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Predictors of Adherence in the Women's Health Initiative Calcium and Vitamin D Trial

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Abstract

The authors analyzed data from the Women's Health Initiative (WHI) Calcium and Vitamin D Supplementation Trial (CaD) to learn more about factors affecting adherence to clinical trial study pills (both active and placebo). Most participants (36,282 postmenopausal women aged 50–79 years) enrolled in CaD 1 year after joining either a hormone trial or the dietary modification trial of WHI. The WHI researchers measured adherence to study pills by weighing the amount of remaining pills at an annual study visit; adherence was primarily defined as taking ≥ 80% of the pills. The authors in this study examined a number of behavioral, demographic, procedural, and treatment variables for association with study pill adherence. They found that relatively simple procedures (ie, phone contact early in the study [4 weeks post randomization] and direct social contact) later in the trial may improve adherence. Also, at baseline, past pill-use experiences, personal supplement use, and relevant symptoms may be predictive of adherence in a supplement trial.

Index Terms

adherence; calcium supplementation; clinical trial; women

In the Women's Health Initiative (WHI) Calcium and Vitamin D Supplementation Trial (CaD), an intention-to-treat analysis showed that active treatment did not significantly reduce hip fracture, which was the primary outcome measure.[1] However, a subanalysis of adherent (at least 80% of study medication taken) participants revealed a significant reduction (29%) in hip fractures; thus, understanding adherence issues is important in reducing such injuries.

Reduced adherence to medications (not always in clinical trials) is associated with increasing age, lower socioeconomic level, smoking, and various indicators of poorer health status.[2,3] In several meta-analyses,[4–7] improved adherence to medical treatments was associated with social support.[8,9] Other meta-analyses have shown that depression (but not anxiety) and hopelessness about one's medical condition reduce adherence.[10–15]

In this study, we evaluated factors that have been demonstrated to generally predict higher levels of adherence[16] and considered variables specific to intervention trials. To conceptualize disparate measures, we categorized variables as sociodemographic, psychosocial, health status, and procedural. This strategy may aid the systematic evaluation and enhancement of adherence in future trials and clinical interventions.

METHODS

Participants

Detailed descriptions of eligibility criteria, recruitment procedures, and primary findings for the WHI are available elsewhere.[17,18] Researchers recruited postmenopausal women (aged 50–79 years) into WHI randomized trials that assessed hormone therapy (HT) or dietary modification (DM) at 40 US centers, and 1 year later invited them to join the CaD trial. Of the 36,282 participants randomized to CaD, we analyzed the 91% who joined initially (not later). Among the participants in the CaD trial, 54% were in HT, 69% percent in DM, and

14% in both. WHI researchers obtained informed consent for each of the trials, using forms approved by local institutional review boards.

Procedure

The trial was a randomized, double-blind, placebo-controlled design[19] in which participants took 2 tablets daily of 1,000 mg of calcium carbonate with 400 IU of Vitamin D_3 or a matching placebo (study pills provided by Glaxo Smith-Kline [Bensalem, PA]). Until October 1997, only a chewable pill was available; the researchers subsequently offered all participants a swallowable form. WHI researchers assessed adherence annually by weighing remaining pills in conjunction with conducting a structured interview. Pill weighing was not observed by or discussed with participants. Adherence below 80% triggered staff efforts to optimize adherence. To assess for side effects, the researchers implemented "step down" procedures (single daily pill, then even fewer) with monthly re-evaluations; a reduced regimen was considered nonadherence in the present analysis.

WHI researchers collected questionnaires at initial enrollment, 1 year prior to CaD trial randomization (see Table 1). Sociodemographic variables included age, ethnicity, marital status, income, education, and insurance status. Psychosocial variables included depression (measured by the Center for Epidemiological Studies Depression Scale [CES-D][20] and the Diagnostic Interview Schedule[21]) and personality traits (measured by the Life Orientation Test-Revised[22] [optimism], the Cook-Medley Hostility Scale,[23] the Ambivalence Over Emotional Expressiveness Questionnaire, and the Emotional Expressiveness Questionnaire[24]). The Medical Outcomes Study Social Support Questionnaire[25] and 4 items taken from the Social Relationships Scale[26] measured social support and social strain. The Alameda County Study questionnaire[27] measured life events in the prior year. The Rand 36-Item Health Survey (RAND36)[28],[29] assessed quality of life and general functioning.

