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Calcium Plus Vitamin D Supplementation and the Risk of Postmenopausal Weight Gain

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Background: Obesity in the United States has increased significantly during the past several decades. The role of calcium in the maintenance of a healthy body weight remains controversial.

Methods: A randomized, double-blinded, placebo-controlled trial was performed with 36 282 postmenopausal women, aged 50 to 79 years, who were already enrolled in the dietary modification and/or hormone therapy arms of the Women's Health Initiative clinical trial. Women were randomized at their first or second annual visit to receive a dose of 1000 mg of elemental calcium plus 400 IU of cholecalciferol (vitamin D) or placebo daily. Change in body weight was ascertained annually for an average of 7 years.

Results: Women receiving calcium plus cholecalciferol supplements vs women receiving placebo had a minimal but consistent favorable difference in weight change (mean difference, –0.13 kg; 95% confidence interval, –0.21 to –0.05; $P = .001$). After 3 years of follow-up, women with daily calcium intakes less than 1200 mg at baseline who were randomized to supplements were 11% less likely to experience small weight gains (1-3 kg) and 11% less likely to gain more moderate amounts of weight (>3 kg) (P for interaction for baseline calcium intake = .008).

Conclusion: Calcium plus cholecalciferol supplementation has a small effect on the prevention of weight gain, which was observed primarily in women who reported inadequate calcium intakes.

Trial Registration: clinicaltrials.gov Identifier: NCT00000611

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The Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System[1] reported that the proportion of women between the ages of 50 and 79 years who are obese (body mass index [BMI; calculated as weight in kilograms divided by the square of height in meters] >30) increased by nearly 50% during the 1990s; however, more recent reports show rates beginning to stabilize.[2] During a 3-year follow-up period in a cohort of 3302 middle-aged women, the Study of Women's Health Across the Nation[3] found that the mean weight and waist circumference gains were 2.1 kg and 2.2 cm, respectively. Other cohort studies[4,5] have previously reported similar findings in perimenopausal and postmenopausal women. Age-related changes in body composition, metabolic factors, and hormone levels, accompanied by declines in physical activity, may provide the underlying mechanisms for the propensity toward postmenopausal gains in fat mass and replacement of lean tissue with adipose tissue.[4,6-8] Because weight loss or prevention of weight gain is likely to have significant health benefits for middle-aged women,[9,10] early to middle menopause may be a critical period of life in which to slow the trajectory of weight gain.

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Some evidence exists that calcium and vitamin D and foods rich in these nutrients may have a role in effective weight management. The biological rationale comes from the observation that calcium and 1,25-hydroxyvitamin D work in concert to regulate lipid metabolism in adipose cells,[11,12] particularly by stimulating fatty acid oxidation and suppressing lipogenesis. Additionally, calcium may decrease fatty acid absorption through the formation of calcium and fatty acid "soaps" in the intestine and increase fecal fat losses.[8,12-14] Studies[11,15-18] in humans offer suggestive, but not definitive,[19] data to support these mechanisms, and a recent report[20] specifically supports the role of calcium supplements in reducing weight gain

among women approaching midlife. The scant published data from intervention trials are also inconclusive[21]; some suggest no relationship,[22,23] whereas others suggest a role for these nutrients in weight management.[8,24,25] Data from large randomized trials such as the Women's Health Initiative (WHI) (see boxed copy on page 901) offer an excellent opportunity to test the hypothesis that calcium and vitamin D are associated with attenuation of weight gain in postmenopausal women.

METHODS

STUDY POPULATION

Between October 29, 1993, and October 11, 1998, women were recruited into the WHI randomized trials that assessed the risks and benefits of hormone therapy (HT) and dietary modification (DM). Eligible women were aged 50 to 79 years and were postmenopausal. One year later, 36 282 of these participants were recruited into a calcium plus cholecalciferol (vitamin D) randomized trial, which was designed to test whether calcium plus cholecalciferol supplementation would reduce the incidence of hip fracture and colorectal cancer. Detailed eligibility criteria and recruitment methods have previously been published.[26] Personal use of calcium (up to 1000 mg/d) and cholecalciferol (up to 600 IU/d and, after 1999, up to 1000 IU/d) was allowed. Among the total participants enrolled in the calcium plus cholecalciferol randomized trial, 91.15% joined at their first annual visit and 8.85% joined the following year. Among the trial participants, 44.34% were in the HT trial, 69.48% were in the DM trial, and 13.83% participated in both trials. The protocol and consent forms were approved by the institutional review boards at participating institutions.

