### Follow-up procedures and ascertainment of outcomes

Four weeks after randomization, participants were telephoned to assess their abdominal symptoms and reinforce adherence. Thereafter, participants were contacted semiannually to obtain self-reported medical history updates. Urinary tract stone occurrence was obtained on the medical history update by asking the following question: "Since (the date given in the front of this form), has your doctor told you for the first time that you have any of the following specific conditions (mark all that apply)" with an item response on that form: "kidney or bladder stones (renal or urinary calculi)." There was no additional follow-up of the clinical evaluation among participants reporting clinical urinary tract stone disease, and information on the type of stone and chemical composition of the stones (ie, oxalate or uric acid) was not obtained. As part of general WHI trial protocols, hospitalization events lasting  $\geq 48$  h were solicited from all participants and medical records were obtained. All hospitalizations of CaD trial participants during which urinary tract stone diagnoses or related surgical procedures occurred were tabulated from the WHI database by using the International Classification of Disease, Ninth Revision (ICD-9-CM) (9).

During the study, adherence was assessed by weighing returned pill bottles. Regardless of their level of adherence, participants were followed up until they died, they were lost to follow-up, they requested no further contact, or the study ended. By protocol, study pills were discontinued if urinary tract stones, hypercalcemia, dialysis, calcitriol use, or daily use of supplements providing  $>1000$  IU vitamin D were reported.

#### Statistical analysis

All analyses were conducted by using SAS version 9.1 (SAS Institute, Cary, NC). Primary analyses used time-to-event methods, according to the intention-to-treat principle. The primary outcome in these analyses was incident self-reported urinary tract stones. We also analyzed hospitalization rates for urinary tract stones or stone-related conditions. Comparison of these outcomes by the 2 groups (active arm compared with placebo) were represented by hazard ratios and 95% CIs from Cox regression models stratified according to baseline age groups and participation in the HT and DM trials (10). Kaplan-Meier estimates were used to present event rates over time. All *P* values were 2-sided. The effect of CaD on stone occurrence according to potential participant and pathogenetic risk factors was also assessed by Cox regression models with *P* for interaction derived from likelihood ratio tests. A total of  $\approx 30$  subgroup analyses were performed. Thus,  $\approx 2$  statistically significant interaction tests would be expected on the basis of chance alone.

To determine the effect of women discontinuing the use of study pills early (active or placebo arm), a sensitivity analysis was conducted, which allowed participants to contribute follow-up time until 6 mo after their first "nonadherent" visit, defined as taking <80% of their study medication. Full adherence hazard ratios were estimated by using inverse adherence censoring weighted estimators with adjustment for 10 covariates associated with adherence.

## RESULTS

The randomization scheme worked without difficulty, and no significant differences in the CaD trial participants at screening were found between the active drug and placebo groups with respect to age at screening, other demographic features, family history of study conditions, body mass index, physical activity, prior use of calcium and vitamin D supplements (both as a percentage of users and amounts), total calcium and vitamin D intake, alcohol use and smoking habits, and calculated sun exposure based on geographic residence. Detailed data on these findings were published previously (2). As shown in **Table 1**, no significant differences were found in the distribution of CaD trial participants enrolled in the other randomized WHI trials. Seventeen percent were enrolled in the HT trials, 69% were enrolled in the DM trials, and 14% participated in both the HT and DM trials.

When the trial was concluded on 31 March 2005, 4.3% of participants had died, and 2.7% had withdrawn from the trial or were lost to follow-up. Progress through the trial is shown in Figure 1. Adherence rates, defined as taking  $\geq 80\%$  of the assigned medication, ranged from 60% to 63% for the first 3 trial years; an additional 13–21% took at least half of their study pills. At the trial's conclusion, 76% were taking study medication, and 59% were still taking  $\geq 80\%$  of the doses.

As noted above, and previously reported, self-reported urinary tract stones were 17% more common in the active CaD medication group than in the placebo group (hazard ratio: 1.17; 95% CI: 1.02, 1.34), as shown in the first row of **Table 2**. Kaplan-Meier analysis of this finding is shown in **Figure 2**. In the active medication group, 449 participants reported a stone during the trial, as opposed to 381 of those in the placebo group.

