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Effects of Calcium, Vitamin D, and Hormone Therapy on Cardiovascular Disease Risk Factors in the Women's Health Initiative: A Randomized Controlled Trial

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Abstract

Objective—To analyze the treatment effect of calcium + Vitamin D supplementation, hormone therapy, both, and neither on cardiovascular disease risk factors.

Methods—We conducted a prospective, randomized, double-blind, placebo controlled trial among Women's Health Initiative participants. The predefined primary outcome was low-density lipoprotein cholesterol (LDL-C).

Results—Between September 1993 to October 1998, a total of 68,132 women aged 50-79 were recruited and randomized to the WHI-Dietary Modification (WHI-DM) (n=48,835) and WHI-Hormone Therapy (WHI-HT) trials (n=27,347). Subsequently, 36,282 women from WHI-HT (16,089) and WHI-DM (n=25,210) trials were randomized in the WHI-calcium + Vitamin D (WHI-CaD) trial to 1,000 mg of elemental calcium carbonate plus 400 IU of vitamin D3 daily or placebo. Our study group included 1,521 women who participated in both the HT and CaD trials and were in the 6% subsample of trial participants with blood sample collections at baseline and years 1, 3, and 6. The average treatment effect with 95% confidence interval, for LDL-C, compared to placebo, was -1.6 (95th CI -5.5, 2.2) mg/dL for calcium + Vitamin D-alone, -9.0 (95th CI, -13.0, -5.1) mg/dL for hormone therapy alone, and -13.8 (95th CI, -17.8, -9.8) mg/dL for the combination. There was no evidence of a synergistic effect of calcium + Vitamin D + hormone therapy on LDL-C (p-value for interaction (p-int) = 0.26) except in those with low total intakes of vitamin D, for whom there was a significant synergistic effect on LDL (p-int = 0.03).

Conclusion—Reductions in LDL-C were greater among women randomized to both calcium + Vitamin D and hormone therapy than for those randomized to either intervention alone or to placebo. The treatment effect observed in the calcium + Vitamin D + hormone therapy combination group may be additive rather than synergistic. For clinicians and patients deciding to begin calcium + Vitamin D supplementation, current use of hormone therapy should not influence that decision.

INTRODUCTION

Whether hormone therapy and vitamin D (or calcium + vitamin D) has a synergistic relationship on the cardiovascular system in women has gained traction in clinical trials and basic science research¹⁻³. A recent study suggested that menopausal monkeys taking daily oral estrogen and who had greater percent plasma 25OHD₃ increases over the course of the study had the least severe cardiovascular disease and greater coronary artery remodeling, compared to those not taking estrogen with lower plasma 25OHD₃ concentrations³. Daily use of 1.25 mg conjugated equine estrogen has been shown to increase the biologically active form of vitamin D (1,25(OH)₂D) and vitamin D carrier protein in menopausal women⁴. In ovariectomized rats, estrogen up-regulates the expression of the vitamin D

receptors in the small intestine⁵. An analysis from the Women's Health Initiative (WHI) reported a statistically significant reduction (a synergistic effect) in the risk of hip fracture attributed to hormone therapy among participants randomized to calcium plus vitamin D, compared to WHI-HT trial participants that were randomized to hormone therapy and placebo¹.

Because women in the WHI were receiving both vitamin D + calcium, this trial offers an ideal opportunity to study whether there is a synergistic effect on cardiovascular disease risk factors in menopausal women with calcium + vitamin D as well as hormone therapy. The WHI Calcium + vitamin D/ trials were double-blinded, randomized, placebo-controlled studies analyzing multiple health outcomes in menopausal women. In the calcium + vitamin D trial, low-density lipoprotein cholesterol (LDL-C) was significantly reduced for women randomized to calcium + vitamin D⁶, and for the WHI-HT trials, both estrogen plus progestin and estrogen alone also significantly reduced LDL-C^{7,8}. Moreover, both hormone therapy preparations had statistically significant favorable effects on high-density lipoprotein cholesterol (HDL-C), glucose and waist circumference, but significantly unfavorable effects on triglycerides and systolic blood pressure^{7,8}.

We measured changes in our primary outcome (LDL-C) as well as our secondary outcomes (multiple cardiovascular disease risk factors) in 4 groups of women randomly assigned to different therapeutic combinations: Calcium + vitamin D alone, hormone therapy alone, both hormone therapy and calcium + vitamin D, and neither hormone therapy nor calcium + vitamin D. The study hypothesis is that a statistically significant interaction exists between hormone therapy and calcium + Vitamin D in terms of the effect on primary study endpoints, LDL-C, as well as secondary outcomes including other cardiovascular risk factors. Conceptually, a significant interaction means that we observed a larger benefit among women randomized to both Calcium + Vitamin D and hormone therapy, than the benefit observed among women randomized to only hormone therapy, plus the benefit observed among women randomized to only Calcium + Vitamin D. In other words, a significant interaction corresponds to a synergistic rather than an additive effect relative to the placebo group.