RANDOMIZATION, BLINDING, INTERVENTION, AND FOLLOW-UP PROCEDURES

Eligible women were randomly assigned in a double-blind fashion to supplement or placebo (provided by GlaxoSmithKline, Pittsburgh, Pa) in equal proportions using a permuted block algorithm stratified by clinical center and age. Each active tablet contained 500 mg of elemental calcium (as calcium carbonate) and 200 IU of cholecalciferol. Participants were instructed to take 2 tablets per day in divided doses with meals to maximize absorption. Two years after randomization, cross-sectional comparison of serum concentrations of 25-hydroxyvitamin D from 227 women taking active supplements and 221 women taking placebo revealed a statistically significant 28% higher serum concentration of 25-hydroxyvitamin D in women assigned to the active calcium plus cholecalciferol group compared with those randomized to the placebo group.

Telephone contact was made 4 weeks after calcium plus cholecalciferol randomization and thereafter semiannually to assess participant symptoms and reinforce adherence. Adherence was assessed by weighing returned pill bottles at annual clinic visits. Follow-up continued regardless of adherence to the protocol until death, loss to follow-up, participant request for no further contact, or study closeout.

Throughout the trial, women with intolerable gastrointestinal tract symptoms were treated by reducing the number of times per day or days per week that study medication was taken without unblinding either the participant or the study staff. Use of study pills was discontinued after report of kidney stones, hypercalcemia, dialysis, calcitriol use, or personal supplementation of more than 1000 IU/d of cholecalciferol, again without unblinding.

DATA COLLECTION

Prerandomization total daily calcium intake was the sum of dietary calcium assessed using the WHI food frequency questionnaire, an adaptation of the Block food frequency questionnaire,[27] plus calcium from supplements in the previous 2 weeks, plus calcium from prescription medications obtained through an interviewer-administered medication survey. Total vitamin D intake was similarly determined from diet and supplement use.

Weight and height were obtained in a standardized manner from all clinical trial participants at each annual visit. Weight was measured with the study participant in light clothing on a calibrated balance beam or digital scale and recorded to the nearest one-tenth kilogram.

STATISTICAL ANALYSIS

The primary outcome measure was weight change: annual weight measurements collected through 7 years of follow-up minus the most recent weight measured before calcium plus cholecalciferol randomization. All participants with at least 1 weight change measurement were included in the intent-to-treat analysis using linear repeated-measures regression modeling with an unstructured covariance matrix (SAS PROC MIXED version 9.1; SAS Institute Inc, Cary, NC). Plots of longitudinal data are based on fitted means from these models in which both treatment assignment and time are modeled as class variables and treatment effect is allowed to vary with time (saturated model). To assess whether the effect of calcium plus cholecalciferol supplementation on weight change varied according to baseline risk factors, including baseline calcium and vitamin D intakes, the same models were extended and formal tests of interactions were performed. To examine the effect of nonadherence (to the calcium plus cholecalciferol supplements or placebo), sensitivity analyses were conducted in which participants were censored after their first annual visit at which nonadherence, defined as the use of less than 80% of the study pills, was detected. The risk of weight gain during follow-up was examined by comparing those who gained weight (>1 kg) with a combined group that consisted of those who either lost weight or remained weight stable (within +1 kg) using generalized estimating equations with a logit link function and unstructured covariance matrix (SAS PROC GENMOD version 9.1; SAS Institute Inc). In a secondary analysis, we examined the prevention of weight gain during a 3-year period after randomization into the calcium plus cholecalciferol trial. Three years after baseline appeared to be the point at which this postmenopausal cohort transitioned from weight gain to weight loss as part of the natural weight trajectory of aging. Using nominal multinomial logistic regression modeling, we estimated the odds ratios (ORs) and their 95% confidence intervals (CIs) of gaining small amounts of weight (1-3 kg) or moderate amounts of weight (>3 kg) compared with remaining weight stable (+1 kg) or losing weight (>1 kg) during this 3-year period.

RESULTS

BASELINE CHARACTERISTICS, ADHERENCE, AND RETENTION

At randomization, 18 176 women were assigned to the active calcium plus cholecalciferol supplementation and 18 106 to placebo. Baseline, demographic, medical, and lifestyle characteristics, including calcium intakes, and randomization into the HT and DM trials were similar between groups (**Table 1**). Mean (SD) follow-up time

Table 1. Characteristics of the 36 282 Participants in the Calcium With Cholecalciferol (Vitamin D) Trial at the Time of the Women's Health Initiative Screening, According to Randomly Assigned Group