Health variables included smoking status, body mass index (BMI), physical activity (eg, walking, housework), and reported breast or colorectal cancer or heart attack in self or immediate family. The WHI researchers assessed physical activity levels with a series of questions with metabolic equivalent time (kcal/kg/wk) scores assigned.[30] They calculated osteoporosis risk using age, ethnicity, exercise level, smoking status, hormone usage, family history, prior fractures, and calcium intake, with scores ranging from 0 to 9 (> 4 was high risk). A standard symptom checklist examined physical complaints, particularly gastrointestinal symptoms (eg, bloating or gas, constipation, belly pain).[31] A detailed questionnaire measured calcium and other supplement use.

Procedural variables were the pill type (swallowable or chewable), change in pill type, clinic site, parallel participation and adherence in HT and DM, completion of the recommended follow-up call scheduled 4 weeks after randomization, and whether the semiannual (ie, each anniversary date of randomization plus 6 months) contact was a visit or by phone.

Statistical Analysis

Using SAS version 9.0 (SAS, Inc, Cary, NC), we first analyzed participants with nonmissing values for all predictors. To address missing values, we also calculated the inverse selection probability weighted estimator.[32],[33] We performed multivariate logistic regression analyses to evaluate the likelihood of adherence (≥ 80% per study protocol) to study pills 1 year after randomization (initial change model). We termed the model, which evaluated adherence at 2 years after randomization, the *maintenance model*. We evaluated the factors in the multivariate logistic regression model simultaneously while adjusting for other covariates in the model. Maximum rescaled R^2, C-statistic, and Hosmer-Lemeshow tests evaluated the

goodness of fit of the logistic regression models. All p values were 2-tailed. Because of the large number of comparisons, $p \leq .01$ was considered statistically significant.

We performed the analyses using a hierarchical stage approach that moves from the person to the context. Stage 1 consisted of intrapersonal variables. We added interpersonal variables in stage 2, treatment variables in stage 3, and organizational variables in stage 4. We made adjustments by clinic to account for operational differences among the centers. We examined parameter estimates between stages for robustness and colinearity.

RESULTS

One year after randomization to CaD or placebo, approximately 61% of participants in this WHI clinical trial were adherent (≥ 80% of pills); after 2 years, approximately 63% were adherent. Table 2 presents means and variability of measures tested for associations with adherence.

Six variables (see Table 3) were associated with a significantly ($p < .001$) higher chance of adherence at 1 year, 4 of which were procedural variables. Completion of the semiannual visit in the clinic rather than by phone or mail nearly doubled the chance of adherence. Similarly, 72% of participants completed the recommended check-up phone call 4 weeks after randomization. These participants had a 37% greater chance of 80% CaD adherence at 1 year. Compared with women who were not in the hormone trial (HT; thus in DM and CaD only), 80% adherence to HT pills was associated with a 66% greater chance of adherence to CaD pills. Women taking the swallowable pill in year 1 had a 28% higher probability of 80% adherence compared with women taking the chewable pill (which was the only type available at the time of randomization for 58% of participants) and 51% higher probability of adherence compared with participants switching between the 2 pill forms.

Among sociodemographic variables, African American participants had a lower chance of adherence by nearly 40%. Regardless of ethnicity, participants aged 50 to 54 years and 65 to 69 years were less likely than 70- to 79-year-olds to be adherent (by 18% and 12%, respectively). Adherence rates were 12% higher overall if married or living with partner and 18% higher for participants with health insurance.

Among health variables, personal use of a supplement (either any supplement or calcium) was associated with a greater chance of adherence by 24% and 17%, respectively. Increased adherence was more likely in diabetic (17%) or physically active (7%) women. Gastrointestinal symptoms (eg, gas, bellyache, constipation) at baseline were associated with an 11% to 24% greater chance of nonadherence compared with participants not reporting symptoms in this category. Current smokers (23%) and drinkers (6%) were less likely to be adherent than the never or former groups combined.

