Vitamin D Intake and Risk of Incident Hypertension: Results From Three Large Prospective Cohort Studies

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Vitamin D Intake and Risk of Incident Hypertension
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John P. Forman, Heike A. Bischoff-Ferrari, Walter C. Willett, Meir J. Stampfer, Gary C. Curhan

Abstract—Emerging evidence suggests an inverse relation between vitamin D and blood pressure. We examined the independent association between intake of vitamin D and the risk of incident hypertension among participants of 3 large and independent prospective cohorts: Nurses Health Study I (NHS I; n=77 436), NHS II (n=93 803), and Health Professionals' Follow-up Study (HPFS; n=38 074). Relative risks and 95% confidence intervals for incident hypertension were computed according to quintiles of vitamin D intake using Cox proportional hazards regression and adjusted for relevant covariates. Each cohort was followed for ≥8 years. Vitamin D intake was not associated with the risk of developing hypertension. The multivariable relative risk estimates for the highest compared with lowest quintile of intake were 0.98 (0.93 to 1.04) in NHS I, 1.13 (0.99 to 1.29) in NHS II, and 1.03 (0.93 to 1.15) in HPFS. When we compared participants who consumed ≥1600 to <400 IU per day and those who consumed ≥1000 to <200 IU per day, no association was found. We conclude that higher intake of vitamin D is not associated with a lower risk of incident hypertension. (*Hypertension*. 2005;46:676-682.)

Key Words: vitamins ■ diet ■ epidemiology ■ human

Hypertension affects an estimated 65 million people in the United States and many more worldwide.[1,2] Growing evidence points to vitamin D as having an important association with blood pressure. Data from animal studies implicate circulating active vitamin D as an inhibitor of renin expression in the juxtaglomerular apparatus as well as an inhibitor of vascular smooth muscle cell proliferation.[3,4] Oral supplementation with vitamin D lowers blood pressure in hypertensive rats.[5–7] In humans, cross-sectional data suggest an association between low vitamin D intake (<400 IU per day) and higher blood pressure,[8] and a single interventional study in vitamin D–deficient elderly women found that a combination of calcium and vitamin D supplementation had a greater blood pressure–lowering effect than calcium supplementation alone.[9] However, there are no prospective data in the general population that higher vitamin D intake lowers the risk of hypertension.

To determine whether higher vitamin D intake is associated with a lower risk of incident hypertension, we analyzed data from 3 large prospective cohort studies that together comprised >200 000 participants from the 2 Nurses' Health Studies and the Health Professionals' Follow-up Study (HPFS).

Methods

Study Populations

The older cohort of women (Nurses' Health Study I [NHS I]) was assembled in 1976, when 121 700 female nurses 30 to 55 years of age returned an initial questionnaire.[10] The younger cohort of women (NHS II) was assembled in 1989, when 116 671 female registered nurses 25 to 42 years of age returned a mailed questionnaire.[11] In 1986, 51 529 male health professionals 40 to 75 years of age who returned an initial questionnaire were enrolled (HPFS).[12] Subsequent questionnaires have been mailed every 2 years to update information on health-related behavior and medical events. Detailed dietary information was collected every 4 years using a semiquantitative food frequency questionnaire.[13] The assembly of the 3 populations for the purpose of this study is outlined in the Figure. Follow-up in this study was 18 years in NHS I (1984 to 2002), 8 years in NHS II (1991 to 1999), and 16 years in HPFS (1986 to 2002). The institutional review board at Brigham and Women's Hospital reviewed and approved this study, and participants provided implied consent by virtue of returning their questionnaires.

Assessment of Vitamin D Intake

The semiquantitative food frequency questionnaire asks about commonly used portion sizes of various foods and prompts participants to record the frequency of consumption during the previous year, with 9 potential response categories ranging from less than once per month to ≥6 times per day; this questionnaire has been validated in these as well as several other cohorts.[13–15] Nutrient intakes were calculated by multiplying the frequency of intake by the nutrient content of the specified portion. Nutrient contents were obtained from the Harvard University food consumption database, which was derived from multiple sources (US Department of Agriculture, manufacturers, and published reports). Use of vitamin D–containing supplements was also collected, including brand name and frequency, and this information was linked to vitamin D content of the supplement. Measurement of the predominant dietary sources of vitamin D by the food frequency questionnaire have been validated

