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Vitamin D Intake and the Risk of Incident Kidney Stones

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Abstract

Purpose—Kidney stones are a common and painful condition. Longitudinal prospective studies on the association between intake of vitamin D and risk of incident kidney stones are lacking.

Materials and Methods—We performed a prospective analysis of 193,551 participants of the Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS) I and II. Participants were divided into categories of total (<100, 100–199, 200–399, 400–599, 600–999, ≥1,000 IU/day) and supplemental (none, <400, 400–599, 600–999, ≥1,000 IU/day) vitamin D intake. During a follow-up of 3,316,846 person-years, there were 6,576 incident kidney stone events. Cox proportional hazards regression models were adjusted for age, BMI, comorbidities, use of medications and intake of other nutrients.

Results—After multivariate adjustment, there was no statistically significant association between intake of vitamin D and risk of stones in HPFS (HR for ≥1,000 vs <100 IU/day 1.08, 95% CI 0.80, 1.47, p-value for trend = 0.92) and NHS I (HR 0.99, 95% CI 0.73, 1.35, p-value for trend = 0.70), whereas there was a suggestion of higher risk in NHS II (HR 1.18, 95% CI 0.94, 1.48, p-value for trend = 0.02). Similar results were found for supplemental vitamin D intake.

Conclusions—Vitamin D intake in typical amounts was not statistically associated with risk of kidney stone formation, though higher risk with higher doses than those studied here cannot be excluded.

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Introduction

Kidney stones are common, with an estimated prevalence of about 10% in the US population.[1] Higher urine calcium excretion is a major risk factor for calcium stone formation,[2] which in turn might be increased by higher circulating levels of 1,25-dihydroxyvitamin D (1,25[OH]$_2$D).[3,4] In a prospective nested case-control study, the odds of kidney stones were 73% higher for those in the highest quartile of 1,25[OH]$_2$D.[5] The association between precursors of 1,25[OH]$_2$D such as circulating 25-hydroxyvitamin D (25[OH]D) and intake of cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) is less clear. Oral supplementation with cholecalciferol has been associated with increased risk of stones when administered together with calcium;[6] however, administration of ergocalciferol in stone formers with vitamin D deficiency did not cause a significant rise in mean urinary calcium excretion.[7] This is an important issue as vitamin D insufficiency and low bone mineral density are common among stone formers,[8,9] and also because associations between vitamin D status and other conditions such as high blood pressure,[10] diabetes,[11,12] and cardiovascular events[13,14] have been reported, all frequent among stone formers[15–18]. To date, only two longitudinal studies investigated the association between intake of vitamin D and risk of kidney stones, reporting no association.[19,20] We designed the current study to investigate total and supplemental intake of vitamin D and the risk of incident kidney stones in three large prospective cohorts, the Health Professionals Follow-up Study (HPFS), and the Nurses' Health Study (NHS) I and II.

Materials and methods

Study cohorts

The HPFS cohort was started in 1986 with the enrollment of 51,529 male health professionals (dentists, optometrists, osteopaths, pharmacists, podiatrists and veterinarians) aged 40 to 75 years; the NHS I cohort was started in 1976 with the enrollment of 121,700 female nurses aged 30 to 55 years; the NHS II cohort was started in 1989 with the enrollment of 116,430 female nurses aged 25 to 42 years. For all the cohorts, participants completed a detailed questionnaire with information on lifestyle, medical history and medications. The questionnaire was subsequently mailed every two years to update information. These studies were approved by the Partners HealthCare Institutional Review Board. Return of completed baseline and biennial questionnaires was accepted by the institutional review board as implied informed consent.