Characteristic	Treatment Assignment: Calcium and Cholecalciferol	Treatment Assignment: Placebo	*P* Value
	No. (%)	No. (%)	
Age group at screening, y			.99*
50-54	2592 (14.26)	2561 (14.14)	
55-59	4134 (22.74)	4135 (22.84)	
60-69	8276 (45.53)	8243 (45.53)	
70-79	3174 (17.46)	3167 (17.49)	
Ethnicity			.45*
White	15 047 (82.78)	15 106 (83.43)	
Black	1682 (9.25)	1635 (9.03)	
Hispanic	789 (4.34)	718 (3.97)	
American Indian	77 (0.42)	72 (0.40)	
Asian/Pacific Islander	369 (2.03)	353 (1.95)	
Unknown	212 (1.17)	222 (1.23)	
Educational level			.94*
≤High school	4286 (23.74)	4289 (23.84)	
School after high school†	7216 (39.96)	7156 (39.78)	
≥College degree	6555 (36.30)	6543 (36.37)	
BMI			.26*
<25	4974 (27.61)	5117 (28.51)	
25 to <30	6409 (35.57)	6327 (35.26)	
30 to <35	4037 (22.41)	3992 (22.24)	
≥35	2621 (14.41)	2539 (13.99)	
Smoking			.31*
Never	9325 (51.85)	9428 (52.62)	
Past	7255 (40.34)	7133 (39.81)	
Current	1405 (7.81)	1356 (7.57)	
Multivitamin use, with or without minerals	6419 (35.32)	6508 (35.94)	.21*
Total calcium intake (dietary and supplements), mg			.31*
<600	3554 (19.94)	3447 (19.42)	
600 to <1200	7265 (40.77)	7211 (40.62)	
≥1200	7002 (39.29)	7095 (39.97)	
Diet modification trial assignment			.30*
Comparison	7827 (43.06)	7738 (42.74)	
Intervention	4767 (26.23)	4878 (26.94)	
Not randomized	5582 (30.71)	5490 (30.32)	
Hormone therapy trial assignment			.80*
CEE active	1531 (8.42)	1543 (8.52)	
CEE placebo	1540 (8.47)	1562 (8.63)	
CEE and MPA active	2508 (13.80)	2535 (14.00)	
CEE and MPA placebo	2475 (13.62)	2395 (13.23)	
Not randomized	10 122 (55.69)	10 071 (55.62)	
	Mean (SD)	Mean (SD)	
Waist, cm	88.9 (13.7) [n = 18 128]	88.8 (13.7) [n = 18 051]	.46§
Weight, kg‡	76.0 (16.9) [n = 18 129]	75.9 (17.1) [n = 18 055]	.53§
BMI‡	28.9 (6.0) [n = 18 016]	28.8 (6.0) [n = 17 946]	.12§
Physical activity, METs/wk	10.7 (12.7) [n = 16 546]	10.6 (12.4) [n = 16 448]	.60§
Dietary energy, kcal	1735 (752) [n = 18 126]	1738 (732) [n = 18 042]	.75§
Dietary protein, g	72 (33) [n = 18 126]	72 (32) [n = 18 042]	.88§
Dietary total carbohydrate, g	202 (87) [n = 18 126]	203 (87) [n = 18 042]	.45§
Dietary total fat, g	70 (38) [n = 18 126]	70 (36) [n = 18 042]	.96§
Calories from fat, %	36 (7) [n = 18 126]	36 (7) [n = 18 042]	.52§
Dairy, medium servings per day	2 (1) [n = 17 821]	2 (1) [n = 17 753]	.96§
Total calcium intake (supplements and dietary), mg	1148 (654) [n = 17 821]	1154 (658) [n = 17 753]	.40§
Total cholecalciferol (supplements and dietary), μg	9 (7) [n = 17 821]	9 (7) [n = 17 753]	.36§
Fruits and vegetables, medium servings per day	4 (2) [n = 17 821]	4 (2) [n = 17 753]	.33§

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate; METs, metabolic equivalents.

*From a χ^2 test of association.

†Includes vocational or training school after high school graduation or some college or associate's degree.

‡For weight and BMI, we present measurements at randomization into the calcium and cholecalciferol trial.

§From a 2-sample *t* test.

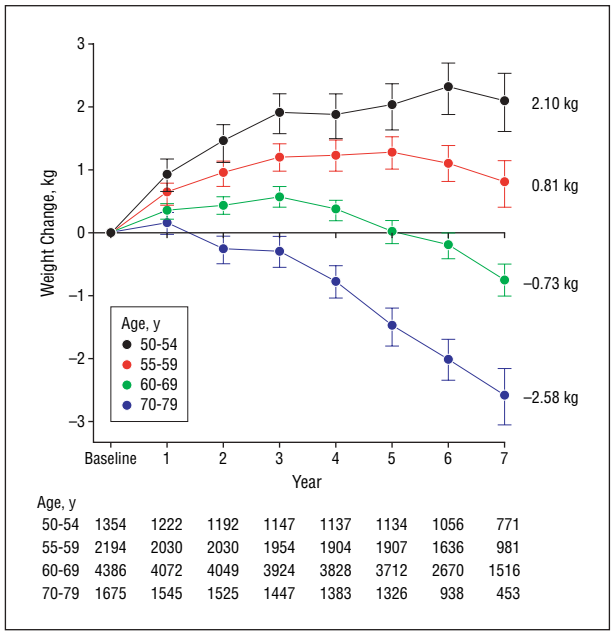

Figure 1. Weight change by age for all 3 trials for participants who were either randomized to placebo or not randomized.

