Association of vitamin D with incident glaucoma: findings from the Women's Health Initiative

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ABSTRACT

The relationship between vitamin D and glaucoma is controversial. The objective of this study was to examine women from the Women's Health Initiative (WHI) to determine if there is an association between vitamin D and incident glaucoma in postmenopausal women. We examined the association between dietary vitamin D intake, vitamin D supplements and serum 25 hydroxyvitamin D (25(OH)D) levels and the risk of developing glaucoma. 143,389 postmenopausal women from the WHI including a subset with serum 25(OH) D measurements were examined to determine the association of dietary, supplemental and serum levels of vitamin D to the development of glaucoma. Dietary intakes of vitamin D, use of vitamin D supplements and serum levels of 25(OH) D were predictors examined for the main outcome of incident glaucoma. In multivariable models adjusted for demographic, clinical variables and medication use, dietary vitamin D, vitamin D supplements, total vitamin D intake (diet plus supplements) and serum 25 (OH) D measurements were not significantly associated with incident glaucoma. In the CaD placebo-controlled intervention clinical trial, there was also no association in the active intervention arm with glaucoma. We conclude that dietary vitamin D intake, supplements and serum levels are not significantly related to the risk of developing glaucoma in postmenopausal women.

Significance of this study

What is already known about this subject?

- Vitamin D deficiency is a worldwide issue.
- Glaucoma is prevalent in postmenopausal women.
- Vitamin D supplementation is common.
- The relationship between vitamin D and glaucoma is controversial.

What are the new findings?

- In multivariable models adjusted for demographic, clinical variables and medication use, dietary vitamin D, vitamin D supplements, total vitamin D intake (diet plus supplements) and serum 25 (OH) D measurements were not significantly associated with incident glaucoma.
- There was also no association between vitamin D supplementation and glaucoma in the active intervention arm CaD placebo-controlled clinical trial.

How might these results change the focus of research or clinical practice?

- We conclude that dietary vitamin D intake, supplements and serum levels are not significantly related to the risk of developing glaucoma in postmenopausal women and that vitamin D supplementation should not be considered as a preventive strategy for glaucoma.

INTRODUCTION

Worldwide, 67 million people suffer from glaucoma and currently over 8 million individuals are blind because of this disorder. With the continued aging of the population, the incidence of glaucoma is expected to rapidly increase.[1] In addition to aging, risk factors associated with glaucoma include elevated intraocular pressure (IOP), high myopia and ethnic background.[2] Vision loss secondary to glaucoma is considered irreversible. Therefore, identification of modifiable risk factors for the development of glaucoma is critically important for prevention of blindness due to this dise

Vitamin D is a hormone with pleiotropic actions.[3] Vitamin D metabolites are present in the eye, including both the aqueous and vitreous humor and in tear fluid.[4–6] Furthermore, both the vitamin D receptor and the enzymes that activate vitamin D are present and active in cells of both the anterior and posterior segments of the eye.[4 7–11]

Several studies suggest that vitamin D homeostasis plays a role in glaucoma. For example, there are differences in vitamin D receptor allelic frequency in normal versus glaucoma patients, and vitamin D polymorphisms have been linked to IOP regulation.[12 13] A recent study using optical coherence tomography found decreased ganglion cell complex thickness in older adults with vitamin D deficiency.[14] Therefore, vitamin D may influence the response of the optic nerve to damage under glaucomatous conditions. However, studies of the association of vitamin D levels with glaucoma are conflicting, with some[15–18] but not

all,[19] suggesting that low vitamin D levels are associated with glaucoma. These studies were limited by a number of factors including the select populations examined (all Asians,[15 16] relatively low numbers of participants[17] and limited potential cofounders examined.[17] Administration of 1, 25 dihydroxyvitamin D eye drops and one of its analogs markedly reduced IOP in non-human primates.[20] However, a nested case-control study in humans revealed no association between serum (25(OH) D) levels and IOP, and administration of vitamin D3 to participants with low levels of 25(OH) D did not affect IOP,[21] although this trial included a relatively low number of (87 total) participants, and none of African American descent.[21] To our knowledge, there are no reports that have simultaneously examined the association of dietary vitamin D, vitamin D supplements and serum (25(OH) D) levels with incident glaucoma in a multiethnic population of postmenopausal women.