Assembly of the study populations.
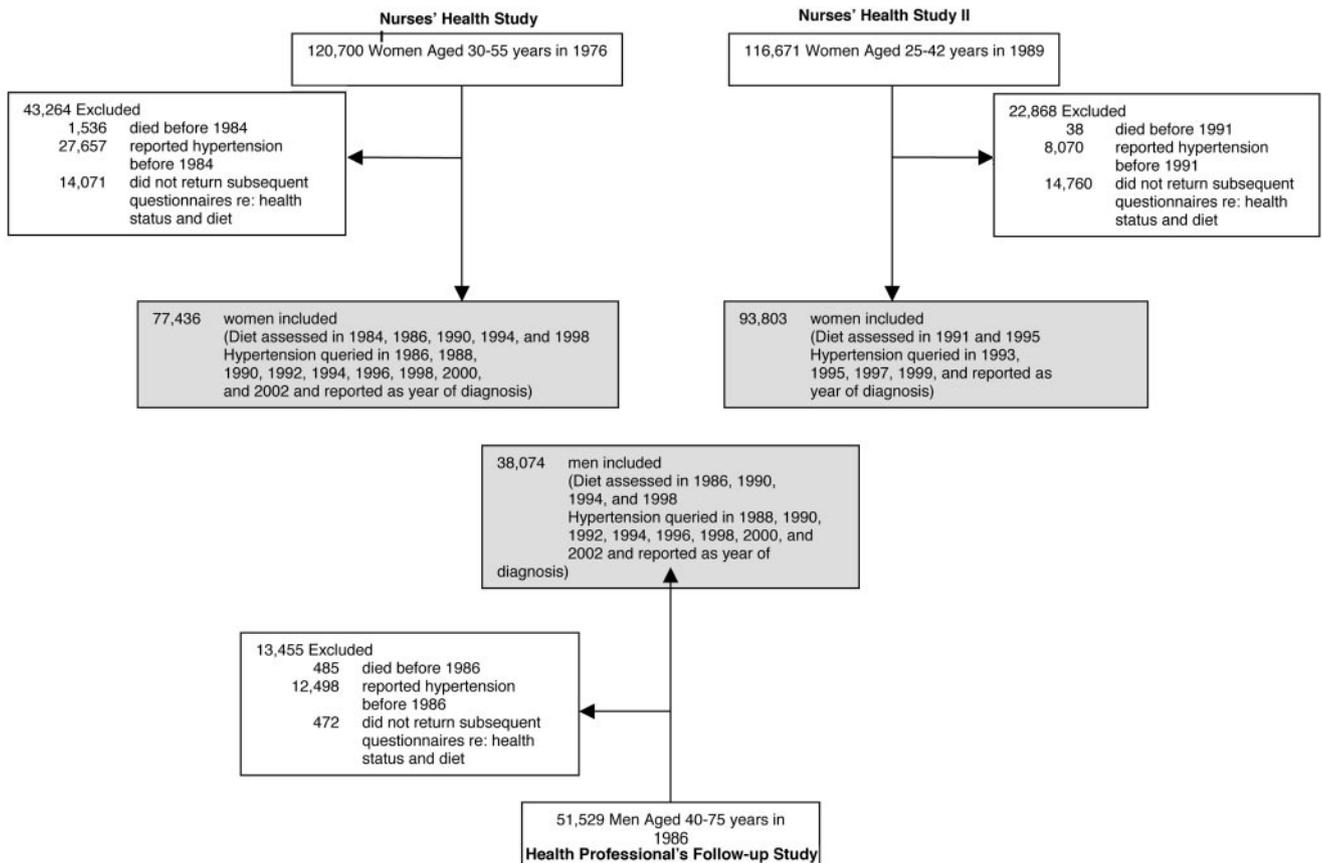
Questionnaires sent biennially to participants ask about personal and physical characteristics, family history, environmental and personal exposures, physical activity, screening and other examination history, medication use, use of supplements and certain dietary features, psychosocial history, and disease outcomes. Dietary questionnaires (food frequency) accompany the standard questionnaires every other questionnaire cycle (every 4 years).

previously in NHS I and HPFS by comparison with dietary records.[16,17] These primary dietary contributors and their correlation coefficients in women (r_w) and men (r_m) are: skim or low-fat milk ($r_w=0.81$; $r_m=0.88$); whole milk ($r_w=0.62$; $r_m=0.67$); yogurt ($r_w=0.94$; $r_m=0.86$); and dark-meat fish ($r_w=0.66$; $r_m=0.58$). Assessment of supplement use by the food frequency questionnaire is also reliable.[18,19] Participants typically returned food frequency questionnaires every 4 years during the follow-up period (1984, 1986, 1990, 1994, and 1998 in NHS I; 1991 and 1995 in NHS II; 1986, 1990, 1994, and 1998 in HPFS), and vitamin D intake was reset for each participant at each of these time points according to the most recent level of intake.