Among the psychosocial variables reflecting emotional status, only depression was associated (negatively) with adherence (12%).

In the second year of the trial (ie, the maintenance phase), logistical regression results for adherence largely paralleled the results for the first year of the trial (ie, initial change). In year 1 but not in year 2, the following factors were significantly related to lower adherence: the youngest (50–54) compared with the oldest (70–79) age group, elevated depression symptoms, the chewable CaD study pill, and elevated negative emotional expressiveness. In year 2 but not in year 1, the following factors were significantly associated with lower adherence: higher social strain (9%) and higher number of negative life events (10%). In year 1 but not in year 2, a diagnosis of diabetes, higher levels of physical activity, and adherence in the DM trial signaled better adherence.

To address missing data, we calculated the inverse selection probability weighted estimator.[34,35] For the CaD first-year adherence, the 2 factors with odds ratios that changed most were ethnicity (Hispanic compared with white dropped from 0.82 [95% confidence interval (CI) = 0.68–0.99] to 0.71 [95% CI = 0.62–0.81]) and age (60–65 compared with 70–79 years, which increased from 1.14 [95% CI = 1.03–1.27] to 1.23 [95% CI = 1.14–1.33]). Because the remaining weighted estimates and their significance levels are fairly close to those from the primary data analysis (ie, excluding participants with missing values), the full results from the weighted estimates are not shown.

Participants assessed their own adherence semiannually as part of the safety interview. We cross-tabulated this subjective assessment with objective pill counts. About 90% of participants who were 80% adherent said they took the pills every day and missed fewer than 10 days in the past month, compared with about 55% of nonadherent participants. Of objectively adherent participants, 51.8% reported taking all pills every day.

COMMENT

Despite a historically perceived ease regarding adherence to pharmacological interventions, data indicate that compliance ranges from 40% to 75%.[36] The perception of ease may arise from underappreciating the fact that taking medications is a behavior. After adopting a behavioral approach, as WHI CaD Trial researchers did by increasing participant contact, adherence increased.

Furthermore, being relatively older, white, married or living with partner, and having health insurance was predictive of adherence in this trial and in previous studies.[37–39] Our findings reinforced previously documented challenges with adherence among racial minorities and women at a higher health risk (ie, smoking, inactivity, and prior health problems), which indicates a clustering of high-risk health behaviors.[40] The finding of better adherence associated with personal supplement use and with hormone trial adherence may have reflected participants' greater inclination or ability to take pills or adopt positive health habits.

In a smaller trial (n = 107) lasting 6 months of 1,260 mg daily calcium and 1,000 IU vitamin D supplementation from 4 caplets (M age = 76 years, SD = 5.6), 60.7% of the participants were 80% adherent,[39] which was nearly identical to the WHI CaD trial rate of 60% of the participants being 80% adherent at year 1. Those researchers found that higher education and income, more alcoholic drinks, and a history of fracture were directly predictive of significantly higher adherence, whereas minority status was indirectly linked to lower adherence through socioeconomic level and no history of hip fracture.

Some findings have suggested that a clinical diagnosis of depression (not self-reported symptoms alone) is necessary to affect adherence,[41] but we found lower levels of adherence associated with reporting of depressive symptoms at baseline. As with studies showing social support positively associated with medication adherence,[42] we found better adherence with higher social functioning and lower social strain.

Several procedural predictors suggested ways of improving clinical trial adherence. A simple follow-up call made soon after starting intervention significantly improved adherence. Dunbar-Jacob and Schlenk[43] found steep declines in adherence at onset of treatment, suggesting that both early and long-term support is important. An in-person visit at the semiannual contact point—compared with contact by phone or mail—was the strongest predictor of 1-year adherence. Adherence rates seemed to increase with more intensive and more direct personal support.[44,45] Last, the type of pill (swallowed, not chewed) benefited adherence, which highlights how ease of treatment benefits adherence.