Therefore, the objectives of this study were to determine the relationship between dietary vitamin D, vitamin D supplements, total vitamin D intake (diet plus supplements) and, in a subset of women, serum levels of 25 (OH) D) with incident glaucoma in postmenopausal women in the Women's Health Initiative (WHI).

METHODS

The study population included women in the WHI observational study (OS) and clinical trials (CT) (Hormone Therapy, Dietary Modification and Calcium and Vitamin D Trials). The WHI included postmenopausal women aged 50–79 years recruited between October 1, 1993 and December 31, 1998, at 40 clinical centers in the USA. Details of the original WHI, in which participants were followed for outcomes between 1993 and 2005, have been previously described.[22] The institutional review board (IRB) at each participating center approved all protocols. This specific study was approved by the University of Tennessee Health Science Center IRB. Women provided written informed consent for their participation in the original WHI study. All protocols in this study adhered to the tenets of the Declaration of Helsinki.

For the purpose of these analyses, incident glaucoma was defined as self-report of glaucoma development during WHI with no history at the baseline visit. Follow-up for incident glaucoma was done through the end of 2005.

Height and weight at the baseline visit were measured in WHI as previously described[23] and used to calculate body mass index (BMI). Questionnaires obtained at the baseline visit were used to collect information regarding age, race and ethnicity, smoking exposure (current, past, never), personal menopausal hormone use and oral corticosteroid use. Questionnaires from the baseline visit also collected history of treated diabetes and hypertension (defined as those who reported that they were told by a doctor that they had high blood pressure and/or that they were currently taking medicine for their hypertension at the baseline WHI visit) and information relative to socioeconomic status including income, education and medical insurance. Total solar irradiation was measured in Langley's for each of the 40 clinical center regions.[24–26] Enrollment in the OS or CT (and particular CT component) was recorded. Indicators were created