MATERIALS AND METHODS

The WHI clinical trials were designed to evaluate the risks and benefits of dietary modification (DM), hormone therapy, and supplementation with calcium + Vitamin D. The protocol and consent forms were approved by the institutional review boards for all participating institutions (see Acknowledgements in Appendix 1 online at <http://links.lww.com/xxx>).

Like previously published secondary analyses⁹, the WHI-HT trials data was combined to improve statistical power, and further justified because both WHI arms had the same qualitative effects on the measured cardiovascular disease risk factors. These results can apply to a population similar to those enrolled in the WHI HT trials; 40% without a uterus taking estrogen therapy or placebo, and 60% with an intact uterus taking estrogen and progestogen therapy or placebo. The WHI is the largest cohort (N=16,089) randomized to

both hormone therapies (active or placebo) and calcium + Vitamin D (active or placebo)¹, from whom blood data was collected on 1,521 participants. Since we are using preexisting data, power calculations were not performed^{10,11}.

A total of 68,132 women aged 50-79 were recruited between September 1993 to October 1998 and were randomly assigned into the WHI-DM trial, WHI-HT trials, or both. A total of 27,347 women in the two parallel WHI-HT trials were randomized to 0.625 mg of conjugated equine estrogen alone or placebo among women that had a hysterectomy, or 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate) or placebo taken daily among women that had not had a hysterectomy. A total of 48,835 women in the WHI-DM trial were randomized to a dietary modification intervention (dietary modification to lower total fat intake; n = 19,541) or Comparison (usual diet; n = 29,294) group. At the first or second annual visit, 36,282 eligible women from WHI-HT (16,089) and WHI-DM (n=25,210) trials were randomized further to calcium + Vitamin D (1,000 mg of elemental calcium [carbonate] plus 400 IU of vitamin D3 daily supplementation [n=18,176]) or placebo (n=18,106)), with 14% (n=5017) of participants in both the DM and Hormone Therapy trials. The eligibility criteria to be enrolled in the calcium + Vitamin D trial included many safety parameters (e.g., no previous hypercalcemia or renal calculi) and no competing risk indicators (e.g., no medical condition associated with survival of less than three years). Eligibility for the WHI-HT trial included post-menopausal (as defined previously¹²) who were between 50 and 79 years at initial screening. Analysis included women that participated in both the calcium + Vitamin D trial and WHI-HT trial (either Estrogen and progestogen or Estrogen alone) and were also part of the 6% blood subsample, Figure 1 (n=1,521). Because the calcium + Vitamin D trial was initiated after 1 year of the WHI-HT, year 1 of the WHI-HT was considered as baseline for the calcium + Vitamin D trial. Lipids along with other cardiovascular risk factors (blood pressure, weight, waist circumference, waist-hip-ratio, glucose, insulin) were measured at baseline and years 1, 3, and 6 after randomization into the hormone therapy trials. The cardiovascular disease risk factors, which were measured after the estrogen plus progestin trial and the conjugated equine estrogen-alone trial stopped on July 7th 2002 and February 29th 2004, respectively, were censored. Details of biomarker analysis and laboratory methods have been published previously¹³.

Repeated measures models with an unstructured variance-covariance matrix were used to model longitudinal means. Per the randomized partial-factorial design, means were assumed to be equal at baseline for all four hormone therapy + randomization groups, and equal at year 1 from hormone therapy randomization for calcium + Vitamin D randomization groups; the latter is the calcium + Vitamin D 'baseline' measure. Constraining the 'baseline' means to be equal prior to randomization is the most efficient use of the data^{14,15}. To allow for parsimonious 1-degree-of-freedom estimates of treatment effects (treatment group minus placebo) and interactions (calcium + Vitamin D + Hormone Therapy), the post-randomization means at years 3 & 6 are averaged.

For the subgroup analysis, we analyzed whether particular subgroups may modify the calcium + Vitamin D + hormone therapy interaction on our main outcome variable, low-density lipoprotein cholesterol (LDL-C) (i.e., whether a synergistic effect of calcium +

Vitamin D + hormone therapy might occur for particular subgroups). Statistical significance was based on a test of interaction. We looked at a total of 13 prespecified baseline subgroups, see Table 1. No adjustment for multiple testing was made; at most, one interaction was expected to be significant by chance alone. The cut points for total vitamin D intake and total calcium were also chosen a-priori. The lower cut point was suggested previously¹ where the effect of hormone therapy appeared to be null for values of total vitamin D below 200 IU and calcium below 800 mg.