Assessment of Other Covariates
Age, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), smoking status, physical activity, and dietary covariates (intakes of alcohol, caffeine, folate, vitamin B_6, vitamin B_{12}, sodium, potassium, calcium, magnesium, fiber, and protein) were ascertained from questionnaires and updated at each time point that vitamin D intake was updated. Questionnaire-derived information about these covariates has also been validated previously, with correlations of 0.97 for weight, 0.79 for physical activity, and among dietary variables, correlations ranging from 0.56 for vitamin B_{12} to 0.90 for alcohol.[11,13,20] Family history of hypertension was available on the 1992 (NHS I), 1989 (NHS II), and 1990 (HPFS) questionnaires. Information regarding use of oral contraceptive drugs was obtained in NHS II from the 1991 and 1995 questionnaires. Participants in NHS II reported their systolic and diastolic blood pressure on the 1989 questionnaire and in HPFS on the 1986 questionnaire. These were used as baseline blood pressures.

Blood pressure was not reported in NHS I until 1986, so no baseline was available for the cohort of older women.

Assessment of Hypertension
The baseline and follow-up biennial questionnaires asked participants to report whether a clinician had made a new diagnosis of hypertension during the preceding 2 years. Self-reported hypertension was shown to be highly reliable in NHS I and HPFS.[21,22] In a subset of women who reported hypertension, medical record review confirmed a documented systolic and diastolic blood pressure >140 and 90 mm Hg, respectively, in 100%; among the men, 100% of a subset who reported hypertension also had the diagnosis confirmed by medical record review.[21,22] In addition, self-reported hypertension was highly predictive of subsequent cardiovascular events. A participant was considered to have prevalent hypertension if he or she reported this diagnosis on any questionnaire up to and including the 1984 (NHS I), 1991 (NHS II), or 1986 (HPFS) questionnaire. Participants with prevalent hypertension were excluded. Cases included individuals who first reported hypertension on subsequent questionnaires and whose year of diagnosis postdated the return of the 1984, 1991, or 1986 questionnaires.

Statistical Analysis
Vitamin D intake was divided into quintiles for the primary analysis. However, because using quintiles may overlook important associations between extremes of intake, we also performed secondary analyses in which categories of intake were examined. These analyses included 5 categories in which the lowest category was defined as less than the US recommended daily allowance (RDA;

TABLE 1. Baseline Characteristics of the NHS I Cohort (Women 37–64 Years of Age) According to Quintile of Vitamin D Intake in 1984

	Quintile of Vitamin D Intake, IU/Day				
Quintile median (Range)	79 (3–117)	150 (117–184)	225 (184–284)	371 (284–494)	646 (494–3519)
	Mean (SD)				
Age, years	48.5 (6.9)	49.0 (7.0)	49.8 (7.2)	50.0 (7.2)	51.1 (7.1)
BMI, kg/m^2	24.3 (4.3)	24.5 (4.2)	24.5 (4.2)	24.3 (4.1)	24.1 (4.0)
Physical activity, METs/week	12.5 (22.0)	13.3 (17.8)	14.4 (21.0)	15.3 (22.6)	17.1 (24.6)
Dietary intake					
Alcohol, g/day	8.5 (12.9)	7.0 (10.7)	5.9 (9.5)	6.5 (10.8)	5.9 (9.5)
Caffeine, mg/day	367 (251)	342 (233)	319 (228)	304 (227)	294 (238)
Total protein, g/day	66.8 (12.9)	69.3 (11.7)	71.6 (11.5)	73.6 (12.6)	74.5 (13.7)
Fiber, g/day	4.2 (1.5)	4.5 (1.4)	4.7 (1.5)	4.7 (1.5)	5.0 (1.7)
Vitamins					
B$_6$, mg/day	5.1 (20.5)	5.9 (21.4)	6.2 (20.9)	9.2 (24.8)	22.1 (44.5)
B$_{12}$, μg/day	7.0 (5.7)	8.2 (5.7)	9.5 (7.7)	12.4 (14.0)	21.0 (44.5)
Folate, μg/day	248 (113)	274 (108)	306 (122)	414 (167)	677 (284)
Minerals					
Sodium, mg/day	1746 (376)	1798 (341)	1827 (343)	1817 (345)	1815 (379)
Potassium, mg/day	2638 (541)	2792 (500)	2941 (502)	3041 (558)	3088 (621)
Calcium, mg/day	527 (128)	640 (146)	749 (182)	831 (286)	827 (310)
Magnesium, mg/day	250 (60.5)	267 (57.7)	287 (61.3)	306 (66.5)	336 (97.7)
	Percentage				
Smoking history					
Past	28.9	30.7	30.9	32.2	35.1
Current	32.5	25.6	22.8	22.1	20.9
Family history of hypertension	40.7	41.9	41.6	41.1	39.7