Our results suggest that self-reported adherence plays a role in predicting adherence rates when study conditions exclude pill counts. Asking whether study pills were taken every day widely separated participants who were at least 80% adherent from those who were not. Although forgetting was the most frequently reported cause of poor adherence,[46] other reported reasons did not distinguish the adherent and nonadherent groups, so reminders (eg, labeled pill containers and calendars) can play a role in adherence.

A randomized, placebo-controlled trial does not tap the full range of factors affecting adherence. Active involvement in one's own treatment decisions improves adherence,[47] possibly through an increase in self-efficacy,[48] and this is limited by strict trial protocols. Also, the use of a placebo may reduce the sense that the treatment has personal health value and thus limit it as an adherence promoter. Nevertheless, the lessons we learned from this analysis may have applications for future studies of nutritional supplements and may be tested in trials and clinical settings where there is an interest in improving adherence to prescribed treatments.

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TABLE 1

Key Adherence Predictors in the Women's Health Initiative (WHI)

Construct	Measure	Items	Subscales	Use	Reliability and validity	Sample item
Sociodemographic variables						
Age, marital status, income, education, insurance status	Multiple single item	5	—	Wide	—	What is your age?
Psychosocial variables						
Optimism	Life Orientation Test[21] Revised (LOT-R)	6	1	Limited	α = .75 in WHI; $r = -0.42$ with depression	I'm always hopeful about my future (1 = *Strongly disagree* to 5 = *Strongly agree*)
Depression	Center for Epidemiological Studies Depression Scale[20]	8	0	Wide	α = .73; compares well to other clinical measures of depression	How often during the past week did you feel sad?
Hostility	Cynicism[23]	13	1	Limited	α = .76; compares well to other trait negativity measures	I think most people would like to get ahead
Social strain	Social Relationships Scales[26]	4	1	Limited	No data available; α = .72 in WHI	Of the people that are important to you, how many get on your nerves?
Social support	MOS Social Support Questionnaire[25]	9	4	Wide	Some data available from MOS; α = .93 in WHI	How often is this available? Someone to love you and make you feel wanted?
Stressful life events	Life Events Scale[27]	11	0	Wide	No info	Did your spouse or partner die?
Quality of Life	RAND–36[28,29]	36	8	Wide	Numerous reliability and validity reports	How would you rate your current sense of well-being?
Health variables						
Disease factors	Self-reported prior diagnosis and family history of outcomes	6	—	Wide	—	Have you ever been told by a health care provider that…?
Symptoms	Symptom checklist[31]	34	No	Modified from PEPI	No psychometrics	Did not occur and how much did they bother you?
Use of personal supplements	WHI supplement use (interview)	7	—	—	—	Multivitamin (no minerals), multivitamin (minerals), etc. Dose, unit, pills per week, etc.
Health habits	Single item questions	4	—	Wide	—	Have you smoked at least 100 cigarettes in your lifetime?
Procedural variables						
Pill type	Swallowed, chewed, or switched between the two	—	—	—	—	—
Clinic identity	—	1	—	—	—	—

Construct	Measure	Items	Subscales	Use	Reliability and validity	Sample item
Other RCT participation	Hormone trial, diet modification trial, or both	—	—	—	—	—
4-week follow-up phone contact	Yes or No	—	—	—	—	—
Type of semiannual contact	In clinic or by phone	—	—	—	—	—