To address the skewed distributions of triglycerides, glucose, insulin, and waist-hip-ratio log-transformation was used, and geometric means are reported. Statistical significance of synergistic effect was based on tests of interaction. A significant interaction corresponds to a synergistic rather than an additive effect relative to the placebo group. To graphically show the presence of an additive or synergistic effect between calcium + Vitamin D and hormone therapy across all cardiovascular disease biomarkers, Z-scores (treatment effect divided by standard error) are shown. All analyses were done with SAS version 9.4 and figures were drawn with R 3.1. All p values are two-sided and p values ≤ 0.05 were regarded as significant.

Results

Baseline characteristics were similarly distributed by treatment groups (Table 2). The effects of calcium + Vitamin D + hormone therapy, on all of the cardiovascular disease risk factors except insulin, were larger in magnitude, and in the same direction, as the effects of hormone therapy alone, regardless of the size or direction of the calcium + Vitamin D effect. In other words, the addition of calcium + Vitamin D enhanced the effects of hormone therapy, either in a positive or a negative direction. However, none of the hormone therapy + calcium + Vitamin D interactions were statistically significant (Figure 2), therefore did not provide statistical evidence for the synergistic effects of hormone therapy + calcium + Vitamin D. For example, although hormone therapy + calcium + Vitamin D had a stronger effect on LDL-C compared to either hormone therapy alone or calcium + Vitamin D alone, the observed effects were additive ($p\text{-int} = 0.26$). Estimates for the primary analysis were precise; the 95% CI for mean LDL-C in all four treatment groups was $\pm 3\text{mg/dL}$. The effects on LDL-C (active minus placebo) were -1.6 ($-5.5, 2.2$) mg/dL for calcium + Vitamin D-alone, -9.0 ($-13.0, -5.1$) mg/dL for hormone therapy alone, and -13.8 ($-17.8, -9.8$) mg/dL for calcium + Vitamin D + hormone therapy (Figure 3). Appendix 2, available online at <http://links.lww.com/xxx>, displays the profile-means for our primary endpoint, LDL-C- by randomization groups during the study. To investigate the influence of temporal trends, we limited post-randomization follow-up to year 3, and observed a similar pattern ($p\text{-int} = 0.44$); the treatment effects on LDL-C for this sensitivity analysis were -1.5 ($-5.1, 2.2$) mg/dL for calcium + Vitamin D-alone, -13.9 . ($-17.8, -10.1$) mg/dL for hormone therapy alone, and -17.4 ($-21.2, -13.6$) mg/dL for calcium + Vitamin D + hormone therapy. Lastly, a sensitivity analysis was conducted to account for compliance to study pills. Specifically, LDL-C measurements that occurred after a participant became non-adherent (took $< 80\%$ of study pills) were censored. Resulting model estimates produced a similar additive pattern without any evidence for a synergistic effect ($p\text{-interaction} = 0.66$).

A sensitivity analysis was conducted to determine whether the calcium + Vitamin D + hormone therapy interaction depended on hormone therapy preparation by testing the three-way interaction calcium + Vitamin D + hormone therapy x cohort (estrogen plus progestagen vs. estrogen therapy alone). As expected, none of the three-way interactions provided statistical evidence against pooling the hormone therapy trials for any of the cardiovascular disease risk factors; all p-values > 0.30. The effect of hormone therapy (active vs. placebo) on LDL-C from baseline to year 1 was -16.8(-20.4, -13.2) and -18.4(-21.5-15.3) mg/dL among estrogen therapy and estrogen + progestagen therapy participants, respectively.

Calcium and vitamin D + hormone therapy had a synergistic effect on LDL-C at low total intakes (dietary and supplements) of vitamin D (p-int = 0.03). In addition, the effect of hormone therapy-alone was more attenuated at lower levels of vitamin D intake. Calcium and vitamin D + hormone therapy had an additive (p-int = 0.06) effect at low intakes of calcium (Figure 3) and calcium + Vitamin D + hormone therapy had a synergistic effect (p-int=0.007) among hypertensive women (self-reported of treatment for hypertension or recorded blood pressure \geq 140/90 mm Hg). The effect of calcium + Vitamin D + hormone therapy did not vary with age (p=0.59). An analysis of the 2 \times 2 factorial for the main effects of calcium + Vitamin D and hormone therapy, without a calcium + Vitamin D + hormone therapy interaction term, is presented in Appendix 3. As previously shown in the full cohort (7, Hsia 2007), calcium + Vitamin D has a favorable effect on LDL-C with a mean decrease of 3.2 mg/dL (CI; -5.9, -0.5). In addition, we demonstrated a favorable effect on total cholesterol with a mean decrease of 3.2 mg/dL (CI: -6.2, -0.3).