All dietary variables are adjusted for total energy intake.
METs indicates metabolic equivalent tasks.

<400 IU per day, 400 to 799 IU per day, 800 to 1199 IU per day, 1200 to 1599 IU per day, and ≥1600 IU per day); we also examined 6 categories (<200 IU per day, 200 to 399 IU per day, 400 to 599 IU per day, 600 to 799 IU per day, 800 to 999 IU per day, and ≥1000 IU per day). Finally, we performed analyses in which vitamin D was treated as a continuous variable. In all categorical analyses, the reference group was the lowest intake category. Vitamin D, as well as other dietary variables, was adjusted for total energy intake.

For each participant, person months of follow-up were counted from the date of return of the first questionnaire to the date of return of the last questionnaire and allocated according to exposure status. Person time was truncated when an event occurred. Participants were censored at the date of death; or if they did not return a subsequent questionnaire, they were censored at the date the subsequent questionnaire was mailed. Participants who did not provide dietary information at baseline but provided this information at subsequent questionnaire cycles contributed person time during those periods in which dietary information was available.

Multivariable relative risks (RRs) were calculated using Cox proportional hazards regression. Multivariable models were adjusted for variables that have been hypothesized to be associated with hypertension (age [continuous], BMI [6 categories], physical activity [quintiles], smoking status [past, current, never], family history of hypertension [yes/no], oral contraceptive use [NHS II, yes/no], alcohol intake [6 categories], and intakes of caffeine, folate, vitamin B$_6$, vitamin B$_{12}$, sodium, calcium, magnesium, fiber, and protein [quintiles]). We also controlled for baseline systolic and diastolic blood pressure in NHS II and HPFS. For all RRs, we calculated 95% confidence intervals (CIs). All P values are 2-tailed.

Statistical tests were performed using SAS statistical software (version 9; SAS Institute Inc).

We had 90% power to detect a 7% decrease in risk of hypertension between the highest and lowest quintiles among the cohort of older women, a 10% decrease among the cohort of younger women, and a 10% decrease among the men.

Results

Nurses' Health Study I

During 950 462 person years of follow-up, 27 084 participants of NHS I reported developing hypertension. At baseline in 1984, the cohort mean age was 49.7 years (median 49 years; interquartile range [IQR] 44 to 56 years), and the mean BMI was 24.3 (median 23.4; IQR 21.5 to 26.3). Baseline characteristics of these women, stratified by quintile of vitamin D intake in 1984, are shown in Table 1. With increasing vitamin D intake, we observed increasing age, more physical activity, less smoking, higher consumption of protein, fiber, B vitamins, potassium, calcium, and magnesium, and lower consumption of alcohol and caffeine.

Vitamin D intake was not associated with a lower risk of incident hypertension (Table 2). Women in the highest quintile of intake had multivariable RR of 0.98 after adjusting for multiple covariates (95% CI, 0.93 to 1.04; P for trend=0.84) compared with women in the lowest quintile of intake.