**TABLE 1**

Baseline characteristics of subjects in the Calcium plus Vitamin D (CaD) Supplementation Study according to participation in the other Women's Health Initiative trials

	CaD randomization arm			
	Active drug (n = 18,106)		Placebo (n = 18,176)	
	n	%	n	%
Estrogen alone				
No	15,105	83.1	15,001	82.9
Yes	881	4.8	861	4.8
Estrogen plus progestin				
No	13,193	72.6	13,176	72.8
Yes	4983	27.4	4930	27.2
Dietary modification				
No	5582	30.7	5490	30.3
Yes	12,594	69.3	12,616	69.7

The remainder of Table 2 shows the rates of self-reported stones for the active medication and placebo groups according to demographic, anthropomorphic, dietary, and other hypothesized risk factors for urinary tract stone disease. Whereas none of these subgroup analyses was statistically significant in a test for interaction with the main outcome effect, some findings were of interest. No obvious effect of age or other sociodemographic characteristics on stone risk was found, and no apparent effect according to participation in any of the other WHI trials was found. Similarly, no significant interactive effect of body weight or body mass index, thiazide diuretic use, regional solar irradiance levels, alcohol use, physical activity, prior menopausal hormone use, or dietary micro- or macronutrient composition on the risk of urinary tract stones was found. Of note, neither the total calcium intake at baseline nor the use of calcium supplements as a single agent at baseline was associated with the risk of stones. Also, as noted in Table 2, reported recurrent stone occurrence during the trial interval was not related to a history of stone disease.

In the sensitivity analysis, including only stone outcomes during active adherence, as defined above, the findings were similar in magnitude to those for the intention-to-treat analysis, yet were statistically insignificant (hazard ratio: 1.21; 95% CI: 0.98, 1.34). Finally, we determined the number of hospital admissions during which any diagnosis used the ICD-9 rubrics for urinary tract stone disease. Only a small proportion of those reporting urinary tract stones had a hospital admission in which urinary tract stone-related diagnoses occurred—35 each in the active medication and placebo groups; these rates were not significantly different.

## DISCUSSION

From the literature, reported rates of urinary tract stone occurrence (history) in the developed world vary according to demographic characteristics and have apparently increased in the past 20–30 y, except in Iceland, where there has been a non-significant increase in men but no increase in women (11–16). A portion of this increase may be related to more frequent use of diagnostic medical imaging incidentally detecting asymptomatic nephrolithiasis. In a recent review of urinary tract stone occurrence in American adults, the lifetime prevalence increased by 37% between 1976 to 1980 and 1988 to 1994, and was higher among men overall, although the rate of increase was higher in women (46%) than in men (29%) (11). Also, the lifetime prevalence was higher in whites than in Hispanics, Mexican Americans, Asians, and blacks, the latter group having the lowest rates (11, 16). Interestingly, the lifetime cumulative incidence of symptomatic stones in women in one US community increased from 4.3% in 1970 to 9.2% in 1990 and declining to 6.8% in 2000, resulting in a decrease in the male to female ratio from 3:2 to 1:3 over the same period. In this same study, the overall stone incidence rates in the population remained unchanged from 1970 to 2000, but the incidence in males decreased (15). Our finding of a 17% increase in the incidence of clinically diagnosed urinary tract stones suggests that one possible factor, CaD dietary supplement use by women, should be considered as a factor that has influenced the change in the rate of urinary tract stones in the population.