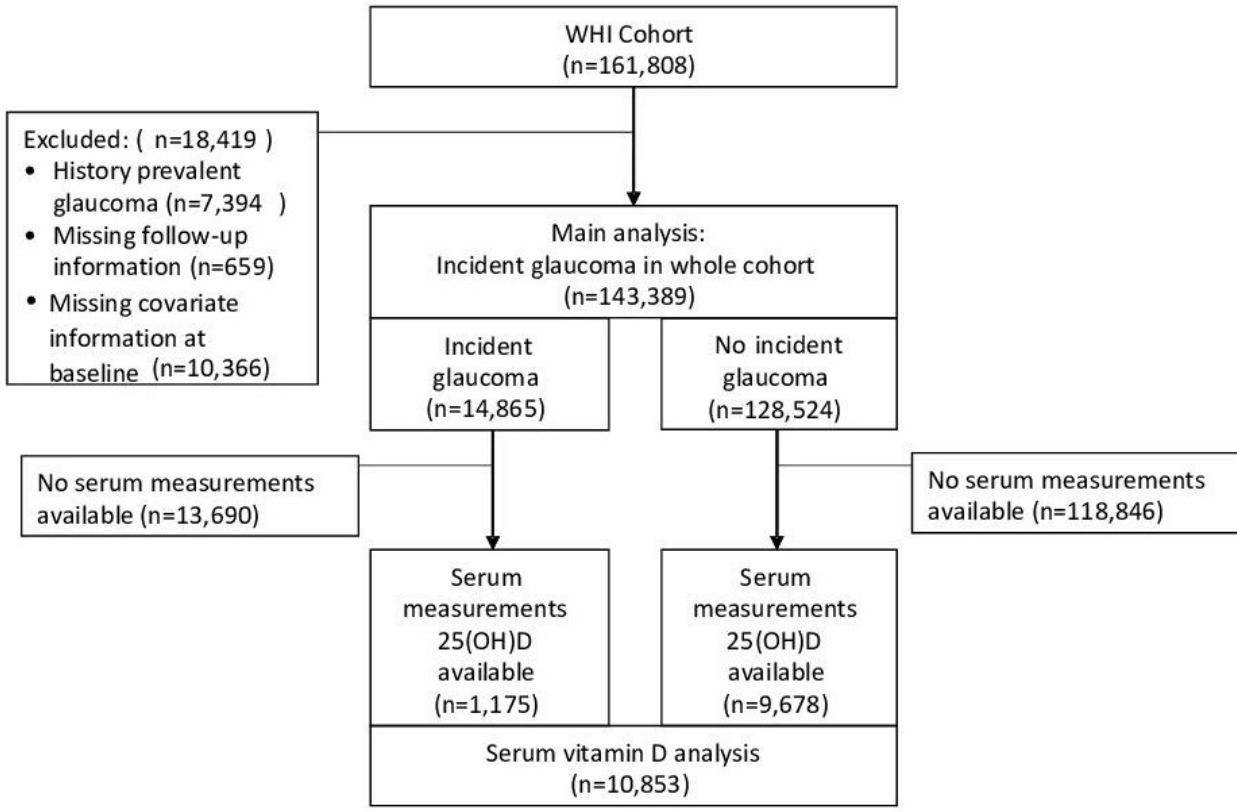

Figure 1 Study population. Derivation of WHI analytic entire cohorts. WHI, Women's Health Initiative.

Table 1 Baseline characteristics of study population (n=143,389)

Baseline Characteristic	Glaucoma present		Glaucoma absent		P value
	n	%	n	%	
Age at screening, mean (SD)	64.5	7.0	63.3	7.2	<0.001
50–59	3890	26.2	42,653	33.2	
60–69	6991	47.0	57,765	44.9	
≥70	3984	26.8	28,106	21.9	
Ethnicity					<0.001
White	11,927	80.2	108,407	84.3	
African American	1732	11.7	9890	7.7	
Hispanic	557	3.7	4721	3.7	
Other/unknown	649	4.4	5506	4.3	
Education					<0.001
≤High school/GED	3416	23.0	27,997	21.8	
School after high school	5641	37.9	48,664	37.9	
≥College graduate	5808	39.1	51,863	40.4	
Income					<0.001
<$35 000	5990	40.3	47,699	37.1	
$35 000–<$50 000	2883	19.4	24,918	19.4	
$50 000–<$75 000	2641	17.8	24,551	19.1	
≥$75 000	2394	16.1	23,227	18.1	
Any insurance					0.11
No	620	4.2	5825	4.5	
Yes	14,125	95.0	121,721	94.7	
Solar irradiance, Langley's					<0.001
300–325	4517	30.4	36,747	28.6	
350	3344	22.5	26,877	20.9	
375–380	1738	11.7	14,670	11.4	
400–430	2387	16.1	22,065	17.2	
475–500	2879	19.4	28,165	21.9	
Body mass index, kg/m^2, mean (SD)	28.1	(6.0)	27.9	(5.9)	<0.001
Underweight (<18.5)	106	0.7	1123	0.9	
Normal (18.5–<25.0)	4970	33.4	44,506	34.6	
Overweight (25.0–<30.0)	5211	35.1	44,695	34.8	
Obese (≥30.0)	4578	30.8	38,200	29.7	
Smoking					0.03
Never	7544	50.8	65,397	50.9	
Past	6363	42.8	54,152	42.1	
Current	958	6.4	8975	7.0	
Hormone use*					<0.001
Never used	5832	39.2	47,914	37.3	
Past user	2208	14.9	18,664	14.5	
Current user	6825	45.9	61,946	48.2	
History of treated hypertension					<0.001
No	10,303	69.3	91,322	71.1	
Yes	4562	30.7	37,202	28.9	
History of treated diabetes					<0.001
No	14,018	94.3	123,568	96.1	
Yes	847	5.7	4956	3.9	
Corticosteroid use					0.99
No	14,744	99.2	127,478	99.2	
Yes	121	0.8	1046	0.8	
WHI study component					<0.001
Clinical trial	7153	48.1	54,682	42.5	
Observational study	7712	51.9	73,842	57.5	
CaD intervention assignment					0.63†
Not randomized to CaD	11,055	74.4	99,149	77.1	
Active	1906	12.8	14,719	11.5	
Placebo	1904	12.8	14,656	11.4	

*Hormone use incorporates WHI Hormone Trial intervention assignment as well as participant self-report at baseline.
†χ^2 p value compares CaD active versus placebo by presence of glaucoma.

