Mediterranean diet adherence and risk of incident kidney stones

Adrian Rodriguez,[1,2] *Gary C Curhan,*[3] *Giovanni Gambaro,*[4] *Eric N Taylor,*[3,5] *and Pietro Manuel Ferraro*[1,2]

[1]U.O.C. Nefrologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia; [2]Università Cattolica del Sacro Cuore, Roma, Italia; [3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [4]Renal Unit, Division of Nephrology and Dialysis, Department of Medicine, University of Verona, Ospedale Maggiore, Verona, Italy; and [5]Division of Nephrology and Transplantation, Maine Medical Center, Portland, ME, USA

ABSTRACT

Background: Diet plays an important role in kidney stone formation. Several individual components have been associated with the risk of kidney stone formation, but there is limited evidence regarding the role of healthful dietary patterns.

Objective: To prospectively study the association between adherence to the Mediterranean diet and the risk of incident kidney stones.

Methods: We conducted a longitudinal study using 3 different cohorts: the Health Professionals Follow-up Study ($n = 42,902$ men), the Nurses' Health Study I ($n = 59,994$ women), and the Nurses' Health Study II ($n = 90,631$ women). We assessed diet every 4 y using an FFQ and calculated adherence to a Mediterranean diet using the alternate Mediterranean diet score (aMED). A subgroup of 6077 participants provided ≥1 24-h urine sample, and urinary solute excretion was analyzed. We used Cox proportional hazards regression to examine the independent association between the aMED and incidence of kidney stones, adjusting for potential confounders. We used adjusted linear regression models to study the relation between aMED and urine composition.

Results: During 3,316,633 person-years of follow-up, 6576 cases of incident kidney stones were identified. For participants in the highest aMED score category, the risk of developing a kidney stone was between 13% and 41% lower compared with participants in the lowest score (pooled HR: 0.72, 95% CI: 0.59, 0.87; P value for trend <0.001). A higher aMED score was associated with higher urinary citrate, magnesium, oxalate, phosphate, uric acid, volume, and pH, and lower urinary sodium, resulting in lower supersaturation for calcium oxalate, calcium phosphate, and uric acid.

Conclusion: Adherence to a Mediterranean diet is associated with a lower risk of developing a kidney stone. *Am J Clin Nutr* 2020;111:1100–1106.

Keywords: cohort studies, epidemiology, Mediterranean diet, nephrolithiasis, nutrition

Introduction

Diet plays an important role in the formation of kidney stones. Over the last few decades, there has been substantial advancement in the understanding of the relation between diet and the risk of nephrolithiasis. Thus, although the higher intake of fruits, vegetables, fibre, potassium (K), calcium (Ca), and fluid are associated with a lower incidence of nephrolithiasis (1–5), higher intakes of oxalate (Ox), animal protein, fructose, and vitamin C are independently associated with a higher incidence of kidney stones in prospective cohort studies (3, 6–8).

Studies on dietary patterns and disease risk have emerged because the relation between diet and health is complex with many potential interactions that may not be captured well by studying individual nutrients (9, 10). To our knowledge, only 2 prospective studies have assessed the relation between dietary patterns and the incidence of kidney stones (11, 12): the Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean diet. Both studies found an inverse association between a higher adherence to these dietary patterns and the incidence of kidney stones. The analysis of 24-h urine samples was available for close to 3500 participants in the first study (13), but there were no urinary composition data available for the Mediterranean diet study (11). Furthermore, compared with the Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS) cohorts, the numbers of participants and outcomes in the previous Mediterranean diet study were

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Supplemental Figures 1–3 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to PMF (e-mail: pietromanuel.ferraro@unicatt.it).

Abbreviations used: aMED, alternate Mediterranean diet score; Ca, calcium; CaOx, calcium oxalate; CaP, calcium phosphate; Cit, citrate; Creat, creatinine; DASH, Dietary Approaches to Stop Hypertension; HPFS, Health Professionals Follow-up Study; K, potassium; MDS, Mediterranean diet score; Mg, magnesium; Na, sodium; NHS, Nurses' Health Study; Ox, oxalate; RSS, relative supersaturation; SS, supersaturation; UA, uric acid; V, urinary volume.