**TABLE 2**Number of self-reported urinary tract stones by baseline demographic and dietary characteristics (annualized rate)<sup>1</sup>

	CaD group (n = 18,106)	Placebo group (n = 18,176)	HR <sup>2</sup> (95% CI)	P for interaction <sup>3</sup>
All self-reported kidney stones	449 (0.35)	381 (0.30)	1.17 (1.02, 1.34)	
Age group at screening				0.194
50–59 y	151 (0.30)	140 (0.28)	1.06 (0.84, 1.33)	
60–69 y	225 (0.39)	168 (0.30)	1.34 (1.10, 1.63)	
70–79 y	73 (0.34)	73 (0.34)	0.99 (0.72, 1.38)	
Ethnicity				0.806
White	367 (0.34)	302 (0.28)	1.21 (1.04, 1.41)	
Black	42 (0.36)	38 (0.33)	1.10 (0.71, 1.71)	
Hispanic	23 (0.42)	24 (0.49)	0.90 (0.50, 1.62)	
American Indian	4 (0.75)	4 (0.79)	0.84 (0.20, 3.61)	
Asian/Pacific Islander	10 (0.40)	8 (0.34)	1.24 (0.49, 3.17)	
Unknown	3 (0.21)	5 (0.34)	0.62 (0.14, 2.73)	
Education (collapsed category)				0.088
None–HS diploma/GED	121 (0.40)	86 (0.29)	1.38 (1.05, 1.82)	
School after HS	166 (0.33)	170 (0.34)	0.97 (0.78, 1.20)	
College degree or higher	154 (0.33)	122 (0.26)	1.25 (0.99, 1.59)	
Baseline weight quartile	126 (0.30)	111 (0.26)	1.17 (0.91, 1.52)	0.866
<67.8 kg				
67.8–80.9 kg	143 (0.33)	122 (0.29)	1.12 (0.88, 1.42)	
>80.9 kg	180 (0.42)	148 (0.35)	1.22 (0.98, 1.52)	
BMI				0.733
<25 kg/m <sup>2</sup>	95 (0.28)	81 (0.24)	1.20 (0.89, 1.61)	
25–30 kg/m <sup>2</sup>	153 (0.33)	141 (0.31)	1.08 (0.86, 1.35)	
>30 kg/m <sup>2</sup>	198 (0.41)	158 (0.34)	1.21 (0.99, 1.50)	
E alone (n = 1742)				0.624
E alone, active	48 (0.45)	37 (0.35)	1.32 (0.82, 2.02)	
E alone, placebo	42 (0.39)	38 (0.35)	1.13 (0.73, 1.75)	
E+P (n = 9913)				0.337
E+P, active	63 (0.36)	45 (0.26)	1.41 (0.96, 2.07)	
E+P, placebo	45 (0.26)	40 (0.24)	1.07 (0.70, 1.64)	
HT intervention (n = 11,655)				0.293
HT, active	111 (0.39)	82 (0.29)	1.37 (1.03, 1.82)	
HT, placebo	87 (0.31)	78 (0.28)	1.10 (0.81, 1.49)	
DM intervention (n = 25,210)				0.587
DM, intervention	115 (0.34)	98 (0.28)	1.20 (0.91, 1.57)	
DM, control	193 (0.35)	175 (0.32)	1.09 (0.88, 1.33)	
Thiazides (like) diuretic use				0.708
No	423 (0.35)	361 (0.30)	1.16 (1.01, 1.34)	
Yes	26 (0.43)	20 (0.34)	1.30 (0.72, 2.34)	
Regional solar irradiance				0.943
475–500 Langley units	99 (0.38)	87 (0.33)	1.12 (0.84, 1.49)	
400–430 Langley units	66 (0.30)	50 (0.23)	1.28 (0.88, 1.84)	
375–380 Langley units	53 (0.37)	45 (0.32)	1.15 (0.77, 1.71)	
350 Langley units	102 (0.37)	82 (0.30)	1.24 (0.92, 1.66)	
300–325 Langley units	129 (0.33)	117 (0.30)	1.10 (0.85, 1.41)	
Smoking				0.422
Never smoker	234 (0.35)	187 (0.28)	1.26 (1.04, 1.53)	
Past smoker	175 (0.34)	162 (0.32)	1.06 (0.86, 1.31)	
Current smoker	29 (0.30)	28 (0.30)	0.99 (0.59, 1.67)	
Alcohol use				0.945
Not a current drinker	139 (0.40)	117 (0.33)	1.19 (0.93, 1.53)	
<1 drink/wk	170 (0.38)	142 (0.32)	1.16 (0.93, 1.45)	
≥1 drink/wk	135 (0.29)	119 (0.26)	1.13 (0.89, 1.45)	
Physical activity				0.383
>0–3.75 METs/wk	142 (0.38)	135 (0.36)	1.03 (0.81, 1.31)	
>3.75–8.75 METs/wk	150 (0.40)	112 (0.30)	1.33 (1.04, 1.70)	
>8.75–17.5 METs/wk	118 (0.31)	99 (0.26)	1.18 (0.90, 1.54)	