was 7.0 (1.4) years. At screening for the WHI, the mean (SD) age was 62.4 (6.9) years, and mean (SD) BMI was 29.0 (5.9). At baseline, 39.63% of the women met the current recommended daily intake (RDI) of 1200 mg/d of calcium from supplements and diet combined, 53.94% reported any personal calcium supplementation, and 28.95% reported calcium supplementation of 500 mg or more. Of the women randomized into the calcium plus cholecalciferol trial, 26.58% had been randomly assigned to the low-fat intervention arm of the DM trial.

At the termination of the trial, 1551 participants (4.27%) had died and 2.70% had withdrawn or been lost to follow-up. In year 1, the proportion consuming 80% or more of the study medication was 60.46% overall and remained relatively stable through year 7, ranging from 55.73% to 62.87%, with small differences between treatment groups. At least 66.18% took 50% or more of their study medications through year 7.

WEIGHT CHANGE DURING THE POSTMENOPAUSAL YEARS

Figure 1 demonstrates the variation by age in the natural trajectory of weight change during the 7-year follow-up period. Postmenopausal women experience slow but steady gains until approximately 60 years of age, at which time they begin to stabilize for a period. They then start to lose weight, beginning in their middle to late 60s, and continue to lose weight throughout their seventh decade. The youngest postmenopausal women (aged 50-54 years) experienced the largest mean weight gain (2.10 kg) and were the only group to experience continuous weight gain throughout the entire follow-up period. In contrast, the oldest women (aged 70-79 years) were the only age group to experience a continuous decrease in weight and experienced the largest overall weight change of any age group, with an average loss of 2.58 kg. The data presented in Figure 1 are from those women randomized to the placebo arm of any WHI clinical trial intervention (HT, DM, or calcium plus cholecalciferol) and thus are free of any WHI-designed interventions that might modify weight.

WEIGHT CHANGE BY CALCIUM PLUS CHOLECALCIFEROL STATUS

Women randomized to the calcium plus cholecalciferol supplements had smaller average annual weight gains than women assigned to placebo (**Table 2** and **Figure 2**A). The small difference between treatment assignments at the first year did not appear to increase linearly with time ($P=.99$). The mean difference between the treatment groups, all in favor of calcium plus cholecalciferol, was −0.13 kg ($P=.001$). Women who were the most adherent (consuming >80% of their pills during follow-up) had a mean difference of −0.14 kg of weight change ($P<.001$). Women who entered the trial with intakes of calcium lower than the current RDI (<1200 mg) had a mean difference between treatment groups of −0.19 kg (Figure 2B), whereas no significant benefit was seen for women whose initial calcium intakes were at or greater than the RDI (>1200 mg) (P for interaction = .09). When calcium intakes lower than the RDI were divided further into quartiles, no evidence was found that the effect of the intervention was more pronounced in those who reported more marginal intakes (data not shown). Women who were heavier also tended to have a slightly higher benefit (P for interaction = .04). Treatment effects did not vary by age or any of the other 12 subgroups of baseline characteristics tested (Table 2).

PREVENTION OF WEIGHT GAIN

At 3 years after randomization, compared with women taking placebo, women randomized to the active intervention had a lower risk of gaining weight in both small amounts (1-3 kg) (OR, 0.95; 95% CI, 0.90-1.01) and moderate amounts (>3 kg) (OR, 0.94; 95% CI, 0.90-0.99) and a higher likelihood of remaining stable (+1 kg) or losing weight (>1 kg) (**Table 3**). Results were similar for the risk of weight gain during the entire 7-year trial (OR, 0.96; 95% CI, 0.93-0.99; $P=.005$ for >1-kg gain vs weight stable or weight loss).

Treatment effects were primarily seen in women who at baseline had calcium intakes less than 1200 mg; those women had an 11% lower risk of gaining 1 to 3 kg (OR, 0.89; 95% CI, 0.83-0.96) and an 11% lower risk of gaining more than 3 kg (OR, 0.89; 95% CI, 0.84-0.95), whereas women whose intakes were greater than 1200 mg/d were unaffected by treatment (P for interaction = .008). Further dividing women who reported intakes lower than the RDI did not demonstrate a more pronounced treatment effect for women with more marginal intakes (data not shown). No other interactions were observed (Table 3).