Discussion

While there are data to suggest calcium + Vitamin D has some beneficial effects on cardiovascular disease risk factors^{11,14,15}, this has not been well-established, and there is a paucity of prospective data regarding the effect of calcium + Vitamin D on cardiovascular disease outcomes^{16,17}. More recent data have suggested that estrogen therapy alone, in younger women closer to the time of menopause (the timing hypothesis) could have beneficial cardiovascular disease outcomes, particularly lower rates of myocardial infarction^{12,18-21}, but no significant reduction was observed with younger women randomized to estrogen plus progestogen therapy⁹. While highly controversial, some observational data have raised questions about the safety of high doses of calcium supplements and potential cardiovascular disease risks²², although the WHI calcium + Vitamin D trial did not⁶. Our findings suggest that calcium combined with vitamin D is not detrimental, at least in regard to most cardiovascular disease risk factors.

The well documented^{7, 23} beneficial effect that hormone therapy has on cholesterol parameters aside from triglyceride is felt to be moderate compared to other cholesterol lowering therapies. Hormone therapy has been shown to have beneficial effects on other cardiovascular disease risks as well, like glucose²⁴ and weight distribution²⁵, but has increased mean systolic blood pressure in both WHI-HT trials²⁶ and in other randomized clinical trials²⁷. It would be helpful to know if the effects of hormone therapy or other interventions with a moderate effect on cardiovascular disease risk, would be additive or

synergistic with calcium + Vitamin D. The data we present suggest an additive relationship with hormone therapy, which is modestly beneficial for some cardiovascular disease risk factors (e.g., LDL-C, HDL-C, total cholesterol, glucose, insulin, waist circumference, and the waist-hip-ratio), but modestly harmful for others (e.g., systolic and diastolic blood pressure, triglycerides), Figure 2.

In a similar study from this population, the effect of calcium + Vitamin D and hormone therapy on bone density was also additive¹. A synergistic effect was identified, however, when the effect of hormone therapy and calcium + Vitamin D was studied on the primary outcome, fracture¹. Hence, it is possible that calcium + Vitamin D and hormone therapy may have a synergistic effect for cardiovascular disease as a primary outcome. Calcium and vitamin D + hormone therapy has a greater effect on cardiovascular disease risk categories when compared with all other combinations. Moreover, for all endpoints except insulin, the effect of calcium + Vitamin D + hormone therapy and hormone therapy alone were in the same direction, but the magnitude of calcium + Vitamin D + hormone therapy was greater. Therefore, results suggest that the addition of calcium + Vitamin D supplementation to a hormone therapy regimen could enhance the effects of hormones. In contrast, for more than half of the endpoints, hormone therapy + calcium + Vitamin D and calcium + Vitamin D alone went in opposite directions, so the addition of hormone therapy may swamp the effect of Calcium and vitamin D supplementation, figure 2.

In the subgroup analysis of total vitamin D intake, the effect of hormone therapy-alone had an impressive decreasing effect on LDL-C as the intake of total vitamin D increased (CI: -3.2, -7.3, -12.2, -22.8), (p=0.03), implying a synergistic relationship (figure 3, Hormone Therapy-alone column for Vitamin D effect). Looking at the effect of hormone therapy + calcium + Vitamin D on LDL-C, the effect (CI: -10.7, -15.5, -20.1, -14.9); p=0.03, seems to progressively increase until the total vitamin D intake exceeds 600 IU (figure 3, hormone therapy + calcium + Vitamin D column for Vitamin D effect). This implies a threshold phenomenon where total vitamin D intake is more beneficial to hormone therapy and calcium + Vitamin D up to a certain point (or threshold). Based on the above findings, for women on estrogens and who have low intake of vitamin D, one should consider supplementation to lower LDL-C that may decrease the risk of heart disease.

A major strength of the study is the double-blinded, randomized, placebo-controlled design in a well-characterized population. Given the numbers and demographic diversity of this cohort, the findings should be generalizable to the U.S. population. This is a large study where women were randomized to calcium + Vitamin D, hormone therapy, or both with nearly 400 women in each arm. Several studies have suggested that vitamin D may have a therapeutic window phenomenon with detriment at the extremes and benefit at midlevel's^{28,29}. This may explain why hormone therapy and calcium + Vitamin D seemed to be synergistic at lower calcium + Vitamin D intakes. Limitations, therefore, include the 400IU of vitamin D, which is typically used to prevent rickets, but may be inadequate to lower LDL-C. Women were allowed to continue their own calcium supplements because it would have been unethical to prohibit concurrent calcium use in a long-term, placebo-controlled trial. Also, the supplement trial used a combination of calcium + Vitamin D so that the effects of either nutrient alone cannot be ascertained. We were not able to further

explore the observations, that calcium + Vitamin D + hormone therapy had a synergistic effect on LDL-C at low total intakes (dietary and supplements) of vitamin D and calcium, by correlating blood concentration of vitamin D and calcium with total intake, since only a small percentage of women had these serum markers measured.