Assessment of vitamin D and other nutrient intakes

Starting in 1986 (for HPFS and NHS I) and 1991 (for NHS II), participants submitted a food-frequency questionnaire (FFQ) with information on average use of more than 130 foods and more than 20 beverages in the previous year. Intake of individual nutrients was calculated from the frequency of consumption of foods and from data on the content of the relevant nutrients obtained from the US Department of Agriculture, except for oxalate intake which was directly measured in foods by capillary electrophoresis.[21] Participants reported intake of vitamin D supplements. Participants reporting intake of a multivitamin were asked to report the specific brand and the amount and frequency of use; this information was used

to calculate supplemental vitamin D intake using a composition database on over 1,000 multivitamin brands. Intakes estimated from the FFQ were validated in the NHS I and HPFS cohorts: intraclass correlation coefficients for total vitamin and mineral intakes assessed by two FFQs 1 year apart ranged from 0.58 to 0.60 in the NHS I and from 0.57 to 0.80 in the HPFS.[22,23]

Assessment of kidney stones

Participants reporting an incident kidney stone were asked to complete a supplementary questionnaire with information about date of occurrence and accompanying symptoms. Self-reported diagnosis was found to be reliable by medical record review of a sample (confirmed in ≥95% who completed the supplementary questionnaire).[24] In a subsample of the study population with stone composition reports, the stone type was predominantly calcium oxalate (>50%) in 86% of participants in the HPFS, 77% of participants in the NHS I, and 79% of participants in the NHS II cohort.[24]

Assessment of other covariates

Information about age, region of living, BMI, history of diabetes, history of hypertension and use of thiazides was obtained from the biennial questionnaire.

Statistical analysis

Participants were divided into categories according to their intake of total (<100, 100–199, 200–399, 400–599, 600–999, ≥1,000 IU/day) and supplemental vitamin D (none, <400, 400–599, 600–999, ≥1,000 IU/day); person-time of follow-up was allocated to each category from start of follow-up (1986 for HPFS and NHS I, 1991 for NHS II) until the date of incident stones, death, or end of follow-up (2012 for HPFS and NHS I, 2011 for NHS II), whichever happened first. Participants were excluded at baseline if they reported a previous history of kidney stones or malignancy (except for non-melanoma skin cancer), and censored during follow-up if they reported an incident malignancy. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident stones for each category of exposure. Models were adjusted for age, region of residence, BMI, history of diabetes, history of hypertension, use of thiazides, use of calcium supplements, intakes of calcium, sodium, potassium, magnesium, animal protein, fructose, oxalate, vitamin C, caffeine, alcohol and fluids; models for supplemental vitamin D intake were further adjusted for dietary vitamin D. Exposures and covariates were updated every four years.

Effect modification of total vitamin D intake by age (<50 vs ≥50 years) or BMI (<25 vs ≥25 kg/m^2) was tested by including interaction terms in the multivariate adjusted models. Effect modification of total vitamin D intake by total calcium intake was tested by interaction terms of the intakes expressed as continuous variables and by generating HRs for joint categories of exposure (total vitamin D: <400, 400–799, ≥800 IU/day; total calcium intake: <600, 600–1,199, ≥1,200 mg/day).

Results

Our analysis included 193,551 participants, whose baseline characteristics are reported in Table 1. Average age (except for NHS II), use of calcium supplements, intakes of potassium, magnesium, animal protein and vitamin C tended to increase with increasing categories of total vitamin D intake, whereas intake of caffeine (except for NHS II) and alcohol tended to decrease. During a follow-up of 3,316,846 person-years, there were 6,576 incident kidney stone events.

Estimates of association between total vitamin D intake and kidney stones are reported in Table 2. After multivariate adjustment, there was no statistically significant association in the HPFS cohort (HR for an intake of ≥1,000 IU/day compared with <100 IU/day 1.08, 95% CI 0.80, 1.47, p-value for trend = 0.92) and in the NHS I cohort (HR 0.99, 95% CI 0.73, 1.35, p-value for trend = 0.70); in the NHS II cohort, there was a suggestion that the highest category of intake of vitamin D was associated with a higher risk of stones (HR 1.18, 95% CI 0.94, 1.48, p-value for trend = 0.02).

Estimates of association between supplemental vitamin D intake and kidney stones are reported in Table 3. Similar to total intake, there was no significant association after multivariate adjustment in HPFS (HR for the highest compared with lowest category 1.23, 95% CI 0.81, 1.86, p-value for trend = 0.34) and NHS I (HR for the highest compared with lowest category 1.03, 95% CI 0.71, 1.51, p-value for trend = 0.26), whereas the association was significant in NHS II (HR for the highest compared with lowest category 1.38, 95% CI 1.03, 1.85, p-value for trend = 0.02). When we examined the cumulative average of total vitamin D intake, we found no association with incident kidney stones in any cohort.