TABLE 2. Vitamin D Intake and Risk of Incident Hypertension in NHS I

	NHS I Cohort (37–64 Years of Age at Baseline in 1984); Follow-Up 1984–2002					
	Quintiles of Vitamin D Intake IU/Day, Median (Range)					
	79 (3–117)	150 (117–184)	225 (184–284)	371 (284–494)	646 (494–3519)	P Trend
Person years	191 498	192 119	191 976	190 342	184 527	
Hypertension cases	5359	5470	5522	5457	5276	
Model 1, RR (95% CI)	1.0 (reference)	1.00 (0.96–1.04)	1.00 (0.96–1.04)	1.00 (0.96–1.03)	0.96 (0.92–1.00)	0.07
Model 2, RR (95% CI)	1.0 (reference)	1.00 (0.96–1.04)	1.00 (0.97–1.04)	1.02 (0.98–1.06)	1.00 (0.96–1.04)	0.38
Model 3, RR (95% CI)	1.0 (reference)	1.00 (0.96–1.04)	1.00 (0.96–1.05)	1.01 (0.96–1.06)	0.98 (0.93–1.04)	0.84

Model 1 is age adjusted. Model 2 adjusts for age and BMI. Model 3 adjusts for age, BMI, physical activity, smoking history, diet (intakes of alcohol, caffeine, total protein, fiber, folate, vitamins B_6 and B_{12}, sodium, potassium, calcium, and magnesium), and family history of hypertension.

Because analysis of quintiles may overlook important associations between the extreme values of vitamin D intake and the risk of incident hypertension, we performed secondary analyses using different categories of intake. First, we divided vitamin D intake into 5 categories in which the lowest category was <400 IU per day (less than the US RDA) and the highest ≥1600 IU per day. Compared with women consuming less than the RDA, the multivariable RR for women who consumed ≥1600 IU per

TABLE 3. Baseline Characteristics of the NHS II Cohort (Women 27–44 Years of Age) According to Quintile of Vitamin D Intake in 1991

	Quintile of Vitamin D Intake, IU/day				
Quintile Median (Range)	128 (3–175)	217 (175–262)	317 (262–383)	472 (383–592)	742 (592–5203)
	Mean (SD)				
Age, years	36.4 (4.6)	36.4 (4.6)	36.1 (4.6)	35.7 (4.7)	35.5 (4.7)
BMI, kg/m^2	24.5 (5.4)	24.4 (5.0)	24.3 (4.9)	24.1 (4.8)	24.1 (4.6)
Physical activity, METs/week	17.8 (24.4)	19.4 (24.8)	21.3 (27.2)	22.4 (28.2)	24.2 (31.5)
Dietary intake					
Alcohol, g/day	3.6 (7.4)	3.3 (6.1)	3.1 (5.7)	3.1 (5.8)	2.5 (5.0)
Caffeine, mg/day	280 (238)	266 (227)	244 (218)	224 (211)	205 (214)
Total protein, g/day	80.1 (15.6)	84.7 (14.0)	88.2 (14.0)	88.4 (15.0)	90.3 (15.6)
Fiber, g/day	4.6 (1.7)	4.8 (1.5)	4.9 (1.5)	4.9 (1.6)	5.1 (1.6)
Vitamins					
B_6, mg/day	4.7 (19.1)	5.1 (19.3)	5.9 (20.0)	9.1 (24.8)	16.3 (36.9)
B_{12}, μg/day	5.8 (5.3)	6.8 (5.9)	8.0 (7.5)	10.7 (8.7)	17.8 (22.6)
Folate, μg/day	287 (110)	326 (113)	369 (134)	542 (222)	872 (326)
Minerals					
Sodium, mg/day	2102 (417)	2169 (362)	2176 (351)	2161 (351)	2156 (355)
Potassium, mg/day	2687 (547)	2868 (496)	2992 (492)	3020 (521)	3102 (540)
Calcium, mg/day	627 (152)	786 (167)	950 (236)	997 (329)	1067 (354)
Magnesium, mg/day	265 (57.6)	292 (52.7)	314 (54.7)	335 (66.5)	371 (88.8)
Baseline blood pressure					
Systolic, mm Hg†	113 (9.0)	113 (9.3)	113 (9.1)	112 (9.2)	112 (9.0)
Diastolic, mm Hg†	71 (7.9)	71 (7.6)	71 (7.7)	70 (7.7)	70 (7.6)
	Percentage				
Smoking history					
Past	20.2	22.2	22.6	22.6	23.3
Current	17.1	13.3	11.3	10.5	9.5
Family history of hypertension	50.9	50.2	49.8	50.1	49.7
Oral contraceptive use	85.3	85.2	84.7	83.3	83.9

All dietary variables are adjusted for total energy intake.
METs indicates metabolic equivalent tasks.
†Baseline blood pressures in NHS II were queried in 1989.