for participation in each arm (treatment and control) of each clinical trial component. Vitamin D intake from foods was estimated from a self-administered food-frequency questionnaire (FFQ) specifically designed for WHI which assessed usual dietary intake over the previous 3 months.[27] For the purposes of these analyses, we used information on use of calcium and vitamin D supplements, including multivitamins containing calcium and/or vitamin D ascertained by medication inventory of current medication use at baseline and year 3 from the OS and from baseline, years 1, 3, 6 and 9 from the CTs at years 1, 3, 6 and 9. Current medication use was ascertained by having the participants bring all the containers for medications taken for the 2 weeks prior to the study visit. Interviewers entered each medication into the database, which assigned drug codes using Medi-Span software (Wolters Kluwer Health; Conshohocken, Pennsylvania). Information on duration of use but not dose was recorded. The correlation coefficient for vitamin D intake was 0.70 between the FFQ and an 8-hour dietary intake assessment (this was done in a subset of WHI participants and consisted of four 24-hour recalls and a 4-hour food record).[27] Dietary and use of calcium and vitamin D supplements were summed to derive total vitamin D intake. Data from the 36,282 participants from CaD placebo-controlled clinical trial were also examined (18,176 Active intervention arm and 18,106 Placebo).

Statistical analyses

Baseline characteristics of all participants and those in the serum vitamin D subsample by incident glaucoma status are presented with means and SD for continuous variables, and frequencies and percentages for categorical variables. Differences between groups were assessed with a t-test for continuous variables and a χ^2 test for categorical variables.

The relationship between vitamin D intake (diet, supplements and diet plus supplements (total)) and incident glaucoma was assessed using proportional hazards models and two levels of adjustment. First, an unadjusted model with incident glaucoma as a function of categorical vitamin D intake was fit, with frequency, event totals, annualized rates and HRs from each category presented. The linear trend across median vitamin D categories was then assessed in a separate model, with the p value for trends tested. Fully

Table 2 Characteristics of serum vitamin D study population at time of phlebotomy (n=10,853)

Characteristic	Glaucoma present n	Glaucoma present %	Glaucoma absent n	Glaucoma absent %	P value
Age at blood draw, mean (SD)	66.1	7.2	65.1	7.3	<0.001
50–59	240	20.4	2440	25.2	
60–69	494	42.0	4255	44.0	
≥70	441	37.5	2983	30.8	
Ethnicity					<0.001
White	879	74.8	7963	82.3	
African American	167	14.2	847	8.8	
Hispanic	71	6.0	448	4.6	
Other/Unknown	58	4.9	420	4.3	
Education					0.14
≤High school/GED	301	25.6	2234	23.1	
School after high school	429	36.5	3601	37.2	
≥College graduate	445	37.9	3843	39.7	
Income					0.003
<$35 000	544	46.3	3950	40.8	
$35 000–<$50 000	212	18.0	1954	20.2	
$50 000–<$75 000	184	15.7	1742	18.0	
≥$75 000	157	13.4	1458	15.1	
Any insurance					0.35
No	58	4.9	391	4.0	
Yes	1108	94.3	9213	95.2	
Solar irradiance, Langley's					0.60
300–325	351	29.9	2829	29.2	
350	342	29.1	2721	28.1	
375–380	104	8.9	904	9.3	
400–430	179	15.2	1417	14.6	
475–500	199	16.9	1807	18.7	
Body mass index, kg/m^2, mean (SD)	28.5	(6.2)	28.0	(5.8)	0.003
Underweight (<18.5)	18	1.5	98	1.0	
Normal (18.5–<25.0)	350	29.8	3234	33.4	
Overweight (25.0–<30.0)	404	34.4	3424	35.4	
Obese (≥30.0)	403	34.3	2922	30.2	
Smoking*					0.27
Never	626	53.3	5393	55.7	
Past	473	40.3	3675	38.0	
Current	76	6.5	610	6.3	
Hormone use*					0.02
Never used	567	48.3	4281	44.2	
Past user	190	16.2	1554	16.1	
Current user	418	35.6	3843	39.7	
History of treated hypertension					0.07
No	769	65.4	6586	68.1	
Yes	406	34.6	3092	31.9	
History of treated diabetes					<0.001
No	1080	91.9	9220	95.3	
Yes	95	8.1	458	4.7	
Corticosteroid use					0.11
No	1161	98.8	9605	99.2	
Yes	14	1.2	73	0.8	
WHI study component					0.43
Clinical trial	562	47.8	4510	46.6	
Observational study	613	52.2	5168	53.4	
CaD intervention assignment					0.79†
Not randomized to CaD	624	53.1	5257	54.3	
Active	271	23.1	2201	22.7	
Placebo	280	23.8	2220	22.9	

*Hormone use incorporates WHI Hormone Trial intervention assignment as well as participant self-report at baseline.
†χ^2 p value compares CaD active versus placebo by presence of glaucoma.

adjusted models were done in the same fashion, with models adjusted for age, race/ethnicity, BMI, smoking, education, Langley sun exposure and hypertension and diabetes (latter as time dependent covariates). Both unadjusted and fully adjusted models are stratified within the model by WHI cohort (CT versus OS) as well as Calcium/ Vitamin D trial intervention assignment (active/placebo/not randomized).