There was no effect modification of total vitamin D intake by age, BMI or total calcium intake.

Discussion

We found that intake of vitamin D was not significantly associated with risk of incident kidney stones in two of the cohorts, whereas there was a suggestion of higher risk in the third cohort. Similar results were obtained when analyzing intake of vitamin D from supplements. The potential relevance of vitamin D in the pathogenesis of kidney stones stems from the reported association between higher levels of $1,25(OH)_2D$ with urinary calcium excretion[4] (a major determinant of calcium stone formation),[2] and with actual stone formation.[5] Since the relation between intake of vitamin D and circulating levels of 25(OH)D, the substrate for $1,25(OH)_2D$, is well-established,[25] one might expect that intake of vitamin D might increase risk of stones, but the formation of $1,25(OH)_2D$ (the active metabolite responsible for intestinal calcium absorption and increased urinary calcium excretion) from 25(OH)D is tightly regulated by either down-regulation of the 1-alpha-hydroxylase enzyme or a reduction in PTH. In fact, previous studies on the association between vitamin D intake and risk of kidney stones do not support this hypothesis: supplemental administration of vitamin D3 to attain circulating levels of 25(OH)D of >32 ng/mL in a group of 138 participants did not significantly increase mean urinary excretion of

calcium.[26] Similarly, administration of up to 4,000 IU/day of vitamin D3 in a group of 73 healthy volunteers did not modify urine calcium substantially.[27] Leaf and colleagues treated 29 calcium stone formers with 25(OH)D levels <30 ng/mL and urine calcium excretion between 150 and 400 mg/24h with vitamin D2 (50,000 IU/week for 8 weeks), and reported that mean urine calcium excretion did not increase overall (from 257±54 to 255±88 mg/24h), though in 11 patients there was an increase in urine calcium of ≥20 mg/24h. In this setting, it is possible that altered function of the 24-hydroxylase, the enzyme degrading 1,25(OH)2D, might play a role in the differential calciuric response to vitamin D.[28]

Previous analyses of the HPFS cohort did not find any association between either total vitamin D intake[19] or circulating levels[5] of 25(OH)D and risk of stones. Similarly, among 2,012 participants of the Grassroots-Health study, no association was observed between intake of D3 and incidence of stones; however, the results were limited by the small number of stone events (13 cases) and the short follow-up time (1.6 years).[20] In the only study reporting an increased risk of kidney stones after administration of vitamin D, supplemental vitamin D was given together with calcium supplements, which might have increased urine calcium excretion.[6] However, in our study we did not observe a higher risk even among those participants with higher intakes of calcium.

We found a statistically significant linear trend for higher risk of stones in the NHS II cohort, but visual inspection of the individual HRs in the vitamin D categories do not support a monotonic increase in risk. It appears that risk of stones was only higher in the highest category of intake, suggesting a non-linear association in this cohort.

Our study has limitations, including the observational study design and the majority of the participants were white. We did not have access to information on stone and urine composition for the majority of the participants. We could not fully explore the association between vitamin D intake and stones across all age ranges of men, but in the NHS II cohort we could analyze 422 incident cases that occurred during 186,286 person-years of follow-up. While it is possible that the association of vitamin D intake with stone risk might vary between younger and older adults, we did not find significant effect modification by age in the participants of the NHS II cohort. We lacked information from the participants about the indication for vitamin D supplementation. Finally, few individuals had intakes of vitamin D >1,000 IU/d.

Taken together, our findings suggest that vitamin D intake in typical amounts was not statistically associated with risk of kidney stone formation; higher risk with higher doses cannot be excluded.

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PMF, ENT, GG and GCC designed research; PMF, ENT and GCC conducted research; PMF analyzed data; PMF, ENT, GG and GCC wrote the paper; PMF and ENT had primary responsibility for final content. All authors read and approved the final manuscript.