(Continued)

TABLE 2 (Continued)

	CaD group (n = 18,106)	Placebo group (n = 18,176)	HR <sup>2</sup> (95% CI)	P for interaction <sup>3</sup>
	n (%)	n (%)		
HT use at WHI baseline				0.351
Never user	221 (0.36)	181 (0.30)	1.20 (0.99, 1.46)	
Past user	63 (0.28)	65 (0.30)	0.92 (0.65, 1.30)	
Current user	163 (0.37)	135 (0.30)	1.23 (0.98, 1.55)	
HT use (self-report/intervention combination)				0.207
Never user	142 (0.33)	126 (0.30)	1.10 (0.86, 1.40)	
Past user	49 (0.27)	52 (0.30)	0.89 (0.60, 1.32)	
Current user	257 (0.39)	203 (0.30)	1.29 (1.07, 1.55)	
Quartile of caffeine intake				0.178
<77.18 mg	138 (0.43)	131 (0.43)	1.01 (0.79, 1.28)	
77.18 to <177.50 mg	108 (0.34)	104 (0.33)	1.04 (0.79, 1.36)	
177.50 to <265.32 mg	114 (0.35)	78 (0.24)	1.46 (1.10, 1.96)	
≥265.32 mg	89 (0.28)	68 (0.21)	1.34 (0.98, 1.84)	
Quartile of protein intake				0.678
<14.57% of energy	128 (0.40)	96 (0.30)	1.32 (1.01, 1.72)	
14.57 to <16.46% of energy	99 (0.31)	83 (0.26)	1.22 (0.91, 1.64)	
16.46 to <18.50% of energy	107 (0.33)	101 (0.32)	1.04 (0.79, 1.37)	
≥18.50% of energy	115 (0.36)	101 (0.32)	1.14 (0.87, 1.49)	
Quartile of fat intake				0.685
<32.25% of energy	101 (0.31)	80 (0.26)	1.24 (0.92, 1.66)	
32.25 to <35.78% of energy	94 (0.30)	94 (0.29)	1.01 (0.75, 1.34)	
35.78 to <40.09% of energy	130 (0.41)	107 (0.34)	1.22 (0.94, 1.57)	
≥40.09 % of energy	124 (0.39)	100 (0.32)	1.23 (0.94, 1.60)	
Quartile of dietary fat intake				0.529
<45.96 g	117 (0.37)	91 (0.29)	1.27 (0.96, 1.67)	
45.96 to <63.79 g	96 (0.30)	93 (0.29)	1.04 (0.78, 1.38)	
63.79 to <86.95 g	103 (0.32)	93 (0.30)	1.07 (0.81, 1.42)	
≥86.95 g	133 (0.42)	104 (0.32)	1.31 (1.01, 1.69)	
Quartile of dietary sodium intake				0.899
<2010.04 mg	117 (0.37)	97 (0.31)	1.21 (0.92, 1.58)	
2010.04 to <2681.65 mg	104 (0.32)	94 (0.30)	1.07 (0.81, 1.41)	
2681.65 to <3514.06 mg	107 (0.34)	87 (0.27)	1.24 (0.93, 1.64)	
≥3514.06 mg	121 (0.38)	103 (0.32)	1.19 (0.91, 1.54)	
Quartile of dietary potassium intake				0.418
<1902.56 mg	125 (0.39)	114 (0.37)	1.06 (0.82, 1.37)	
1902.56 to <2486.46 mg	107 (0.34)	87 (0.27)	1.25 (0.94, 1.66)	
2486.46 to <3161.51 mg	112 (0.34)	103 (0.33)	1.06 (0.81, 1.39)	
≥3161.51 mg	105 (0.33)	77 (0.24)	1.41 (1.05, 1.89)	
Quartile of dietary iron intake				0.895
<8.77 mg	114 (0.36)	103 (0.33)	1.09 (0.83, 1.42)	
8.77 to <11.86 mg	115 (0.36)	100 (0.32)	1.15 (0.88, 1.50)	
11.86 to <15.53 mg	104 (0.33)	83 (0.26)	1.25 (0.94, 1.67)	
≥15.53 mg	116 (0.36)	95 (0.30)	1.22 (0.93, 1.60)	
Quartile of dietary oxalic acid intake				0.776
<201.98 mg	121 (0.38)	112 (0.36)	1.07 (0.83, 1.38)	
201.98 to <276.35 mg	115 (0.35)	93 (0.30)	1.17 (0.89, 1.55)	
276.35 to <371.41 mg	100 (0.31)	87 (0.27)	1.14 (0.86, 1.53)	
≥371.41 mg	113 (0.36)	89 (0.28)	1.30 (0.99, 1.72)	
Quartile of dietary vitamin C intake				0.761
<53.28 mg	122 (0.38)	97 (0.31)	1.22 (0.94, 1.60)	
53.28 to <84.68 mg	128 (0.40)	103 (0.32)	1.22 (0.94, 1.59)	
84.68 to <120.79 mg	105 (0.33)	103 (0.32)	1.02 (0.78, 1.34)	
≥120.79 mg	94 (0.29)	78 (0.25)	1.22 (0.90, 1.64)	
Quartile of total calcium intake <sup>d</sup>				0.243
<674.58 mg	131 (0.41)	98 (0.32)	1.31 (1.01, 1.71)	
674.58 to <1030.36 mg	102 (0.32)	102 (0.33)	0.98 (0.74, 1.29)	
1030.36 to <1490.12 mg	117 (0.37)	82 (0.26)	1.41 (1.06, 1.87)	
≥1490.12 mg	93 (0.30)	87 (0.28)	1.12 (0.83, 1.50)	