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TABLE 2

Characteristics by Adherence Status

	CaD 1st-year adherence ≥ 80%					CaD 2nd-year adherence ≥ 80%				
	No (*N* = 12,611)		Yes (*N* = 19,771)			No (*N* = 12,083)		Yes (*N* = 20,299)		
Characteristic	***n***	**%**	***n***	**%**	***p***	***n***	**%**	***n***	**%**	***p***
Sociodemographic factors										
Age group at screening (years)										
50–55	2,207	17.5	2,310	11.7	< .0001	2,028	16.8	2,489	12.3	< .0001
55–60	3,121	24.7	4,245	21.5		2,892	23.9	4,474	22.0	
60–65	3,008	23.9	5,082	25.7		2,893	23.9	5,197	25.6	
65–70	2,242	17.8	4,492	22.7		2,205	18.2	4,529	22.3	
70+	2,033	16.1	3,642	18.4		2,065	17.1	3,610	17.8	
Race or ethnicity										
White	99,46	78.9	17,047	86.2	< .0001	9,526	78.8	17,467	86.0	< .0001
African American	1,579	12.5	1,301	6.6		1,505	12.5	1,375	6.8	
Hispanic	645	5.1	696	3.5		6,40	5.3	701	3.5	
Asian or Pacific Islander	227	1.8	427	2.2		196	1.6	458	2.3	
Unknown	214	1.7	300	1.5		216	1.8	298	1.5	
College or higher										
No	8,007	63.5	12,467	63.1	.3428	7,714	63.8	12,760	62.9	.0735
Yes	4,511	35.8	7,184	36.3		4,289	35.5	7,406	36.5	
Medical insurance										
No	790	6.3	922	4.7	< .0001	7,47	6.2	965	4.8	< .0001
Yes	11,682	92.6	18,697	94.6		11,212	92.8	19,167	94.4	
Current health care provider										
No	1,056	8.4	1,464	7.4	.0013	1,009	8.4	1,511	7.4	.0033
Yes	11,420	90.6	18,134	91.7		10,961	90.7	18,593	91.6	
Health variables										
Prior history of CVD										
No	10,547	83.6	16,757	84.8	.0097	10,008	82.8	17,296	85.2	< .0001
Yes	2,032	16.1	2,977	15.1		2,044	16.9	2,965	14.6	

	CaD 1st-year adherence ≥ 80%					CaD 2nd-year adherence ≥ 80%				
	No (*N* = 12,611)		Yes (*N* = 19,771)			No (*N* = 12,083)		Yes (*N* = 20,299)		
Characteristic	***n***	**%**	***n***	**%**	***p***	***n***	**%**	***n***	**%**	***p***
Prior history of cancer										
No	11,984	95.0	18,822	95.2	.588	11,456	94.8	19,350	95.3	.352
Yes	496	3.9	804	4.1		500	4.1	800	3.9	
Diabetes at baseline										
No	11,892	94.3	18,613	94.1	.6054	11,342	93.9	19,163	94.4	.0486
Yes	717	5.7	1,151	5.8		737	6.1	1,131	5.6	
High risk (≥ 4) of osteoporosis										
No	9,460	75.0	14,404	72.9	< .0001	9,052	74.9	14,812	73.0	< .0001
Yes	3,139	24.9	5,350	27.1		3,017	25.0	5,472	27.0	
Family history of breast cancer or colorectal cancer or MI										
No	4,489	35.6	6,850	34.6	.0615	4,237	35.1	7,102	35.0	.7508
Yes	7,957	63.1	12,698	64.2		7,681	63.6	12,974	63.9	
Polyps removal prior to AV2										
No	12,201	96.7	19,173	97.0	.2524	11,673	96.6	19,701	97.1	.025
Yes	410	3.3	598	3.0		410	3.4	598	2.9	
BMI										
< 25	3,239	25.7	5,273	26.7	.0952	3,037	25.1	5,475	27.0	.0004
25–30	4,518	35.8	7,063	35.7		4,333	35.9	7,248	35.7	
≥ 30	4,792	38.0	7,326	37.1		4,649	38.5	7,469	36.8	
On any special diet at baseline										
No	7,187	57.0	10,974	55.5	.0008	6,842	56.6	11,319	55.8	.1311
Yes	5,424	43.0	8,796	44.5		5,241	43.4	8,979	44.2	
Total energy expenditure from physical activities ≥ 11 METs										
No	7,766	61.6	11,812	59.7	< .0001	7,423	61.4	12,155	59.9	< .0001
Yes	3,840	30.4	6,971	35.3		3,709	30.7	7,102	35.0	
Current smoker vs. never or former smoker										
No	11,311	89.7	18,302	92.6	< .0001	10,882	90.1	18,731	92.3	< .0001
Yes	1,148	9.1	1,285	6.5		1,053	8.7	1,380	6.8	
Current vs. past or nondrinker										