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Abbreviations

25(OH)2D	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
BMI	body mass index
CI	confidence interval
FFQ	food-frequency questionnaire
HPFS	Health Professionals Follow-Up Study
HR	hazard ratio
IU	International Units
NHS	Nurses' Health Study

References

1. Scales CD, Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. Eur Urol. 2012; 62:160–165. [PubMed: 22498635]
2. Curhan GC, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. Kidney Int. 2008; 73(4):489–96. [PubMed: 18059457]
3. Broadus AE, Insogna KL, Lang R, Ellison AF, Dreyer BE. Evidence for disordered control of 1,25-dihydroxyvitamin D production in absorptive hypercalciuria. N Engl J Med. 1984; 311(2):73–80. [PubMed: 6330548]
4. Shakhssalim N, Gilani KR, Parvin M, et al. An assessment of parathyroid hormone, calcitonin, 1,25 (OH)2 vitamin D3, estradiol and testosterone in men with active calcium stone disease and evaluation of its biochemical risk factors. Urol Res. 2011; 39(1):1–7. [PubMed: 20490785]
5. Taylor EN, Hoofnagle AN, Curhan GC. Calcium and phosphorus regulatory hormones and risk of incident symptomatic kidney stones. Clin J Am Soc Nephrol CJASN. 2015; 10(4):667–75. [PubMed: 25623233]
6. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006; 354(7):669–83. [PubMed: 16481635]
7. Leaf DE, Korets R, Taylor EN, et al. Effect of vitamin D repletion on urinary calcium excretion among kidney stone formers. Clin J Am Soc Nephrol CJASN. 2012; 7(5):829–34. [PubMed: 22422535]
8. Ticinesi A, Nouvenne A, Ferraro PM, et al. Idiopathic Calcium Nephrolithiasis and Hypovitaminosis D: a Case-Control Study. Urology. 2015
9. Jaeger P, Lippuner K, Casez JP, Hess B, Ackermann D, Hug C. Low bone mass in idiopathic renal stone formers: magnitude and significance. J Bone Miner Res Off J Am Soc Bone Miner Res. 1994; 9(10):1525–32.
10. Vimaleswaran KS, Cavadino A, Berry DJ, et al. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. Lancet Diabetes Endocrinol. 2014; 2(9):719–29. [PubMed: 24974252]
11. Pittas AG, Dawson-Hughes B, Li T, et al. Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care. 2006; 29(3):650–6. [PubMed: 16505521]
12. Afzal S, Brøndum-Jacobsen P, Bojesen SE, Nordestgaard BG. Vitamin D concentration, obesity, and risk of diabetes: a mendelian randomisation study. Lancet Diabetes Endocrinol. 2014; 2(4): 298–306. [PubMed: 24703048]

13. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med. 2008; 168(11):1174–80. [PubMed: 18541825]
14. Welles CC, Whooley MA, Karumanchi SA, et al. Vitamin D deficiency and cardiovascular events in patients with coronary heart disease: data from the Heart and Soul Study. Am J Epidemiol. 2014; 179(11):1279–87. [PubMed: 24699783]
15. Madore F, Stampfer MJ, Rimm EB, Curhan GC. Nephrolithiasis and risk of hypertension. Am J Hypertens. 1998; 11(1 Pt 1):46–53. [PubMed: 9504449]
16. Madore F, Stampfer MJ, Willett WC, Speizer FE, Curhan GC. Nephrolithiasis and risk of hypertension in women. Am J Kidney Dis Off J Natl Kidney Found. 1998; 32(5):802–7.
17. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. Kidney Int. 2005; 68(3):1230–5. [PubMed: 16105055]
18. Ferraro PM, Taylor EN, Eisner BH, et al. History of kidney stones and the risk of coronary heart disease. JAMA J Am Med Assoc. 2013; 310(4):408–15.
19. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. J Am Soc Nephrol JASN. 2004; 15(12):3225–32. [PubMed: 15579526]
20. Nguyen S, Baggerly L, French C, Heaney RP, Gorham ED, Garland CF. 25-Hydroxyvitamin D in the range of 20 to 100 ng/mL and incidence of kidney stones. Am J Public Health. 2014; 104(9): 1783–7. [PubMed: 24134366]
21. Holmes RP, Kennedy M. Estimation of the oxalate content of foods and daily oxalate intake. Kidney Int. 2000; 57(4):1662–7. [PubMed: 10760101]
22. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985; 122(1):51–65. [PubMed: 4014201]
23. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol. 1992; 135(10):1114–26–36. [PubMed: 1632423]
24. Taylor EN, Fung TT, Curhan GC. DASH-style diet associates with reduced risk for kidney stones. J Am Soc Nephrol JASN. 2009; 20:2253–2259. [PubMed: 19679672]
25. Heaney RP, Armas LAG, French C. All-Source Basal Vitamin D Inputs Are Greater Than Previously Thought and Cutaneous Inputs Are Smaller. J Nutr. 2013; 143(5):571–5. [PubMed: 23514768]
26. Aloia JF, Patel M, Dimaano R, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. Am J Clin Nutr. 2008; 87(6):1952–8. [PubMed: 18541590]
27. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. Am J Clin Nutr. 2001; 73(2):288–94. [PubMed: 11157326]
28. Cools M, Goemaere S, Baetens D, et al. Calcium and bone homeostasis in heterozygous carriers of CYP24A1 mutations: A cross-sectional study. Bone. 2015; 81:89–96. [PubMed: 26117226]