(Continued)

TABLE 2 (Continued)

	CaD group (n = 18,106)	Placebo group (n = 18,176)	HR <sup>2</sup> (95% CI)	P for interaction <sup>3</sup>
	n (%)	n (%)		
Taking calcium as a single supplement				0.741
No	374 (0.36)	315 (0.30)	1.18 (1.02, 1.37)	
Yes	75 (0.31)	66 (0.28)	1.10 (0.79, 1.53)	
Quartile of total vitamin C intake <sup>5</sup>				0.982
<77.33 mg	124 (0.38)	100 (0.31)	1.21 (0.93, 1.57)	
77.33 to <136.81 mg	106 (0.33)	93 (0.29)	1.11 (0.84, 1.46)	
136.81 to <356.65 mg	102 (0.32)	87 (0.27)	1.19 (0.89, 1.58)	
≥356.65 mg	117 (0.37)	101 (0.32)	1.18 (0.90, 1.54)	
Quartile of total vitamin D intake <sup>5</sup>	121 (0.37)	105 (0.33)	1.11 (0.85, 1.44)	0.397
<3.25 μg				
3.25 to <6.64 μg	106 (0.33)	103 (0.32)	1.01 (0.77, 1.32)	
6.64 to <13.28 μg	109 (0.34)	76 (0.24)	1.42 (1.06, 1.91)	
≥13.28 μg	113 (0.37)	97 (0.30)	1.21 (0.92, 1.58)	
Quartile of total potassium intake <sup>5</sup>	122 (0.38)	112 (0.36)	1.06 (0.82, 1.37)	0.281
<1908.58 mg				
1908.58 to <2495.70 mg	109 (0.34)	88 (0.27)	1.25 (0.94, 1.66)	
2495.70 to <3172.10 mg	112 (0.34)	106 (0.33)	1.03 (0.79, 1.35)	
≥3172.10 mg	106 (0.33)	75 (0.23)	1.45 (1.08, 1.95)	
Quartile of total iron intake <sup>5</sup>	117 (0.36)	109 (0.35)	1.05 (0.81, 1.36)	0.685
<10.32 mg				
10.32 to <15.67 mg	106 (0.33)	84 (0.26)	1.25 (0.94, 1.67)	
15.67 to <27.32 mg	118 (0.37)	92 (0.29)	1.30 (0.99, 1.71)	
≥27.32 mg	108 (0.34)	96 (0.30)	1.15 (0.87, 1.52)	
History of kidney stone	444 (0.35)	372 (0.30)	1.18 (1.03, 1.36)	0.200
No				
Yes	5 (0.45)	9 (0.73)	0.58 (0.19, 1.75)	