Separate models were run to evaluate the relationship between vitamin D categories (diet, supplement, total, serum vitamin D levels) and glaucoma in African American and Caucasian participant subsets.

To adjust for being an unrepresentative sample of the full WHI set, serum Vitamin D models were inverse probability weighted to represent the full WHI population and were additionally adjusted for potential laboratory effects as not all vitamin D levels were measured in the same laboratory by the same methodology at the same time.

RESULTS

There were 161,808 women in the WHI cohort; of these, we excluded, in order, 7394 for a history of prevalent glaucoma, 659 who were missing follow-up information and 10,366 for missing information on covariates at baseline. For the main analyses, there were 143,389 women included, 14,865 with incident glaucoma and 128,524 who did not develop glaucoma during WHI follow-up, with 10,853 having measurements of serum 25 (OH)D. For the serum vitamin D analyses, there were 1175 women with incident glaucoma and 9678 who did not develop incident glaucoma during WHI follow-up (figure 1).

Baseline characteristics of the study population by self-report of incident glaucoma during WHI are shown in the whole cohort (table 1) and in the subset with serum vitamin D measurements (table 2). In the whole cohort, compared with those without glaucoma, those with glaucoma were older, had a higher BMI and were more likely to have hypertension or diabetes and to be in the WHI Clinical Trial Component (p<0.001). There were also differences in ethnicity, education, income, hormone use (personal as well as WHI Hormone Trial Assignment) and smoking status between those with and without glaucoma. There were no significant differences between the groups relative to medical insurance, use of corticosteroids or CaD intervention assignment in the CaD clinical trial (p≥0.05)