COMMENT

We found significantly smaller, albeit modest, weight increases and a significantly lower risk of weight gain in

Table 2. Mean Difference in Weight Change During Follow-up: Overall and by Baseline Subgroups

Variable	Mean Difference (Range)	*P* Value*
Overall effect of calcium and cholecalciferol	−0.13 (−0.21 to −0.05)	.001†
Age at screening, y		.98
50-54	−0.24 (−0.45 to −0.03)	
55-59	−0.08 (−0.24 to 0.09)	
60-69	−0.15 (−0.27 to −0.03)	
70-79	−0.10 (−0.29 to 0.09)	
Ethnicity		.38
White	−0.13 (−0.22 to −0.04)	
Black	−0.32 (−0.59 to −0.06)	
Hispanic	−0.08 (−0.48 to 0.32)	
American Indian	−0.56 (−1.81 to 0.69)	
Asian/Pacific Islander	0.19 (−0.37 to 0.75)	
Unknown	0.33 (−0.40 to 1.07)	
Educational level		.45
≤High school	−0.13 (−0.30 to 0.03)	
School after high school‡	−0.08 (−0.21 to 0.05)	
≥College degree	−0.20 (−0.33 to −0.07)	
BMI		.04
<25	−0.08 (−0.23 to 0.06)	
25 to <30	−0.09 (−0.22 to 0.04)	
30 to <35	−0.23 (−0.40 to −0.06)	
≥35	−0.17 (−0.38 to 0.04)	
Waist circumference, cm		.96
≤88	−0.16 (−0.27 to −0.05)	
>88	−0.12 (−0.23 to 0.00)	
Total calcium intake (dietary and supplements), mg		.09
<1200	−0.19 (−0.29 to −0.09)	
≥1200	−0.05 (−0.17 to 0.08)	
Total cholecalciferol intake (diet and supplements), IU		.37
<400	−0.16 (−0.27 to −0.06)	
≥400	−0.09 (−0.21 to 0.03)	
Energy intake, kcal		.13
<1382.1	−0.17 (−0.31 to −0.03)	
1382.1-1909.5	−0.17 (−0.31 to −0.03)	
>1909.5	−0.06 (−0.20 to 0.08)	
Energy from fat, %		.90
<33.5	−0.11 (−0.25 to 0.03)	
33.5-38.5	−0.09 (−0.23 to 0.05)	
>38.5	−0.20 (−0.34 to −0.06)	
Fruits and vegetables, medium servings per day		.90
<2.7	−0.13 (−0.27 to 0.01)	
2.7-4.3	−0.14 (−0.28 to 0.00)	
>4.3	−0.15 (−0.29 to −0.01)	
Smoking		.21
Never	−0.17 (−0.28 to −0.06)	
Past	−0.07 (−0.20 to 0.05)	
Current	−0.34 (−0.63 to −0.04)	
Physical activity, METs/wk		.82
<3	−0.16 (−0.30 to −0.01)	
3-11.75	−0.14 (−0.29 to 0.00)	
>11.75	−0.11 (−0.26 to 0.03)	
DM arm§		.60
Control	−0.12 (−0.24 to 0.00)	
Intervention	−0.07 (−0.22 to 0.09)	
HT arm‖		.42
E alone	−0.33 (−0.62 to −0.05)	
E alone placebo	−0.03 (−0.31 to 0.25)	
E and P	−0.14 (−0.36 to 0.08)	
E and P placebo	−0.26 (−0.49 to −0.04)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DM, dietary modification; E, estrogen; HT, hormone therapy; METs, metabolic equivalents; P, progesterone.

*F test of interaction between calcium and cholecalciferol treatment and variable of interest from a linear repeated-measures model with an unstructured correlation matrix.

†F test of main effect of calcium and cholecalciferol treatment from a linear repeated-measures model with an unstructured correlation matrix.

‡Includes vocational or training school after high school graduation or some college or associate's degree.

§Subset (n = 25 210) of the calcium and cholecalciferol randomized trial; see Table 1 for details.

‖Subset (n = 16 089) of the calcium and cholecalciferol randomized trial; see Table 1 for details.