	CaD 1st-year adherence ≥ 80%					CaD 2nd-year adherence ≥ 80%				
	No (*N* = 12,611)		Yes (*N* = 19,771)			No (*N* = 12,083)		Yes (*N* = 20,299)		
Characteristic	***n***	**%**	***n***	**%**	***p***	***n***	**%**	***n***	**%**	***p***
No	3,490	27.7	5,567	28.2	.4385	3,452	28.6	5,605	27.6	.0496
Yes	9,011	71.5	14,093	71.3		8,534	70.6	14,570	71.8	
Take calcium supplement at AV1										
No	10,475	83.1	15,616	79.0	< .0001	10,023	83.0	16,068	79.2	< .0001
Yes	1,970	15.6	3,952	20.0		1,893	15.7	4,029	19.8	
Psychosocial variables										
Shortened CES-D/DIS ≥ .06										
No	10,750	85.2	17,564	88.8	< .0001	10,275	85.0	18,039	88.9	< .0001
Yes	1,442	11.4	1,758	8.9		1,401	11.6	1,799	8.9	
Had ≥ 3 life events										
No	8,724	69.2	14,474	73.2	< .0001	8,318	68.8	14,880	73.3	< .0001
Yes	3,608	28.6	4,914	24.9		3,486	28.9	5,036	24.8	
Emotion expressiveness ≥ 3										
No	802	6.4	1,397	7.1	.0178	774	6.4	1,425	7.0	.0397
Yes	11,674	92.6	18,242	92.3		11,187	92.6	18,729	92.3	
Optimism ≥ 19										
No	1,074	8.5	1,474	7.5	.0002	1,071	8.9	1,477	7.3	< .0001
Yes	11,196	88.8	17,974	90.9		10,693	88.5	18,477	91.0	
Hostility ≥ 8										
No	10,742	85.2	17,297	87.5	< .0001	10,206	84.5	17,833	87.9	< .0001
Yes	1,331	10.6	1,842	9.3		1,352	11.2	1,821	9.0	
Take any supplement at AV1										
No	4,838	38.4	5,986	30.3	< .0001	4,593	38.0	6,231	30.7	< .0001
Yes	7,607	60.3	13,582	68.7		7,323	60.6	13,866	68.3	
Take any medication at AV1										
No	2,774	22.0	4,123	20.9	.0122	2,579	21.3	4,318	21.3	.7942
Yes	9,715	77.0	15,480	78.3		9,378	77.6	15,817	77.9	
Interpersonal variables										
Social support ≥ 25										

	CaD 1st-year adherence ≥ 80%					CaD 2nd-year adherence ≥ 80%				
	No (*N* = 12,611)		Yes (*N* = 19,771)			No (*N* = 12,083)		Yes (*N* = 20,299)		
Characteristic	***n***	**%**	***n***	**%**	***p***	***n***	**%**	***n***	**%**	***p***
No	1,188	9.4	1,696	8.6	.0058	1,192	9.9	1,692	8.3	< .0001
Yes	11,104	88.1	17,686	89.5		10,598	87.7	18,192	89.6	
Social strain ≥ 5										
No	3,247	25.7	5,722	28.9	< .0001	3,027	25.1	5,942	29.3	< .0001
Yes	9,054	71.8	13,683	69.2		8,759	72.5	13,978	68.9	
Caregiving construct (0, 1 scoring)										
No	7,202	57.1	11,371	57.5	.7135	6,854	56.7	11,719	57.7	.1476
Yes	5,305	42.1	8,305	42.0		5,130	42.5	8,480	41.8	
Married or with partner vs. divorced, separated, widowed, or single										
No	4,787	38.0	6,942	35.1	< .0001	4,664	38.6	7,065	34.8	< .0001
Yes	7,760	61.5	12,759	64.5		7,362	60.9	13,157	64.8	
Procedural variables										
Had 4-week contact										
No	4,482	48.6	4,741	51.4	< .0001	4,274	46.3	4,949	53.7	< .0001
Yes	8,129	35.1	15,030	64.9		7,809	33.7	15,350	66.3	
CaD 1st-year pill type										
Chewable	6,611	52.4	8,532	43.2	< .0001	—	—	—	—	—
Mixed	2,358	18.7	2,814	14.2		—	—	—	—	
Swallowable	3,591	28.5	8,425	42.6		—	—	—	—	
CaD 2nd-year pill type										
Chewable	—	—	—	—	—	5,019	41.5	6,534	32.2	< .0001
Mixed	—	—	—	—		1,867	15.5	2,716	13.4	
Swallowable	—	—	—	—		5,053	41.8	11,049	54.4	
DM 1st-year adherence										
Not in DM trial	3,711	29.4	7,136	36.1	< .0001	3,506	29.0	7,341	36.2	< .0001
DM 1st-year adherence: energy from fat < 25%	6,897	54.7	9,339	47.2		6,607	54.7	9,629	47.4	
DM 1st-year adherence: energy from fat ≥ 25%	2,003	15.9	3,296	16.7		1,970	16.3	3,329	16.4	
HT 1st-year adherence										