TABLE 4.   Vitamin D Intake and Risk of Incident Hypertension in NHS II

	NHS II Cohort (27–44 Years of Age at Baseline in 1991); Follow-Up 1991–1999					
	Quintiles of Vitamin D Intake IU/Day, Median (Range)					
	128 (3–175)	217 (175–262)	317 (262–383)	472 (383–592)	742 (592–5203)	P Trend
Person years	127 289	129 183	130 306	130 221	129 168	
Hypertension Cases	1555	1588	1402	1410	1417	
Model 1, RR (95% CI)	1.0 (reference)	1.01 (0.94–1.08)	0.90 (0.84–0.97)	0.94 (0.87–1.01)	0.94 (0.88–1.01)	0.05
Model 2, RR (95% CI)	1.0 (reference)	1.02 (0.95–1.10)	0.94 (0.87–1.01)	1.00 (0.93–1.08)	1.03 (0.96–1.11)	0.42
Model 3, RR (95% CI)	1.0 (reference)	1.10 (1.02–1.18)	1.05 (0.96–1.15)	1.11 (0.99–1.23)	1.13 (0.99–1.29)	0.11

Model 1 is age adjusted. Model 2 adjusts for age and BMI. Model 3 adjusts for age, BMI, physical activity, smoking history, diet (intakes of alcohol, caffeine, total protein, fiber, folate, vitamins B_6 and B_{12}, sodium, potassium, calcium, and magnesium), family history of hypertension, use of oral contraceptives and baseline systolic and diastolic blood pressure.

day was 0.94 (95% CI, 0.85 to 1.03). We further tested 6 categories of vitamin D intake, defining the lowest category as <200 IU per day and ≥1000 IU per day as the highest; no independent association was found (multivariable RR, 0.96 [95% CI, 0.73 to 1.26]). Finally, vitamin D intake as a continuous variable had no association with risk of hypertension (multivariable $P=0.22$).

Nurses' Health Study II

During 646 167 person years of follow-up in this cohort of younger women, 7372 reported the development of hypertension. At baseline in 1991, the mean age was 36.0 years (median 36 years; IQR 33 to 40), and the mean BMI was 24.3 (median 23.0; IQR 21.0 to 26.2). Baseline characteristics of this cohort by quintile of vitamin D intake in 1991 appear in

TABLE 5.   Baseline Characteristics of the HPFS (Men 40–75 Years of Age) According to Quintile of Vitamin D Intake in 1986

	Quintile of Vitamin D Intake, IU/day				
Quintile Median (Range)	99 (3–139)	174 (139–212)	263 (212–334)	428 (334–560)	748 (560–3702)
	Mean (SD)				
Age, years	51.0 (9.0)	52.3 (9.6)	53.2 (9.7)	53.5 (9.8)	55.0 (9.7)
BMI, kg/m²	25.0 (4.8)	24.8 (4.9)	24.7 (4.7)	24.5 (4.9)	24.3 (4.8)
Physical activity, METs/wk*	19.8 (29.6)	21.0 (27.2)	22.1 (32.8)	22.1 (28.8)	24.0 (31.5)
Dietary intake					
Alcohol, g/day	13.7 (17.7)	10.9 (14.1)	10.1 (13.9)	10.4 (14.7)	9.1 (12.5)
Caffeine, mg/day	301 (277)	260 (256)	230 (240)	221 (236)	214 (248)
Total protein, g/day	87.5 (17.2)	90.1 (15.2)	92.3 (15.2)	94.9 (16.2)	96.0 (17.2)
Fiber, g/day	5.6 (2.1)	5.8 (1.9)	6.0 (2.0)	5.9 (2.1)	6.4 (2.3)
Vitamins					
B_6, mg/day	3.8 (12.6)	4.4 (14.2)	5.1 (15.8)	7.6 (19.9)	22.5 (43.4)
B_{12}, μg/day	8.7 (7.1)	9.6 (7.5)	10.3 (8.2)	13.2 (14.4)	21.6 (36.5)
Folate, μg/day	327 (133)	363 (137)	399 (148)	496 (194)	824 (361)
Minerals					
Sodium, mg/day	3387 (1264)	3355 (1155)	3309 (1075)	3247 (1053)	3191 (1073)
Potassium, mg/day	3070 (635)	3242 (584)	3423 (600)	3554 (668)	3729 (776)
Calcium, mg/day	578 (147)	705 (160)	844 (213)	940 (350)	929 (386)
Magnesium, mg/day	313 (67.8)	329 (64.4)	349 (66.0)	368 (73.8)	409 (101)
Baseline blood pressure					
Systolic, mm Hg	128 (9.8)	127 (9.5)	127 (9.8)	128 (9.8)	127 (9.9)
Diastolic, mm Hg	80 (6.3)	80 (6.3)	80 (6.4)	80 (6.3)	79 (6.4)
	Percentage				
Smoking history					
Past	42.1	39.7	38.7	39.2	41.3
Current	12.6	9.5	9.0	9.0	8.2
Family history of hypertension	31.2	30.8	30.2	31.2	30.0