<sup>1</sup> CaD, calcium plus vitamin D; HS, high school; GED, general educational development; E, estrogen; P, progestin; HT, hormone therapy; WHI, Women's Health Initiative; DM, dietary modification; METs, metabolic equivalents; HR, hazard ratio.

<sup>2</sup> From Cox proportional hazards regression models stratified according to age, DM participation, and history of kidney stone.

<sup>3</sup> Test of linear trend for continuous variables. For categorical variables, *P* values for interaction from likelihood ratio test comparing models with and without interaction terms.

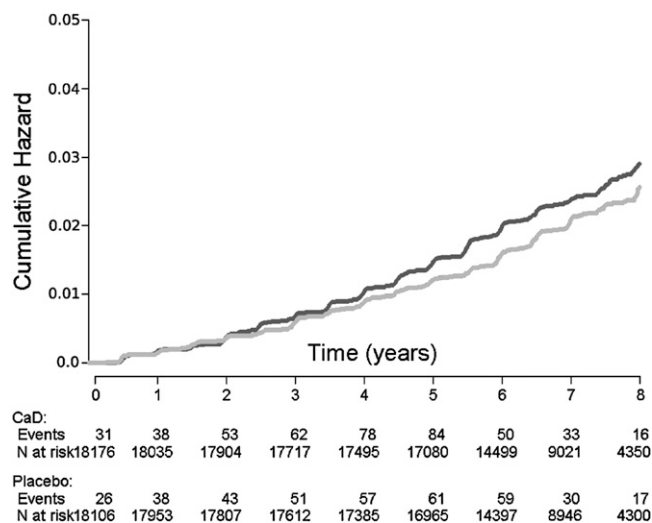
<sup>4</sup> Combination of diet + supplements + medication.

<sup>5</sup> Combination of diet + supplements.

Numerous dietary, anatomic, metabolic, and endocrine risk factors have been variously associated with the risk of stones. With respect to calcium and vitamin D, our basically healthy population of postmenopausal women had a calculated total dietary calcium intake of ≈1150 mg and dietary vitamin D intake of ≈365 IU at baseline before study medication was begun, including dietary and supplement sources, so that the addition of further dietary calcium may have promoted hypercalciuria in the active medication group. However, no clear association of baseline total calcium intake with overall stone risk was observed, and the incident risk of stones was not excessively elevated in those taking calcium as a single supplement at baseline (Table 2). Most urinary tract stones contain calcium oxalate, and many stone formers have elevated concentrations of both urinary calcium and oxalate (17). In the current study, we did not perform urinary biochemical determinations, nor did we have any information regarding the chemical analysis of the incident stones. In women, supplementary calcium intake has been associated with a 17–20% increase in stone risk in observational studies, regardless of the relation to meals (18–20). It is also important to note that this study could not discriminate between the relative effects of calcium and vitamin D with respect to the occurrence of urinary stones.

Calcium intake over 12 y was assessed in 91,731 women (aged 34–59 y at entry) with no history of urinary tract stones in the Nurses' Health Study (12) to determine the incidence of symptomatic stones. After adjustment for multiple factors, including age, high dietary calcium intake was associated with a lower incidence of stones (35% decrease in the highest quintile, 1098 mg/d), whereas supplement intake, at all amounts, was associated with an increased risk of 20%. Most women took the supplemental calcium either between meals or with meals that may have had a low oxalate content, based on food-frequency questionnaires (20). Magnesium and phosphorus intakes were not associated with a change in stone risk. It was not clear whether the women in that study also took vitamin D, as did the women in the WHI trial, the participants of which were also instructed to take study medications with meals. In addition to enhancing intestinal absorption of calcium, vitamin D may increase the renal tubular absorption of calcium (21).