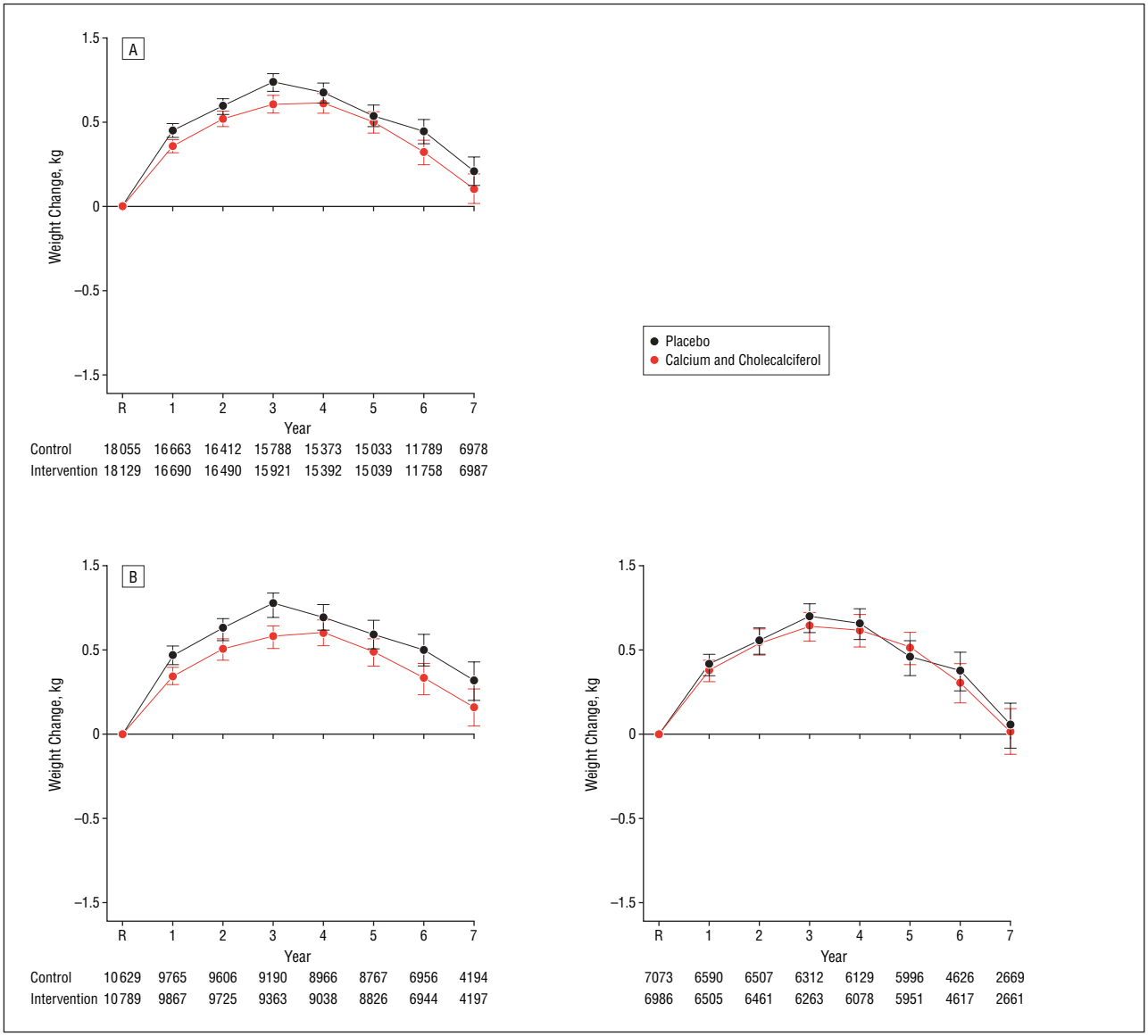

Figure 2. A, Weight change by treatment assignment; B, weight change by treatment assignment and total calcium intake of less than 1200 mg (left) and 1200 mg or more (right) at baseline. R indicates calcium plus cholecalciferol (vitamin D) randomization, which occurred 1 to 2 years after baseline.

women randomized to calcium plus cholecalciferol supplements compared with placebo in this large, double-blinded, placebo-controlled clinical trial. However, the effect was seen primarily for women whose total calcium intakes were lower than 1200 mg/d, the current RDI for women this age.

Our findings of calcium plus cholecalciferol for long-term weight maintenance support some[11,15-18,20,24] but not all[19] of the previous studies, suggesting an inverse association between calcium intake and body weight. The National Health and Nutrition Examination Survey III reported that, compared with adult women in the lowest quartile of calcium intake, those in the top quartile had an 85% reduced risk of obesity.[11] The Coronary Artery Risk Development in Young Adults study[18] reported that baseline dairy intake was inversely associated with BMI and that throughout the 10-year follow-up of this cohort, each daily serving of a dairy food was associated with a 21% reduced risk of the development of insulin resistance syndrome, a serious consequence of obesity. In contrast, a Norwegian cross-sectional study[15] reported a positive association of calcium with BMI for men and no association of calcium with BMI among women. Two more recent reports, one from the Health Professionals Follow-up Study,[19] showed no relationship between baseline or change in intake of calcium and weight change during a 12-year follow-up, whereas another from the Vitamins and Lifestyle cohort study[20] demonstrated that women who were currently taking individual calcium supplements had a lower mean 10-year weight gain than nonusers.