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relatively low (16,094 participants with 735 confirmed kidney stones), and participants were grouped into 3 categories of exposure (low, medium, and high adherence to the Mediterranean diet), making a finer analysis of the trend across the individual categories of the Mediterranean diet score (MDS) more difficult.

Adherence to the Mediterranean diet can be estimated by means of different patterns, including the MDS (14) and the alternate Mediterranean diet score (aMED) (15). Apart from the lower incidence of kidney stones, a higher adherence to the Mediterranean diet has been shown to be associated with a variety of important health outcomes, such as a lower risk of cardiovascular disease (15, 16) and diabetes (17), among others.

In this study, we evaluated the association between adherence to the Mediterranean diet, measured as the aMED score, and the risk of incident kidney stones, in 3 large well-established prospective cohorts. We also examined the cross-sectional relation between adherence to the Mediterranean diet and 24-h urine composition in a subgroup of participants with available data.

Methods

Study population

HPFS was established in 1986 with the enrollment of 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians between the ages of 40–75 y. NHS I was established in 1976 with the enrollment of 121,700 female registered nurses between the ages of 30–55 y, and NHS II was established in 1989 with the enrollment of 116,430 registered nurses aged 25–42 y.

At enrollment, participants from each cohort completed a questionnaire with detailed information on diet, medical history, and medications. Participants were then followed by biennial mailed questionnaires, which included inquiries about new episodes of kidney stones.

For this analysis, follow-up started at enrollment for HPFS (1986). For NHS I and NHS II follow-up started in 1986 and 1991, respectively, and continued until the last available information of incident kidney stones: 2012 for HPFS and NHS I and 2011 for NHS II.

Participants who reported a history of kidney stones prior to baseline or those with a history of cancer (except for nonmelanoma skin cancer) were excluded. Those participants who developed cancer during follow-up were censored.

The studies were approved by the Partners HealthCare Institutional Review Board, which considered the return of completed baseline and biennial questionnaires as implied informed consent.

Exposure assessment

A semiquantitative FFQ was used to assess dietary intake. The FFQ asked about the average annual intake of >130 individual foods and >20 beverages, and the information was updated every 4 y. Data from the USDA was used to compute the intake of nutrients from the information in the FFQ. The FFQ has been shown to be reproducible and valid in these cohorts (18–20). We used the FFQ to measure the dietary components of the aMED, as a modification of the original score proposed by Trichopoulou et al. (14, 15). The score was constructed taking into account the consumption of 9 foods or nutrients that were categorized using the sex-specific median values of each component of the score as cut-off points (except for alcohol intake). For the next 7 components (ratio of MUFAs to SFAs, legumes, whole grains, fruits, nuts, vegetables [excluding potatoes], and fish), a participant was assigned a value of 1 if the intake was above the median value of the sample, and 0 otherwise. For red/processed meat consumption, a participant was assigned a value of 1 if the intake was below the median value of the sample and 0 otherwise. For alcohol, a value of 1 was assigned to men who consumed 10–25 g/d and to women who consumed 5–15 g/d, or 0 otherwise. The score ranges from 0 to 9 points; the higher the score, the greater the adherence to the Mediterranean diet.

Covariates assessment

For each cohort, information on age, weight, height and BMI, history of high blood pressure, history of diabetes, and use of thiazides was obtained at baseline and updated every 2 y. Self-reported weight was validated in 2 of the cohorts (HPFS and NHS I) (21). Updated information on intake of Ca, vitamin C and vitamin D supplements, and intake of fluid and caffeine was also recorded from the FFQ.

Outcome assessment

The primary outcome was incidence of a kidney stone episode associated with pain or hematuria. We defined participants as having a symptomatic incident kidney stone when they were free of nephrolithiasis at baseline and reported a kidney stone during follow-up. In these cases, participants received an additional questionnaire about the date of occurrence and associated signs and symptoms such as pain or hematuria. Medical record validation studies confirmed the nephrolithiasis diagnosis in >95% of the cases among participants that submitted the additional questionnaire (12). Participants who reported an asymptomatic episode were censored.