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	CaD 1st-year adherence ≥ 80%					CaD 2nd-year adherence ≥ 80%				
	No (*N* = 12,611)		Yes (*N* = 19,771)			No (*N* = 12,083)		Yes (*N* = 20,299)		
Characteristic	***n***	**%**	***n***	**%**	***p***	***n***	**%**	***n***	**%**	***p***
Not in HT trial	7,821	62.0	10,022	50.7	< .0001	7,592	62.8	10,251	50.5	< .0001
HT 1st-year adherence < 80%	857	6.8	801	4.1		815	6.7	843	4.2	
HT 1st-year adherence ≥ 80%	3,933	31.2	8,948	45.3		3,676	30.4	9,205	45.3	
Bloating or gas										
No	4,240	33.6	7,111	36.0	< .0001	4,032	33.4	7,319	36.1	< .0001
Yes	8,345	66.2	12,627	63.9		8,022	66.4	12,950	63.8	
Constipation										
No	8,219	65.2	13,725	69.4	< .0001	7,844	64.9	14,100	69.5	< .0001
Yes	4,366	34.6	6,013	30.4		4,210	34.8	6,169	30.4	
Diarrhea										
No	9,377	74.4	14,870	75.2	.0938	8,941	74.0	15,306	75.4	.0071
Yes	3,208	25.4	4,868	24.6		3,113	25.8	4,963	24.4	
Nausea										
No	11,111	88.1	17,849	90.3	< .0001	10,597	87.7	18,363	90.5	< .0001
Yes	1,474	11.7	1,889	9.6		1,457	12.1	1,906	9.4	
Increasing appetite										
Missing	26	0.2	33	0.2	< .0001	29	0.2	30	0.1	< .0001
No	8,136	64.5	13,726	69.4		7,716	63.9	14,146	69.7	
Yes	4,449	35.3	6,012	30.4		4,338	35.9	6,123	30.2	
Decreasing appetite										
No	11,666	92.5	18,473	93.4	.0018	11,131	92.1	19,008	93.6	< .0001
Yes	919	7.3	1,265	6.4		923	7.6	1,261	6.2	
Heartburn										
No	7,685	60.9	12,701	64.2	< .0001	7,287	60.3	13,099	64.5	< .0001
Yes	4,900	38.9	7,037	35.6		4,767	39.5	7,170	35.3	
Upset stomach										
No	8,494	67.4	14,288	72.3	< .0001	8,126	67.3	14,656	72.2	< .0001
Yes	4,091	32.4	5,450	27.6		3,928	32.5	5,613	27.7	

Note. Percentages may not add to 100% due to round-off error or missing values. AV1 = annual visit 1; AV2 = annual visit 2; BMI = body mass index; CED-D/DIS = Center for Epidemiological Studies Depression Scale; CaD = calcium and vitamin D clinical trial; CVD = cardiovascular disease; DM = dietary modification; HT = hormone treatment; MET = metabolic equivalent; MI = myocardial infarction.