The limited experimental data in this area are inconclusive, with some studies[21-23] demonstrating that in adults calcium derived from either supplements or dairy products has no benefit, whereas other studies[8,24,25] suggest a positive role in weight management. However, many of these experimental studies are limited by small sample sizes or short study durations.

Table 3. Odds of Weight Gain (as Opposed to Weight Loss or Weight Stable) for 3 Years After Randomization Into the Calcium and Cholecalciferol (Vitamin D) Trial: Overall and by Subgroup

Variable	OR (95% CI)*		*P* Value†
	Weight Gain of 1-3 kg	Weight Gain of >3 kg	
Overall effect of calcium and cholecalciferol	0.95 (0.90-1.01)	0.94 (0.90-0.99)	.05‡
Age, y			.18
50-54	0.88 (0.75-1.03)	0.92 (0.81-1.05)	
55-59	0.96 (0.85-1.09)	1.00 (0.90-1.10)	
60-69	0.97 (0.89-1.05)	0.94 (0.87-1.01)	
70-79	0.96 (0.84-1.10)	0.87 (0.76-0.99)	
Race			.52
White	0.96 (0.90-1.02)	0.94 (0.89-0.99)	
Black	0.95 (0.78-1.16)	0.92 (0.78-1.09)	
Hispanic	0.94 (0.70-1.27)	0.92 (0.72-1.19)	
Asian	0.89 (0.61-1.29)	0.82 (0.56-1.22)	
American Indian	0.65 (0.25-1.65)	0.74 (0.33-1.67)	
Unknown	1.10 (0.65-1.86)	1.85 (1.14-3.00)	
Educational level			.98
≤High school	0.97 (0.86-1.10)	0.96 (0.87-1.07)	
School after high school§	0.96 (0.87-1.05)	0.93 (0.86-1.01)	
≥College degree	0.95 (0.86-1.04)	0.95 (0.87-1.03)	
BMI			.27
<25	0.97 (0.88-1.08)	0.99 (0.90-1.09)	
25 to <30	0.98 (0.89-1.07)	0.93 (0.85-1.01)	
30 to <35	0.95 (0.83-1.08)	0.93 (0.84-1.04)	
≥35	0.88 (0.74-1.05)	0.88 (0.77-1.01)	
Waist circumference, cm			.93
≤88	0.93 (0.86-1.00)	0.93 (0.86-1.00)	
>88	0.99 (0.91-1.09)	0.96 (0.89-1.03)	
Total calcium intake (dietary and supplements), mg			.008
<1200	0.89 (0.83-0.96)	0.89 (0.84-0.95)	
≥1200	1.05 (0.96-1.15)	1.01 (0.93-1.10)	
Total cholecalciferol intake (dietary and supplements), IU			.41
<400	0.92 (0.85-0.99)	0.94 (0.88-1.00)	
≥400	0.99 (0.91-1.08)	0.94 (0.87-1.02)	
Energy intake, kcal			.59
<1382.1	0.92 (0.83-1.01)	0.93 (0.85-1.01)	
1382.1-1909.5	0.93 (0.85-1.03)	0.90 (0.83-0.99)	
>1909.5	1.00 (0.91-1.11)	0.99 (0.91-1.08)	
Energy from fat, %			.25
<33.5	0.88 (0.79-0.97)	0.95 (0.87-1.04)	
33.5-38.5	1.02 (0.92-1.13)	0.95 (0.86-1.03)	
>38.5	0.97 (0.87-1.07)	0.92 (0.84-1.00)	
Fruits and vegetables, medium servings per day			.70
<2.7	1.02 (0.92-1.13)	0.95 (0.87-1.04)	
2.7-4.3	0.87 (0.79-0.97)	0.90 (0.82-0.98)	
≥4.3	0.98 (0.88-1.08)	0.96 (0.88-1.05)	
Smoking status			.66
Never	0.93 (0.86-1.01)	0.95 (0.88-1.01)	
Past	0.98 (0.90-1.08)	0.95 (0.88-1.03)	
Current	0.90 (0.72-1.13)	0.84 (0.70-1.01)	
Physical activity, METs/wk			.49
<3	1.00 (0.90-1.12)	0.90 (0.82-0.99)	
3-11.75	0.89 (0.80-0.99)	0.93 (0.84-1.01)	
≥11.75	0.97 (0.88-1.07)	0.99 (0.90-1.08)	
DM arm‖			.34
Control	0.94 (0.87-1.03)	0.93 (0.86-1.01)	
Intervention	1.04 (0.92-1.16)	1.01 (0.91-1.11)	
HT arm¶			.34
E alone	0.94 (0.76-1.15)	0.89 (0.75-1.06)	
E alone placebo	0.81 (0.66-0.98)	0.83 (0.70-0.99)	
E and P	0.98 (0.84-1.14)	1.06 (0.92-1.21)	
E and P placebo	0.99 (0.85-1.16)	0.96 (0.84-1.11)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; DM, dietary modification; E, estrogen; HT, hormone therapy; METs, metabolic equivalents; OR, odds ratio; P, progesterone.