Urine collection and analysis

The 24-h urine samples were collected in 3 cycles. In the first cycle, participants were eligible if they were 70 y or younger in the HPFS or aged 65 y or younger in the NHS I, and had no history of cancer or cardiovascular disease. In the second cycle, participants were eligible if they were younger than 75 y without a history of cancer (except nonmelanoma skin cancer). Finally, the third cycle consisted only of participants in the NHS II cohort with the following characteristics: <55 y, white race, and no previous history of high blood pressure, coronary heart disease, or cancer.

Urine samples collected in the first 2 cycles were analyzed by Mission Pharmacal, whereas the samples collected in the third cycle were analyzed by the Litholink Corporation. Participants with a history of kidney stones were oversampled in the first 2 cycles.

To avoid possible over- or undercollections, participants in the top or bottom 1% of the nonstone-formers urinary creatinine

TABLE 1 Age-adjusted baseline characteristics and dietary intake of the aMED components for HPFS, NHS I, and NHS II cohorts

	aMED score					
	HPFS ($n = 42,902$)		NHS I ($n = 59,994$)		NHS II ($n = 90,631$)	
	0	8–9	0	8–9	0	8–9
N	655	2079	1366	1610	1501	2453
Age, y	52 ± 9	56 ± 10	50 ± 7	56 ± 10	36 ± 5	37 ± 4
BMI, kg/m^2	26 ± 3	25 ± 3	26 ± 5	24 ± 4	26 ± 7	23 ± 4
High blood pressure, %	23	21	25	22	7	4
Diabetes, %	2	2	3	3	1	1
Thiazide use, %	11	8	13	12	2	1
Calcium suppl. use, %	17	35	39	72	24	43
Suppl. calcium, mg/d	53 ± 176	166 ± 335	230 ± 364	488 ± 460	84 ± 223	182 ± 319
Suppl. vitamin C, mg/d	160 ± 338	410 ± 543	119 ± 278	295 ± 422	68 ± 184	209 ± 356
Vitamin D, IU/d	331 ± 263	510 ± 341	273 ± 239	405 ± 246	323 ± 249	425 ± 233
Dietary fluid intake, l/d	2.0 ± 0.8	2.0 ± 0.7	1.8 ± 0.7	2.1 ± 0.6	1.9 ± 0.7	2.3 ± 0.8
Caffeine intake, mg/d	337 ± 303	164 ± 183	346 ± 254	224 ± 176	280 ± 260	229 ± 191
aMED components						
Alcohol, g/d	14 ± 21	13 ± 10	6 ± 13	8 ± 7	2 ± 6	6 ± 5
MUFA/SFA, mg/mg	0.98 ± 0.10	1.32 ± 0.20	0.96 ± 0.10	1.22 ± 0.18	0.97 ± 0.08	1.22 ± 0.17
Fish, servings/d	0.14 ± 0.09	0.73 ± 0.41	0.12 ± 0.07	0.61 ± 0.35	0.11 ± 0.07	0.51 ± 0.30
Red meat, servings/d	1.44 ± 0.63	0.52 ± 0.47	1.18 ± 0.45	0.53 ± 0.40	1.50 ± 0.51	0.71 ± 0.45
Whole grains, servings/d	0.45 ± 0.36	2.72 ± 1.66	0.38 ± 0.31	2.21 ± 1.19	0.46 ± 0.33	2.51 ± 1.34
Legumes, servings/d	0.18 ± 0.08	0.72 ± 0.47	0.19 ± 0.08	0.61 ± 0.32	0.07 ± 0.06	0.49 ± 0.41
Fruits, servings/d	0.98 ± 0.58	3.88 ± 1.81	1.17 ± 0.56	4.19 ± 1.71	0.74 ± 0.43	3.24 ± 1.66
Nuts, servings/d	0.07 ± 0.06	0.91 ± 0.87	0.02 ± 0.03	0.47 ± 0.59	0.03 ± 0.03	0.34 ± 0.31
Vegetables, servings/d	1.26 ± 0.59	4.68 ± 2.13	1.57 ± 0.62	5.45 ± 2.22	1.32 ± 0.53	4.45 ± 1.94

Data are reported as means ± SD unless otherwise indicated.

aMED, alternate Mediterranean diet score; HPFS, Health Professionals Follow-up Study; NHS I, Nurses' Health Study I; NHS II, Nurses' Health Study II.

(Creat) distribution were excluded. For those participants who provided >1 urine sample, only the first urine collection was considered.