In one study of men younger than 60 y, high dietary calcium was associated with decreased stone formation, but there was no effect on men older than 60 y, nor was supplemental dietary intake of >500 mg Ca associated with an increase in incident stone risk (22). As in the current study, and in another study (18), past or current hormone use in menopausal women was not



**FIGURE 2.** Kaplan-Meier survival curve for risk of self-reported urinary tract stones in the calcium plus vitamin D (CaD; black line) and placebo (gray line) groups.

associated with an increased rate of stones, regardless of the type of menopause.

Dietary factors variously associated with urinary tract stones, in addition to calcium and vitamin D, have included oxalate, sucrose, sodium, animal protein, and fluids, with some differences observed between men and women (12, 19, 22–24). Because most stones contain calcium oxalate, the role of oxalates is becoming of particular interest to investigators. Oxalate absorption from the gastrointestinal tract is normally low, except in stone formers, in whom it appears to be elevated. The rate of absorption may be related to the amount that is ionized and available at lower oxalate intakes, whereas higher intakes may lead to more complex forms that are not easily absorbed. Dietary calcium may have a protective effect on stone formation by increasing calcium oxalate binding in the gastrointestinal tract, which decreases its absorption (19, 26). A great deal is yet to be learned about the oxalate content of foods, some of which are eaten erratically, and the factors that affect absorption and metabolism. Gene variation and expression may also play a role in the absorption and/or excretion of oxalate (27).

Overall, dietary fluid intake has been associated with a beneficial effect on the occurrence of urinary tract stones. The calcium content of community water does not appear to be associated with an increase in history of urinary tract stones in women (28). Tea and coffee use has been associated with a minimally increased risk, and wine has been associated with a decreased risk (22). Other associations with an increase in stone risk having a greater effect in women than in men are body mass index, obesity, waist circumference and weight gain (29), and histories of either hypertension, especially in larger women (30, 31), or diabetes (32, 33). None of these factors substantially altered the effect of the primary CaD intervention in this study.

With regard to selected nondietary factors, the highest rate of stone occurrence in the United States has been reported in the southeast—associated with an increased sun exposure (10). Similar findings were seen in an Italian study (12). Yet, in the current study using Langley categories, no significant effect of sun exposure on the renal effect of the CaD intervention was seen. A family history of stones has a significant effect on risk, which

suggests an important genetic or familial component to the intervention effect; however, little is known about the relative effects of genetics and environment on this finding. Of interest, some participants in the study had a personal history of stone disease, in violation of the WHI protocol; however, this history was not associated with an increase in stone risk. It is possible that calcium citrate as a supplement might be associated with a lesser risk of urinary tract stones, as was suggested in one small study of 18 postmenopausal women (34). This finding warrants further study.

In summary, in this experimental intervention of generally healthy postmenopausal women, a 17% increased risk of self-reported urinary tract stones was observed. This finding was generally not altered by other proven or potential risk factors for such stones. An increased risk of self-reported urinary tract stone was found in women in the intervention group, which could have important population implications because of the large number of women consuming these supplements and the changes in over-the-counter doses now available. The absolute difference in occurrence of urinary tract stones between the groups was small: 0.35% of women in the intervention group and 0.30% of women in the control group reported stones. Furthermore, <10% of women who reported urinary tract stones had related hospitalizations. Note that other adverse effects of calcium and vitamin D supplements have been described, including hypercalcemia, renal function abnormalities, and acute vitamin D toxicity. Furthermore, the possibility exists that an increased calcium intake (without vitamin D supplementation) is associated with a higher risk of myocardial infarction (35).

A major potential limitation of this study was that the reported stone occurrence was not validated by clinical records; recurring stones may not have been reported by some participants because the questionnaire only specifically addressed the first occurrence of urinary tract stones. However, the blinded experimental design greatly enhanced the probability that the reports were not biased. No other intervention study of similar or larger size has reported this effect. It would be very helpful for other studies of similar scope and design to carefully monitor participants for incident urinary tract stone outcomes.

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