*Odds of gaining weight divided by odds of losing weight or remaining weight stable.

†χ^2 Test of interaction between calcium and cholecalciferol randomized treatment and variable of interest from a nominal generalized logistic regression model.

‡χ^2 Test of main effect of calcium and cholecalciferol randomized treatment from a nominal generalized logistic regression model.

§Includes vocational or training school after high school graduation or some college or associate's degree.

‖Subset (n = 25 210) of the calcium and cholecalciferol randomized trial; see Table 1 for details.

¶Subset (n = 16 089) of the calcium and cholecalciferol randomized trial; see Table 1 for details.

The small magnitude of the effect observed in this study has several possible explanations. The benefit of calcium on weight maintenance may, in fact, be small and detected in this trial only because of our large sample size. Others have also proposed that the benefit of calcium in the absence of an energy deficit is likely to be small. Heaney et al[28] summarized data from 9 studies of calcium intake in which body weight could be assessed as a secondary outcome, concluding that in middle-aged and older women a calcium intake difference of 300 mg/d (approximately 1 dairy serving) is associated with a decreased weight gain of 0.11 to 0.16 kg/y. Additionally, based on the observation that calcium affects fecal fat excretion in a dose-dependent fashion, Welberg et al[29] predicted that supplementation of 2 g/d of elemental calcium as calcium carbonate might result in a change of body weight of approximately -0.4 kg/y. In contrast to the conclusions from the studies cited herein, both of which are predictions based on studies of shorter durations, the effect observed in the WHI at year 1 was not cumulative during the 7 years of observation but appeared to peak by year 3 and then stabilize.

Alternatively, the relatively small effect observed in the WHI may have been because the source of calcium supplementation was from nondairy products. This finding is supported by several studies[13,30] that showed larger beneficial effects from calcium derived from consumption of dairy products compared with supplements. It is also possible that the effects of calcium may be enhanced under conditions of energy deficit, and larger differences between the intervention and control groups may have been seen if supplementation was accompanied by energy restriction or increased energy output. One recent study,[31] which demonstrated that a dairy-based high-calcium diet increased fat oxidation under conditions of acute energy deficit, proposed that the effects were due to an increase in exercise. In our data, we saw no interaction across baseline levels of physical activity or energy intakes.

This investigation has some notable limitations. First, the WHI obtained repeated measures of anthropometry (eg, dual-energy x-ray absorptiometry and waist circumference) only on a small subset of women; we were therefore unable to identify whether observed weight changes were due to changes in fat mass or other critical components of body composition. Second, we were unable to adequately examine whether the effect of the intervention varied by baseline vitamin D status, since we did not routinely conduct serum concentrations of 25-hydroxyvitamin D, the preferred measure of vitamin D status. Several studies[32-35] have demonstrated lower levels of 25-hydroxyvitamin D among obese compared with nonobese individuals, suggesting a possible role for vitamin D in weight. However, the strengths of this study are considerable. To our knowledge, this is the largest double-blind, placebo-controlled clinical trial to report the effects of calcium plus cholecalciferol supplementation on weight change. Our long study duration of 7 years allowed us to collect multiple weight measurements using a standardized protocol that enabled precise measures of weight change during the entire follow-up period. It also allowed us to see the true trajectory of weight change rather than the extrapolated magnitude of yearly weight change reported in previous studies of shorter durations. Moreover, the large sample size of women provided ample power to detect small differences in weight change, and the postmenopausal population allowed us to generalize to a group of women for whom slow but steady weight gain can be a common health concern.

In conclusion, even though the overall mean weight change difference between groups was small (–0.13 kg), women in the active intervention who had inadequate baseline dietary calcium had an 11% lower risk of weight gain during the first 3 years of the trial compared with women with calcium-deficient diets in the placebo group, a more compelling finding. Prevention of weight gain is an important public health goal, and caloric restriction and daily physical activity should still be considered the basic tenets of weight management. Further research should be undertaken to address the effect of calcium supplementation combined with caloric restriction and physical activity on weight gain prevention. Our findings do not alter current dietary recommendations. Postmenopausal women should continue to be advised to consume 1200 mg/d of calcium as recommended by of the Food and Nutrition Board of the National Academy of Sciences.[36]

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