All dietary variables are adjusted for total energy intake.
METs indicates metabolic equivalent tasks.

TABLE 6.   Vitamin D Intake and Risk of Incident Hypertension in HPFS

	HPFS Cohort (40–75 Years of Age at Baseline in 1986); Follow-Up 1986–2002					
	Quintiles of Vitamin D Intake IU/Day, Median (Range)					
	99 (3–139)	174 (139–212)	263 (212–334)	428 (334–560)	748 (560–3702)	*P* Trend
Person years	79 904	79 859	79 525	77 113	74 699	
Hypertension cases	1872	1755	1686	1732	1789	
Model 1, RR (95% CI)	1.0 (reference)	0.92 (0.86–0.98)	0.88 (0.82–0.94)	0.92 (0.86–0.98)	0.96 (0.90–1.02)	0.72
Model 2, RR (95% CI)	1.0 (reference)	0.92 (0.86–0.98)	0.89 (0.93–0.95)	0.95 (0.89–1.01)	1.00 (0.94–1.07)	0.24
Model 3, RR (95% CI)	1.0 (reference)	0.95 (0.88–1.02)	0.93 (0.85–1.01)	0.94 (0.86–1.04)	1.03 (0.93–1.15)	0.48

Model 1 is age adjusted. Model 2 adjusts for age and BMI. Model 3 adjusts for age, BMI, physical activity, smoking history, diet (intakes of alcohol, caffeine, total protein, fiber, folate, vitamins B_6 and B_{12}, sodium, potassium, calcium, and magnesium), family history of hypertension, and baseline systolic and diastolic blood pressure.

Table 3. Similar relationships between vitamin D quintile and the covariates were noted among these younger women as in NHS I, with the exception of age, which decreased with increasing vitamin D intake.

As in NHS I, vitamin D intake was not associated with a lower risk of incident hypertension (Table 4). Women in the highest quintile of intake had a nonsignificant 13% increase in risk of hypertension after adjusting for multiple covariates (multivariable RR, 1.13 [95% CI, 0.99 to 1.29]; *P* for trend=0.11), compared with women in the lowest quintile of intake. Although the risk seemed to decline with higher vitamin D intake in the age-adjusted models, further adjustment for BMI eliminated the association (Table 4).

Compared with those who consumed <400 IU per day, the multivariable RR for women whose intake exceeded 1600 IU per day was 1.01 (95% CI, 0.65 to 1.58). Compared with women with still lower intake of vitamin D (<200 IU per day), there was no increase in risk for those whose intake exceeded 1000 IU per day (multivariable RR, 1.03; 95% CI, 0.85 to 1.25). Vitamin D intake as a continuous variable was not associated with risk of hypertension (multivariable *P*=0.44).

Health Professionals' Follow-Up Study

Among the men, we observed 8834 incident cases of hypertension during 391 100 person years of follow-up. The mean age in 1986 was 53.0 years (median 52 years; IQR 44 to 61), and the mean BMI was 24.6 (median 24.8, IQR 23.1 to 26.6). Baseline characteristics of the male cohort by quintile of vitamin D intake in 1986 are shown in Table 5. Similar characteristics between vitamin D quintile and variables were observed as in NHS I.