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Table 1

Age-standardized baseline characteristics by categories of total vitamin D

	Vitamin D intake (IU/day)					
	HPFS		NHS I		NHS II	
	<100 (n=2,390)	≥1,000 (n=2,292)	<100 (n=6,247)	≥1,000 (n=1,252)	<100 (n=4,786)	≥1,000 (n=2,328)
Total vitamin D, IU/day	76(18)	1,317(331)	74(17)	1,261(281)	74(18)	1,250(328)
Dietary vitamin D, IU/day	78(19)	410(279)	75(18)	76(19)	401(213)	308(210)
Supplemental vitamin D, IU/day	0(3)	802(328)	0(4)	0(4)	639(301)	839(312)
Age, years *	51.6(9.1)	56.5(9.6)	51.5(7.0)	54.4(6.9)	37.0(4.7)	37.0(4.7)
BMI, kg/m^2	25.6(3.4)	25.2(3.2)	25.2(4.9)	24.7(4.8)	24.7(5.8)	24.3(5.0)
History of diabetes, %	2	4	3	4	1	1
History of hypertension, %	22	23	26	23	8	7
Thiazide use, %	8	10	14	13	3	2
Calcium supplements use, %	9	65	41	88	12	75
Dietary calcium, mg/day	554(158)	886(373)	515(137)	817(319)	549(139)	1,140(468)
Potassium, mg/day	3057(766)	3951(877)	2,731(603)	3,493(795)	2,580(614)	3,219(608)
Magnesium, mg/day	309(76)	433(121)	256(55)	372(99)	251(64)	412(125)
Animal protein, g/day	55.7(17.5)	74.4(20.6)	46.5(13.0)	59.7(16.2)	55.3(18.5)	69.8(20.9)
Fructose, g/day	27.1(15.2)	27.1(11.7)	22.6(11.5)	22.7(9.6)	27.2(18.2)	24.3(11.3)
Oxalate, mg/day	139(126)	169(163)	109(83)	150(143)	122(115)	158(148)
Dietary vitamin C, mg/day	143(108)	167(90)	141(87)	143(73)	103(70)	107(64)
Supplemental vitamin C, mg/day	112(296)	859(594)	87(252)	672(546)	45(181)	426(506)
Caffeine, mg/day	311(301)	198(232)	334(255)	266(241)	289(253)	223(244)
Alcohol intake, g/day	14.4(19.6)	9.0(12.4)	7.8(13.4)	4.8(8.5)	3.5(7.8)	2.2(4.3)
Fluid volume, L/day	1.8(0.8)	1.9(0.8)	1.8(0.7)	2.0(0.7)	1.9(0.8)	2.1(0.9)

Values are means(SD) or percentages and are standardized to the age distribution of the study population.