In summary, with the exception of insulin, the absolute effect of calcium + Vitamin D and hormone therapy on cardiovascular disease risk factors was larger compared to hormone therapy alone or calcium + Vitamin D alone, including LDL-C our primary endpoint. For clinicians and most patients deciding to begin calcium + Vitamin D supplementation, current use of hormone therapy should not influence that decision. However, based on the above findings, for women on estrogens and who have low intake of vitamin D, one should consider calcium + Vitamin D supplementation to lower LDL-C that may decrease the risk of heart disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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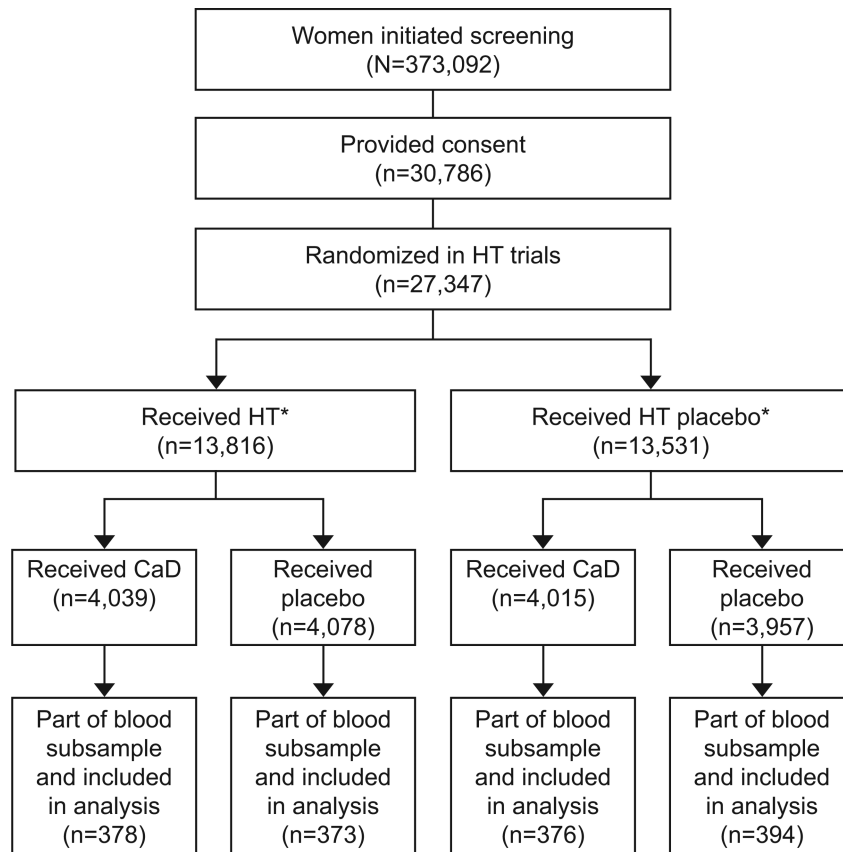


Figure 1.

Flow diagram of the Women's Health Initiative (WHI) trials of menopausal hormone therapy (HT) and calcium plus vitamin D (CaD). There were 27,347 women randomized in the menopausal HT trials, and 16,089 participants were also randomized in the CaD trial. Of these, 1,521 were part of the blood subsample and included in this analysis. *The WHI clinical trial used a partial fractional design, so not all HT trial participants were later randomized to CaD; details have been previously published.¹ Among the 16,089 participants in the WHI-CaD trial, 5,017 were also a part of the WHI-DM cohort.