TABLE 3

CaD adherence at AV2 (1 Year Post-CaD Randomization), Initial Change Model

	Logistic regression model of CaD first-year adherence > 80%		
Effect	***p***	**Odds ratio**	**95% Confidence limits**
Sociodemographic variables			
Age group			
50–55 vs. 70–79	< .001	0.82	0.73–0.92
55–60 vs. 70–79	.438	0.96	0.87–1.06
60–65 vs. 70–79	.309	1.05	0.95–1.16
65–70 vs. 70–79	.021	1.12	1.02–1.24
Race or ethnicity			
African American vs. white	< .001	0.62	0.55–0.70
Hispanic vs. white	.052	0.84	0.71–1.00
Others or unknown vs. white	.091	0.86	0.72–1.03
College or higher vs. high school or less	.084	1.06	0.99–1.12
Had medical insurance			
Yes vs. no	.019	1.18	1.03–1.35
Married or with partner vs. divorced, separated, widowed, or single	< .001	1.12	1.06–1.20
Prior history of CVD			
Yes vs. no	.349	0.96	0.89–1.04
Prior history of cancer			
Yes vs. no	.495	1.05	0.91–1.21
Diabetes			
Yes vs. no	.019	1.17	1.03–1.33
High risk (≥ 4) of osteoporosis			
Yes vs. no	.652	0.98	0.92–1.06
Family history of breast cancer or colorectal cancer or MI			
Yes vs. no	.298	1.03	0.97–1.10
Shortened CES-D/DIS ≥ .06			
Yes vs. no	.013	0.88	0.80–0.97
Had > 3 life events			
Yes vs. no	.162	0.95	0.89–1.02
Emotion expressiveness > 3			
Yes vs. no	.031	0.88	0.79–0.99
Optimism ≥ 19			
Yes vs. no	.825	1.01	0.91–1.13
Hostility ≥ 8			
Yes vs. no	.521	0.97	0.88–1.07
On any special diet at baseline			
Yes vs. no	.976	1.00	0.94–1.06
Total expenditure from physical act ≥ 11			
Yes vs. no	.024	1.07	1.01–1.14

	Logistic regression model of CaD first-year adherence > 80%		
Effect	***p***	**Odds ratio**	**95% Confidence limits**
Current smoker vs. never or former smoker			
Yes vs. no	< .001	0.77	0.69–0.86
Current drinker vs. past or nondrinker			
Yes vs. no	.06	0.94	0.88–1.00
Take any supplement at AV1			
Yes vs. no	< .001	1.24	1.16–1.33
Taking any medication at AV1			
Yes vs. no	.231	1.05	0.97–1.13
Take calcium supplement at AV1			
Yes vs. no	< .001	1.17	1.08–1.27
Psychosocial variables			
Social support ≥ 25			
Yes vs. no	.81	0.99	0.89–1.10
Social strain ≥ 5			
Yes vs. no	.617	0.98	0.92–1.05
Caregiving burden			
Yes vs. no	.552	1.02	0.96–1.08
Treatment factors			
Total number of GI symptoms at baseline			
1 vs. none	.003	0.89	0.82–0.96
2 vs. none	< .001	0.78	0.72–0.85
3 vs. none	< .001	0.76	0.68–0.84
Had 4-week contact			
Yes vs. no	< .001	1.37	1.27–1.48
Contact type 6 months after CaD randomization			
Visit vs. phone or mail	< .001	2.09	1.92–2.27
CaD 1st-year pill type			
Chew vs. swallow	< .001	0.72	0.67–0.77
Mix vs. swallow	< .001	0.49	0.45–0.53
1st-year DM adherence			
Adherent in DM vs. not in DM	.004	1.17	1.05–1.31
Not adherent in DM vs. not in DM	.707	1.02	0.93–1.11
1st-year HT adherence			
< 80% vs. not in HT	.06	0.87	0.75–1.01
≥ 80% vs. not in HT	< .001	1.66	1.53–1.81
Change clinic from CaD randomization to CaD1			
Yes vs. no	.17	0.69	0.40–1.18

Note. Max-rescaled R^2 = 0.11; AV1 = annual visit 1; C statistics = 0.670; Hosmer-Lemeshow goodnessof-fit test p = .3118. BMI = body mass index; CED-D/DIS = Center for Epidemiological Studies Depression Scale; CaD = calcium and vitamin D clinical trial; CVD = cardiovascular disease; DM = dietary modification; HT = hormone treatment.