* Value is not age adjusted. Total vitamins do not equal to the sum of dietary and supplemental vitamins because dietary intakes are energy-adjusted

Table 2

Total vitamin D intake and risk of kidney stones

	<100 IU/day	100–199 IU/day	200–399 IU/day	400–599 IU/day	600–999 IU/day	≥1,000 IU/day	p-value trend
HPFS							
Cases	101	384	609	392	372	105	
Person-time	30,193	108,964	199,858	132,268	155,101	43,104	
Age-adjusted HR	1.00 (Ref)	1.05 (0.84,1.31)	0.93 (0.76,1.16)	0.94 (0.75,1.17)	0.80 (0.64,1.00)	0.84 (0.64,1.11)	0.09
MV-adjusted HR	1.00 (Ref)	1.10 (0.88,1.37)	1.09 (0.87,1.34)	1.17 (0.92,1.49)	1.05 (0.82,1.35)	1.08 (0.80,1.47)	0.92
NHS I							
Cases	160	338	353	344	317	87	
Person-time	91,707	231,579	293,235	260,494	261,169	80,841	
Age-adjusted HR	1.00 (Ref)	0.85 (0.71,1.03)	0.71 (0.59,0.86)	0.78 (0.64,0.95)	0.74 (0.61,0.90)	0.71 (0.54,0.94)	0.09
MV-adjusted HR	1.00 (Ref)	0.94 (0.77,1.15)	0.89 (0.72,1.09)	1.00 (0.81,1.24)	1.00 (0.79,1.26)	0.99 (0.73,1.35)	0.70
NHS II							
Cases	291	611	819	578	547	168	
Person-time	105,456	272,411	408,970	288,731	280,840	71,929	
Age-adjusted HR	1.00 (Ref)	0.83 (0.72,0.95)	0.75 (0.65,0.85)	0.73 (0.63,0.84)	0.70 (0.60,0.80)	0.82 (0.67,0.99)	0.41
MV-adjusted HR	1.00 (Ref)	0.92 (0.80,1.06)	0.97 (0.83,1.13)	0.96 (0.82,1.13)	0.97 (0.81,1.16)	1.18 (0.94,1.48)	0.02

Multivariate model adjusted for age, region of living, body mass index, history of diabetes, history of hypertension, use of thiazides, use of calcium supplements, intakes of calcium, sodium, potassium, magnesium, animal protein, fructose, oxalate, vitamin C, caffeine, alcohol and fluids

Table 3

Supplemental vitamin D intake and risk of kidney stones

	None	<400 IU/day	400–599 IU/day	600–999 IU/day	≥1,000 IU/day	p-value for trend
HPFS						
Cases	1,068	343	426	98	28	
Person-time	333,293	127,922	159,707	38,509	10,057	
Age-adjusted HR	1.00 (Ref)	0.87 (0.77,0.99)	0.91 (0.81,1.02)	0.85 (0.69,1.05)	1.12 (0.75,1.66)	0.66
MV-adjusted HR	1.00 (Ref)	0.90 (0.78,1.04)	1.00 (0.86,1.15)	0.93 (0.74,1.18)	1.23 (0.81,1.86)	0.34
NHS I						
Cases	671	250	340	62	8	
Person-time	480,572	214,937	252,492	53,291	9,150	
Age-adjusted HR	1.00 (Ref)	0.83 (0.72,0.96)	0.98 (0.87,1.12)	0.90 (0.73,1.12)	0.88 (0.61,1.26)	0.70
MV-adjusted HR	1.00 (Ref)	0.89 (0.76,1.04)	1.09 (0.94,1.27)	1.05 (0.83,1.33)	1.03 (0.71,1.51)	0.26
NHS II						
Cases	1,357	770	635	196	56	
Person-time	624,460	393,051	304,519	86,544	19,761	
Age-adjusted HR	1.00 (Ref)	0.85 (0.78,0.93)	0.92 (0.84,1.02)	0.96 (0.82,1.13)	1.18 (0.90,1.56)	0.76
MV-adjusted HR	1.00 (Ref)	0.94 (0.84,1.04)	1.00 (0.89,1.13)	1.10 (0.92,1.32)	1.38 (1.03,1.85)	0.02

Multivariate model adjusted for age, region of living, body mass index, history of diabetes, history of hypertension, use of thiazides, use of calcium supplements, intakes of calcium, sodium, potassium, magnesium, animal protein, fructose, oxalate, vitamin C, caffeine, alcohol, fluids and dietary vitamin D