CVD risk factor	Placebo mean (95%CI)	CaD-alone mean (95%CI)	HT-alone mean (95%CI)	HT+CaD combined mean (95%CI)	P	P-int
LDL-C (mg/dL)	130.1(127.0, 133.3)	128.5(125.3, 131.7)	121.1(117.9, 124.3)	116.3(113.1, 119.6)	<.001	.26
HDL-C (mg/dL)	55.3(54.1, 56.4)	55.0(53.8, 56.1)	60.9(59.8, 62.1)	61.1(59.9, 62.2)	<.001	.63
Triglycerides (mg/dL)	133.7(128.7, 138.9)	132.5(127.5, 137.6)	141.7(136.5, 147.2)	143.7(138.3, 149.3)	<.001	.47
Total cholesterol (mg/dL)	215.1(211.7, 218.5)	213.0(209.6, 216.4)	213.2(209.9, 216.6)	208.8(205.4, 212.3)	.03	.43
Glucose (mg/dL)	100.1(98.1, 102.1)	102.3(100.3, 104.4)	98.8(96.8, 100.7)	98.3(96.3, 100.3)	.006	.11
Insulin (μ U/ml)	12.8(11.5, 14.4)	13.4(12.1, 14.9)	11.4(10.3, 12.7)	11.6(10.4, 13.1)	.05	.83
Systolic BP (mm Hg)	126.0(125.5, 126.5)	126.4(125.9, 126.9)	127.6(127.1, 128.1)	128.0(127.5, 128.5)	<.001	.94
Diastolic BP (mm Hg)	73.0(72.7, 73.3)	73.4(73.2, 73.7)	73.3(73.0, 73.6)	73.5(73.2, 73.8)	.02	.40
Weight (kg)	77.3(77.0, 77.7)	77.3(76.9, 77.7)	77.2(76.8, 77.6)	77.1(76.8, 77.5)	.66	.83
Waist (cm)	91.3(90.8, 91.7)	91.4(91.0, 91.8)	90.9(90.4, 91.3)	90.6(90.2, 91.0)	.004	.22
Waist-hip-ratio	0.830(0.827, 0.833)	0.831(0.828, 0.834)	0.827(0.825, 0.830)	0.824(0.822, 0.827)	.003	.15

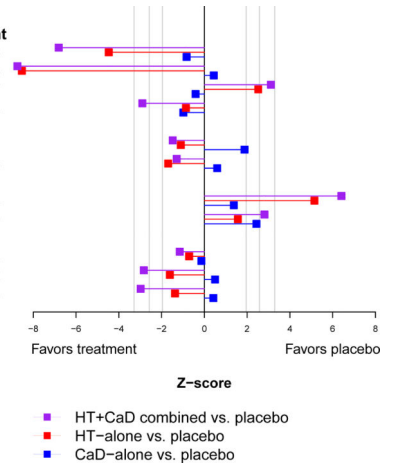


Figure 2.

Average group means (95%CI) during follow-up and corresponding Z-scores of treatment group effects. Group means for each randomization group were obtained by averaging the follow-up measurements collected at years 3 and 6. HT indicates menopausal hormone therapy; CaD, calcium plus vitamin D; P, the p-value of the 3 degree-of-freedom test for the main-effect of randomization group; P-int, p-value of the 1 degree-of-freedom test for interaction.