In the male cohort, there was no association between vitamin D intake and risk of incident hypertension. After adjustment for multiple covariates, the RR for men in the highest quintile of intake was 1.03 (95% CI, 0.93 to 1.15; *P* for trend=0.48) compared with men in the lowest quintile of intake (Table 6).

When men whose daily vitamin D intake was ≥1600 IU were compared with men whose intake was <400 IU, the multivariable RR was 1.05 (95% CI, 0.77 to 1.43). Furthermore, there was no association when men who consumed ≥1000 IU per day were compared with men who consumed <200 IU per day (multivariable RR, 1.06 [95% CI, 0.92 to 1.22]). Vitamin D as a continuous variable was not associated with incident hypertension in multivariable analysis (*P*=0.10).

Discussion

To our knowledge, this is the first prospective cohort study to examine whether higher vitamin D intake is associated with a lower risk of hypertension, a hypothesis that has gained emerging support from animal and cross-sectional human studies. Among 209 313 participants in 3 cohort studies including older and younger women as well as men, we found no evidence that higher vitamin D consumption altered the risk of incident hypertension.

Animal studies have suggested a link between vitamin D and blood pressure. In wild-type mice, Li et al recently showed that physiological levels of 1.25 dihydroxy vitamin D (1.25(OH)$_2$D) inhibited renin expression in juxtaglomerular cells, whereas an inhibitor of 1.25(OH)$_2$D biosynthesis increased the expression of renin.[3] In addition, vitamin D receptor–null mice have a 7-fold increased expression of renin and develop hypertension as well as cardiac hypertrophy.[3] Studies in spontaneously hypertensive rats have shown decreased blood pressure on oral administration of supplemental vitamin D, as well as improvements in endothelial cell–dependent vasodilation.[5–7]

Two cross-sectional studies examining vitamin D intake and blood pressure in humans reported conflicting results. Sowers et al examined 86 normotensive young women (20 to 35 years of age) and 222 normotensive older women (55 to 80 years of age).[8] Vitamin D intake was estimated by 24-hour recall. In the younger women, an estimated vitamin D intake <400 IU per day was associated with 6 mm Hg greater systolic blood pressure compared with women whose vitamin D intake was ≥400 IU per day after adjustment for age, BMI, alcohol use, and calcium intake. The same comparison in older women was associated with a 4 mm Hg greater systolic blood pressure.[8] A larger study including 15 000 Norwegian men and women 25 to 69 years of age assessed vitamin D intake from a food frequency questionnaire and found no association with blood pressure after multivariable adjustment for age, BMI, alcohol, caffeine, physical activity, and smoking; however, relatively few participants of this study had vitamin D intakes that met or surpassed the recommended 400 IU per day.[23] A single published interventional trial exists.[9] A total of 148 elderly women were random-

ized to receive either supplemental calcium (1200 mg per day) or supplemental calcium (same dose) and vitamin D (800 IU per day) for 8 weeks. Compared with the calcium-only group, the calcium–vitamin D group had a 9.3% decrease in systolic BP (P=0.02). However, entry criteria into this interventional trial required participants to have vitamin D insufficiency. Before now, no prospective population study has tested this association.

The absence of an association between intake of vitamin D and incident hypertension does not demand that a potential relationship between circulating levels of vitamin D metabolites and risk of hypertension also be null. Indeed, some cross-sectional human studies have found lower blood pressure with higher plasma dihydroxy vitamin D levels,[24–26] and sun exposure plays a large role in the biosynthesis of vitamin D.[27,28] However, we found no influence on risk of hypertension even with very high intakes (≥1600 IU per day).

Our study has limitations and strengths that deserve mention. First, we did not directly measure the participants' blood pressure, and the diagnosis of hypertension was self-reported. However, self-reported hypertension is highly reliable in these cohorts of health professionals. Second, in any study with null findings, the possibility that random misclassification of the exposure (such as vitamin D intake) could dilute and even nullify a true association must be considered. Nevertheless, the large number of participants (and high level of power), the reliability of vitamin D reporting as assessed by the food frequency questionnaire, the long follow-up, and the similar null findings among 3 large independent cohorts provides assurance that an important association was unlikely to be missed.

Perspectives

These large prospective cohort studies do not indicate an inverse association between higher vitamin D intake and risk of hypertension. Because intake does not fully account for circulating levels, future prospective studies investigating levels of vitamin D metabolites and risk of incident hypertension are indicated.

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