Table 3 Vitamin D and incident glaucoma

Model	n	Events	Ann %	Unadjusted HR (95% CI)	Unadjusted P value	Model 1 HR (95% CI)	Model 1 P value	Model 2 HR (95% CI)	Model 2 P value
CaD trial intervention					0.45				
Placebo	17,172	1804	1.56	1.00 (ref)		N/A		N/A	
Active	17,236	1777	1.52	0.98 (0.91 to 1.04)					
Dietary vitamin D, IU/day*					0.18		0.16		0.38
<200	99,362	10,292	1.39	1.00 (ref)		1.00 (ref)		1.00 (ref)	
200–<400	36,681	3776	1.38	0.99 (0.96 to 1.03)		1.00 (0.97 to 1.04)		0.99 (0.96 to 1.03)	
400–<600	5921	631	1.43	1.03 (0.95 to 1.11)		1.04 (0.96 to 1.13)		1.03 (0.95 to 1.11)	
600–<800	978	118	1.65	1.21 (1.01 to 1.45)		1.16 (0.97 to 1.39)		1.15 (0.96 to 1.38)	
≥800	417	48	1.59	1.17 (0.88 to 1.55)		1.11 (0.84 to 1.48)		1.10 (0.83 to 1.46)	
Continuous: 200 IU increase				1.01 (0.99 to 1.04)	0.29	1.02 (0.99 to 1.05)	0.18	1.01 (0.98 to 1.04)	0.49
Vitamin D supplements, IU/day*					0.77		0.45		0.29
<200	81,504	8623	1.41	1.00 (ref)		1.00 (ref)		1.00 (ref)	
200–<400	7214	721	1.35	0.98 (0.91 to 1.06)		1.01 (0.93 to 1.09)		1.01 (0.94 to 1.09)	
400–<600	46,053	4660	1.37	1.00 (0.96 to 1.03)		1.00 (0.96 to 1.04)		1.00 (0.97 to 1.04)	
600–<800	4843	457	1.31	0.98 (0.89 to 1.08)		1.00 (0.91 to 1.10)		1.01 (0.92 to 1.11)	
≥800	3775	404	1.47	1.07 (0.97 to 1.19)		1.10 (0.99 to 1.21)		1.11 (1.01 to 1.23)	
Continuous: 200 IU increase				1.00 (0.99 to 1.01)	>0.99	1.00 (0.99 to 1.02)	0.59	1.01 (0.99 to 1.02)	0.39
Total vitamin D, IU/day*					0.69		0.34		0.33
<200	53,749	5691	1.41	1.00 (ref)		1.00 (ref)		1.00 (ref)	
200–<400	26,569	2775	1.39	0.99 (0.95 to 1.04)		1.01 (0.97 to 1.06)		1.01 (0.96 to 1.05)	
400–<600	35,359	3584	1.36	0.99 (0.95 to 1.03)		1.00 (0.96 to 1.04)		1.00 (0.96 to 1.04)	
600–<800	18,587	1885	1.38	1.01 (0.96 to 1.06)		1.02 (0.97 to 1.08)		1.02 (0.97 to 1.08)	
≥800	9125	930	1.40	1.03 (0.96 to 1.10)		1.04 (0.97 to 1.11)		1.04 (0.97 to 1.11)	
Continuous: 200 IU increase				1.00 (0.99 to 1.01)	0.62	1.01 (0.99 to 1.02)	0.29	1.01 (0.99 to 1.02)	0.29
Serum 25(OH), ng/mL, weighted†					0.14		0.37		0.41
<30	9904	13,714	1.46	1.00 (ref)		1.00 (ref)		1.00 (ref)	
≥30	948	1028	1.19	0.81 (0.61 to 1.08)		0.88 (0.66 to 1.17)		0.89 (0.67 to 1.18)	
Continuous: 5 ng/mL increase				0.96 (0.91 to 1.01)	0.11	0.98 (0.93 to 1.04)	0.56	0.99 (0.94 to 1.04)	0.60
Serum 25(OH), ng/mL, weighted†					0.02		0.15		0.16
<20	6684	9461	1.56	1.00 (ref)		1.00 (ref)		1.00 (ref)	
20–50	4141	5255	1.25	0.83 (0.70 to 0.97)		0.89 (0.75 to 1.05)		0.89 (0.75 to 1.05)	
>50	28	26	1.18	0.74 (0.18 to 3.06)		0.84 (0.21 to 3.43)		0.82 (0.20 to 3.37)	
Continuous: 5 ng/mL increase				0.96 (0.91 to 1.01)	0.11	0.98 (0.93 to 1.04)	0.56	0.99 (0.94 to 1.04)	0.60

All models except the CaD trial intervention model are stratified by WHI cohort (clinical trial versus observational study) and time-dependent calcium vitamin D trial intervention (active, placebo, not randomized).
Model 1: Age, race/ethnicity, BMI.
Model 2: Model 1+education, smoking, time-dependent treated hypertension, time-dependent treated diabetes, solar irradiance.
*P values for five level variables computed from a separate model for linear trend across Vitamin D levels.
†Serum subsample event totals, annualized percentages, and models are inverse probability weighted to the full analysis sample. Serum analyses are additionally adjusted for serum study source.
BMI, body mass index.

(table 1). Among those included in the association of serum measurements of vitamin D with incident glaucoma, those with glaucoma were older, had a higher BMI and were more likely to have treated diabetes (p≤0.003). There were also differences in ethnicity, income and hormone use (incorporating personal use as well as WHI Hormone Trial Assignment), between those with and without glaucoma. There were no significant differences between the groups in education, insurance, solar irradiance category, smoking history, corticosteroid use or WHI study component or CaD intervention assignment (table 2).

In unadjusted and both adjusted models, there was no significant association between dietary vitamin D, vitamin D supplement intake or total vitamin D intake with incident glaucoma (table 3). In addition, in the CaD clinical trial, the active intervention was not significantly associated with glaucoma compared with placebo (HR=0.98, 95% CI 0.91 to 1.04). Similarly, there was no association of serum vitamin D levels either as a continuous variable or by categories (25(OH) D<30 ng/mL compared with those ≥30 ng/mL)[28] and by Institute of Medicine categories of low (<20 ng/mL), normal (20–50 ng/mL)) and high (>50 ng/mL) serum 25 (OH) D levels[29] (table 3).