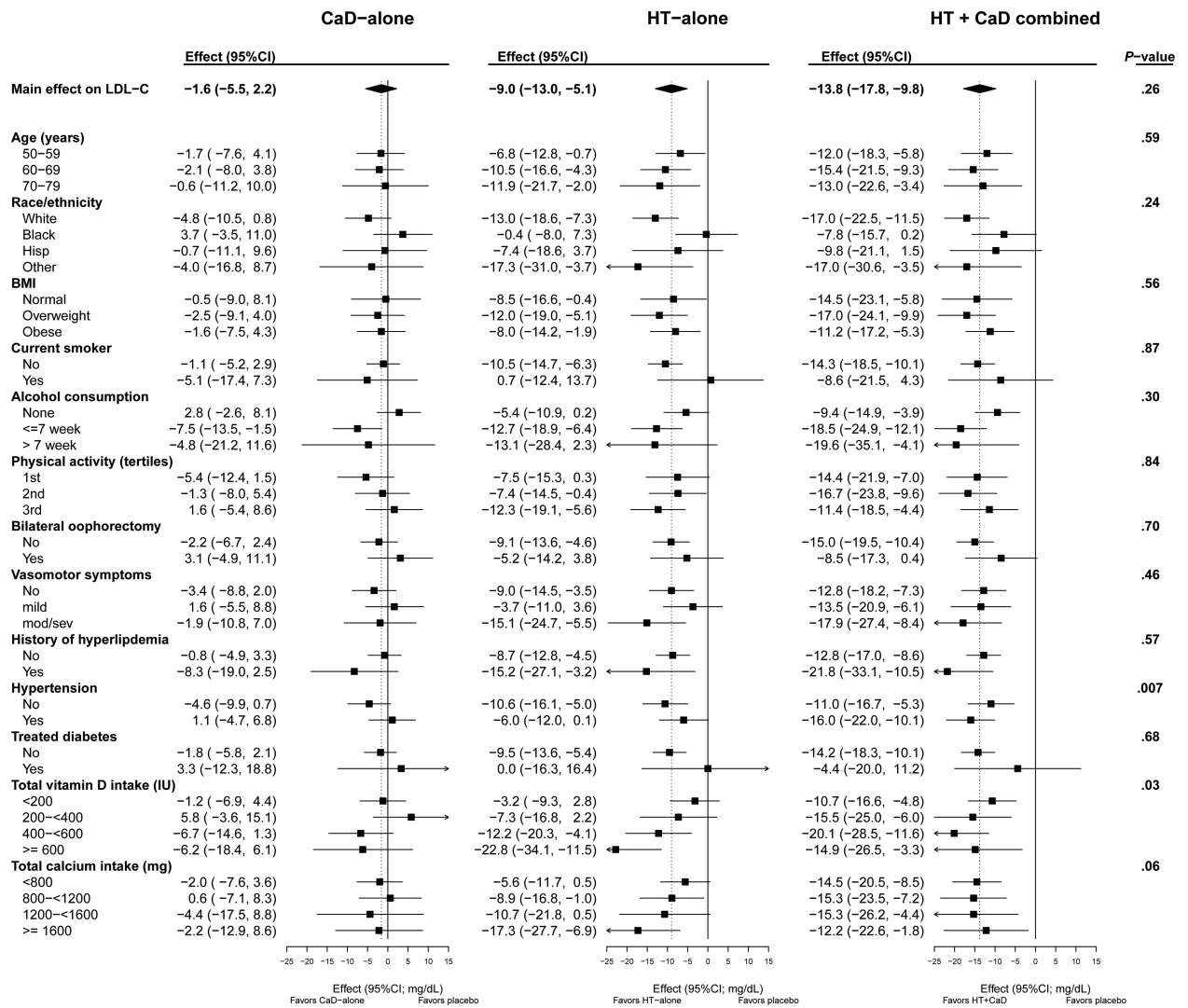


Figure 3. Average group effect (treatment minus placebo; mg/dL; 95%CI) on LDL-C by subgroups. P-value corresponds to the test of a three-way interaction between HT randomization group x CaD randomization group x subgroup. HT indicates menopausal hormone therapy; CaD, calcium plus vitamin D.

Table 1

Pre-specified baseline subgroups analyzed for test of interaction in subgroup analysis

Subgroups	Characteristics
Age (Years)	50-59
	60-69
	70-79
Race/Ethnicity	White
	Black
	Hispanic
	Other
Body Mass Index (BMI, kg/m ²)	Normal, <25
	Overweight, 25-<30
	Obese >=30
Current Smoker	No
	Yes
Alcohol use	Nondrinker
	<=7 drinks/week
	>7 drinks/week
Physical activity (Tertiles, METs/week)	<2.5
	2.5-10.5
	>=10.5
Bilateral oophorectomy	No
	Yes
Vasomotor symptoms	None
	Mild
	Moderate
	Severe
History of hyperlipidemia (self-report or medications)	No
	Yes
Hypertension (self-report of treated hypertension or high blood pressure)	No
	Yes
Treated for diabetes	No
	Yes
Total vitamin D (dietary and supplements, IU/day)	200
	400
	600
Total calcium (dietary, supplements, medications, mg/day)	800
	1200
	1600

Table 2

Baseline characteristics for the subsample with blood collections of the 2×2 factorial portion of the WHI HT and Calcium + Vitamin D trials (n = 1,521) by randomization group