There was a significant interaction of serum levels of 25(OH) D<30 ng/mL compared with those ≥30 ng/mL with race (p=0.04). Serum vitamin D levels>30 ng/mL were inversely associated with incident glaucoma in Whites but positively associated with incident glaucoma in African Americans although the findings were not statistically significant in either race. There were no significant associations of dietary vitamin D, vitamin D supplements

Table 4 Vitamin D and incident glaucoma by race

	African American					White					
Model	n	Events	Ann %	HR (95% CI)	P value	n	Events	Ann %	HR (95% CI)	P value	Interaction P value
CaD trial intervention*					0.80					0.46	0.61
Placebo	1502	219	2.22	1.00 (ref)		14,387	1445	1.48	1.00 (ref)		
Active	1520	224	2.27	1.02 (0.85 to 1.23)		14,336	1414	1.45	0.97 (0.90 to 1.05)		
Dietary vitamin D, IU/day†					0.63					0.47	0.49
<200	9296	1383	2.09	1.00 (ref)		81,433	8018	1.31	1.00 (ref)		
200–<400	1922	292	2.16	1.00 (0.88 to 1.13)		32,440	3223	1.32	0.99 (0.95 to 1.03)		
400–<600	302	41	1.90	0.91 (0.67 to 1.25)		5301	553	1.40	1.03 (0.94 to 1.12)		
600–<800	73	14	2.68	1.16 (0.69 to 1.97)		808	91	1.54	1.13 (0.92 to 1.39)		
≥800	29	2	0.97	0.45 (0.11 to 1.81)		352	42	1.63	1.17 (0.86 to 1.59)		
Continuous: 200 IU increase				1.00 (0.92 to 1.08)	0.97				1.01 (0.98 to 1.04)	0.71	0.87
Vitamin D supplements, IU/day†					0.30					0.12	0.15
<200	8511	1295	2.13	1.00 (ref)		65,644	6538	1.31	1.00 (ref)		
200–<400	401	53	1.83	0.90 (0.68 to 1.18)		6277	617	1.32	1.04 (0.95 to 1.12)		
400–<600	2441	351	2.03	0.96 (0.85 to 1.08)		40,580	4006	1.33	1.02 (0.98 to 1.06)		
600–<800	117	14	1.76	0.83 (0.49 to 1.40)		4437	409	1.28	1.01 (0.91 to 1.11)		
≥800	152	19	1.77	0.90 (0.57 to 1.42)		3396	357	1.43	1.12 (1.01 to 1.25)		
Continuous: 200 IU increase				0.97 (0.93 to 1.02)	0.26				1.01 (1.00 to 1.02)	0.20	0.15
Total vitamin D, IU/day†					0.30					0.22	0.17
<200	6591	989	2.10	1.00 (ref)		41,826	4147	1.30	1.00 (ref)		
200–<400	1842	283	2.17	1.01 (0.89 to 1.16)		22,699	2267	1.32	1.00 (0.95 to 1.05)		
400–<600	2218	333	2.12	1.02 (0.90 to 1.16)		30,618	3009	1.32	1.01 (0.96 to 1.06)		
600–<800	640	91	2.01	0.92 (0.74 to 1.14)		16,915	1665	1.33	1.01 (0.96 to 1.07)		
≥800	331	36	1.54	0.75 (0.54 to 1.05)		8276	839	1.38	1.06 (0.98 to 1.14)		
Continuous: 200 IU increase				0.98 (0.94 to 1.02)	0.32				1.01 (1.00 to 1.02)	0.19	0.18
Serum 25(OH), ng/mL, weighted‡					0.10					0.18	0.04
<30	989	1715	2.21	1.00 (ref)		7981	10,687	1.35	1.00 (ref)		
≥30	25	72	4.01	1.95 (0.89 to 4.27)		861	848	1.07	0.80 (0.58 to 1.11)		
Continuous: 5 ng/mL increase				0.97 (0.88 to 1.07)	0.56				0.99 (0.93 to 1.05)	0.69	0.78
Serum 25(OH), ng/mL, weighted‡					0.99					0.04	0.50
<20	860	1493	2.24	1.00 (ref)		5155	7129	1.46	1.00 (ref)		
20–50	154	295	2.32	1.00 (0.59 to 1.68)		3660	4380	1.15	0.82 (0.69 to 0.99)		
>50	0	0	0.00	–		27	26	1.21	0.83 (0.20 to 3.43)		
Continuous: 5 ng/mL increase				1.03 (0.90 to 1.18)	0.69				0.96 (0.91 to 1.03)	0.25	0.40