Characteristic	Placebo (n=394)		Calcium + Vitamin D-alone (n=376)		Hormone Therapy-alone (n=373)		Hormone Therapy + Calcium + Vitamin D (n=378)		P-Value
	N	%	N	%	N	%	N	%	
Age at screening, y, mean (SD)	62.3	(7.4)	61.7	(7.0)	62.0	(7.0)	62.3	(6.8)	0.61
Age group at screening (10 yr intervals)									0.44
50-59	162	41.1	157	41.8	154	41.3	141	37.3	
60-69	154	39.1	163	43.4	153	41.0	171	45.2	
70-79	78	19.8	56	14.9	66	17.7	66	17.5	
Race/ethnicity									0.13
White	186	47.2	169	44.9	190	50.9	199	52.6	
Black	114	28.9	101	26.9	89	23.9	79	20.9	
Other	94	23.9	106	28.2	94	25.2	100	26.5	
Hormone use									0.77
Never used	267	67.8	245	65.2	255	68.4	263	69.6	
Past user	97	24.6	92	24.5	84	22.5	85	22.5	
Current user ¹	30	7.6	39	10.4	34	9.1	30	7.9	
Baseline vasomotor symptoms, %									0.50
None	202	51.4	203	54.6	205	55.4	203	54.4	
Mild	127	32.3	99	26.6	106	28.6	99	26.5	
Moderate/severe	64	16.3	70	18.8	59	15.9	71	19.0	
Body mass index, kg/m ² , median (IQR)	29.1 (25.2, 33.1)		28.9 (25.3, 34.2)		28.9 (24.9, 33.4)		29.4 (25.3, 34.0)		0.69
Smoking, %									0.15
Never	216	55.5	176	47.7	206	55.7	213	57.0	
Past	128	32.9	151	40.9	130	35.1	124	33.2	
Current	45	11.6	42	11.4	34	9.2	37	9.9	
Hysterectomy, %	175	44.4	160	42.6	158	42.4	157	41.5	0.87
Bilateral oophorectomy, %	71	18.5	68	19.0	54	15.0	54	15.0	0.30
Medical treatment, %									
Treated for diabetes	21	5.3	30	8.0	23	6.2	28	7.4	0.46
Hypertensive or BP 140/90	164	43.4	182	49.3	164	46.7	169	47.5	0.43
High cholesterol levels (medication)	42	10.7	53	14.1	37	9.9	44	11.6	0.30
Statin use at baseline	20	5.1	32	8.5	17	4.6	24	6.3	0.11
Aspirin use (< 80mg/d) at baseline	71	18.0	62	16.5	58	15.5	72	19.0	0.59
Medical History, %									

Characteristic	Placebo (n=394)		Calcium + Vitamin D-alone (n=376)		Hormone Therapy-alone (n=373)		Hormone Therapy + Calcium + Vitamin D (n=378)		P-Value
	N	%	N	%	N	%	N	%	
Myocardial infarction	8	2.0	4	1.1	5	1.3	9	2.4	0.48
Angina	18	4.6	14	3.8	13	3.5	22	5.9	0.39
CABG/PCI ²	6	1.5	3	0.8	1	0.3	6	1.6	0.24
Stroke	8	2.0	7	1.9	5	1.3	1	0.3	0.15
Deep vein thrombosis or pulmonary embolism	3	0.8	4	1.1	2	0.5	3	0.8	0.88
Family history of breast cancer	53	14.6	51	15.0	63	17.9	50	13.9	0.46
> High school degree/GED	278	70.9	253	68.2	269	72.9	268	71.3	0.56
Family income \$50,000, %	97	26.2	82	23.4	102	29.2	96	26.4	0.39
LDL-C (mg/dL), mean (SD)	140.3	(36.8)	136.1	(34.1)	140.4	(34.2)	140.0	(35.1)	0.28
HDL-C (mg/dL), mean (SD)	56.0	(14.1)	55.5	(13.9)	57.3	(14.6)	56.4	(14.3)	0.36
Triglyceride (mg/dL), median (IQR)	128.0 (95.0, 169.0)		126.0 (98.0, 174.0)		127.0 (93.5, 176.5)		128.0 (93.0, 173.0)		0.90
Total cholesterol (mg/dL) mean (SD)	225.9	(39.8)	220.4	(37.6)	226.7	(36.7)	225.8	(38.8)	0.10
Glucose (mg/dL), median (IQR)	96.0 (89.0, 105.0)		95.5 (89.0, 106.0)		94.0 (88.5, 104.0)		96.0 (89.0, 106.0)		0.37
Insulin (uIU/ml), median (IQR)	10.6 (7.9, 15.6)		10.9 (7.6, 15.9)		10.3 (7.5, 14.3)		10.5 (7.4, 15.6)		0.47
Systolic BP (mm Hg), mean (SD)	127.6	(17.2)	127.0	(16.9)	129.6	(17.4)	129.0	(18.1)	0.15
Diastolic BP (mm Hg), mean (SD)	76.1	(9.1)	76.6	(9.5)	76.5	(8.6)	76.0	(9.6)	0.78
Weight (kg), mean (SD)	77.7	(16.8)	78.7	(18.5)	76.9	(17.7)	77.2	(18.5)	0.53
Height (cm), mean (SD)	160.9	(7.7)	161.1	(7.4)	160.8	(6.8)	159.9	(7.4)	0.09
Waist/hip ratio, median (IQR)	0.82(0.77, 0.87)		0.83 (0.78, 0.88)		0.82 (0.77, 0.88)		0.82 (0.78, 0.87)		0.46
Waist (cm), mean (SD)	90.3	(13.2)	91.0	(14.2)	89.5	(13.6)	90.6	(14.4)	0.51

HORMONE THERAPY=Hormone therapy,

¹Required a 3-month washout prior to randomization

²CABG/PCI=coronary artery bypass graft/percutaneous coronary intervention