All models except the CaD trial intervention model are stratified by WHI cohort (clinical trial versus observational study) and time-dependent calcium vitamin D trial intervention (active, placebo, not randomized) and are adjusted for age, BMI, education, smoking, time-dependent treated hypertension, time-dependent treated diabetes and solar irradiance.
*CaD intervention model is unadjusted.
†P values for five level variables computed from separate models for linear trend across vitamin D levels.
‡Serum subsample event totals, annualized percentages, and models are inverse probability weighted to the full analysis sample. Serum analyses are additionally adjusted for serum study source.
BMI, body mass index.

or total vitamin D intake with incident glaucoma in either race (table 4).

DISCUSSION

The major findings of our study are that there is no association between the development of glaucoma and dietary vitamin D, vitamin D supplements or serum 25 hydroxyvitamin D levels (including serum levels of vitamin D below optimal recommendations)[30] in postmenopausal women. Further, the large CaD placebo-controlled clinical trial data also support no association between Vit D and incident glaucoma.

To our knowledge, ours is the first report to examine the relationship between dietary vitamin D and total vitamin D intake (diet plus supplements) with incident glaucoma. In support of our findings, a randomized clinical trial including 87 healthy participants with low serum vitamin D3 levels randomized to vitamin D3 20,000 IU twice per week versus placebo revealed no significant differences in IOP, one of the primary risk factors for glaucoma, at 6 months between the groups.[21]

In agreement with our findings of no significant association between serum 25 (OH) D levels and incident glaucoma in the cohort of postmenopausal women in WHI, a

recent meta-analysis also reported no significant association.[19] Limitations noted in this meta-analysis included significant heterogeneity among the study designs and considerable differences in sample sizes and in the vitamin D assays used.[19] In contrast, however, two studies from Korea did report a significant correlation between low serum vitamin D levels and prevalent glaucoma.[15 16] These reports differ from ours in that they examined prevalent and not incident glaucoma and were derived from primarily Asian populations. Notably, several studies suggest that specific race-based factors may contribute to the pathogenesis of glaucoma.[31 32] Our findings in WHI, although not statistically significant, suggest that higher serum 25 (OH) D levels, might be protective against glaucoma in White women.

Our study has a number of important strengths. To our knowledge, this is the first study to examine the association of dietary vitamin D intake with incident glaucoma. Further, ours is the largest sample of multiethnic postmenopausal women in which the association of supplemental vitamin D and serum 25 (OH) D levels with incident glaucoma has been examined. Moreover, the large placebo-controlled clinical trial of calcium plus vitamin D in the WHI yielded similar results of no association. We were able to control for a number of important covariates associated with glaucoma including demographic characteristics, lifestyle factors, socioeconomic status, prevalent medical conditions and medication use (corticosteroids).

There are also a number of limitations to consider. To start, glaucoma was defined by self-report. However, agreement between self-report and medical records for glaucoma in previous studies has been reported to be substantial (κ=0.73).[33] Second, we did not have the ability to distinguish specific types of glaucoma. In addition, serum 25 (OH) D levels were not measured in all women in WHI and the methodology for these measurements differed. Characteristics of women who donated blood at the baseline visit did not differ significantly from women who did not donate blood.[34] Moreover, to at least partially account for these differences, scaling was used to standardize across laboratory/methodology effects. We defined optimal serum levels of vitamin as 30 ng/mL or greater,[30] and by Institute of Medicine cut points;[29] however, there is considerable disagreement as to the definition of "optimal levels"[35] and this may also depend on the outcome being evaluated.[36] Notably, however, our findings were consistent when we examined continuous measures for serum 25 (OH)D. Less than 2.5% of the population was Asian; therefore, we were unable to examine the association of vitamin D categories with incident glaucoma in this subgroup. Finally, the findings were from postmenopausal women enrolled in WHI, and the results may not be generalizable to other groups.

In conclusion, our findings suggest no association between vitamin D (as diet, supplements or serum levels) and the development of glaucoma in postmenopausal women. Optimizing vitamin D status is unlikely to impact the risk of glaucoma in postmenopausal women.

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Correction: *Association of vitamin D with incident glaucoma: findings from the Women's Health Initiative*

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