Urinary supersaturation (SS) of calcium oxalate (CaOx), calcium phosphate (CaP), and uric acid (UA) were measured by Mission Pharmacal and Litholink using different computer programs. While Mission Pharmacal reported RSSs, Litholink reported urinary SSs.

Statistical analysis

This is a prospective cohort study where the exposure (aMED) was measured before the outcome (incident symptomatic kidney stones). We analyzed the association between aMED and risk of nephrolithiasis using 9 categories of the aMED score (we collapsed scores 8 and 9 to have a sufficient number of outcomes). Time at risk was calculated as time from the start of follow-up to an incident kidney stone, loss to follow-up, death, or censoring, whichever occurred first. Cox proportional hazards regression models were used to calculate the HRs and 95% CIs, adjusted for age (continuous), BMI (13 categories), history of high blood pressure (yes/no), history of diabetes (yes/no), use of thiazides (yes/no), supplemental Ca intake (4 categories), supplemental vitamin C intake (5 categories), total vitamin D intake (quintiles), and fluid and caffeine intake (quintiles). We considered the lowest score of the aMED as the referent category.

We also assessed the association of each component of the aMED score with the incidence of kidney stones. We included the 9 components of the aMED score (as 0 or 1 as described previously) in the Cox regression model, adjusting simultaneously for all of the other components of the aMED score and the potential confounders.

Linear trends were evaluated using the aMED score as a continuous variable. Effect modification by age (50 y or less versus >50 y) and BMI (25 kg/m^2 or less versus >25) was also assessed.

Differences in urinary composition across the groups of aMED were assessed by means of linear regression models, using each urinary parameter as the dependent variable, and adjusting for age, BMI, urinary Creat excretion, study cohort, and history of kidney stones. Results are expressed as adjusted means (SEs) for each urinary parameter.

After assessing the between-cohort heterogeneity, we obtained pooled estimates using random-effects meta-analysis. All *P* values are 2-tailed. Data were analyzed using SAS version 9.4 (SAS Institute).

Results

After exclusions, a total of 193,527 participants were included in the study (42,902 for HPFS, 59,994 for NHS I, and 90,631 for NHS II), contributing 3,316,633 person-years of follow-up. There were 6576 cases of incident kidney stones in the 3 cohorts, 1963 for HPFS, 1599 for NHS I, and 3014 for NHS II (**Supplementary Figures 1–3**).

Baseline characteristics of the study participants in the lowest and highest aMED score categories are shown in **Table 1**.

TABLE 2 Age- and multivariable-adjusted HRs for the risk of incident kidney stones by aMED categories in HPFS, NHS I, and NHS II, and pooled using random-effect meta-analysis

	aMED categories									*P* value for trend
	0	1	2	3	4	5	6	7	8–9	
HPFS										
Cases	41	142	253	349	373	319	263	158	65	—
Person-years	10,488	39,519	77,518	108,484	122,113	118,260	96,456	63,280	33,339	—
Age-adjusted HR	1.00	0.88	0.83	0.85	0.80	0.71	0.73	0.66	0.55	<0.001
95% CI	ref	0.62, 1.25	0.59, 1.15	0.61, 1.17	0.58, 1.11	0.51, 0.99	0.52, 1.01	0.47, 0.94	0.37, 0.81	
Multivariable HR	1.00	0.88	0.83	0.85	0.82	0.73	0.74	0.69	0.57	<0.001
95% CI	ref	0.62, 1.25	0.59, 1.16	0.61, 1.18	0.59, 1.13	0.52, 1.02	0.53, 1.04	0.48, 0.97	0.38, 0.85	—
NHS I										
Cases	33	125	208	302	316	258	202	105	50	—
Person-years	18,971	77,770	150,463	204,619	227,969	214,621	169,765	106,184	48,451	—
Age-adjusted HR	1.00	0.95	0.80	0.85	0.79	0.69	0.67	0.56	0.59	<0.001
95% CI	ref	0.64, 1.39	0.55, 1.16	0.59, 1.22	0.55, 1.14	0.48, 1.00	0.46, 0.97	0.38, 0.83	0.38, 0.91	—
Multivariable HR	1.00	0.97	0.83	0.89	0.85	0.76	0.75	0.65	0.71	0.001
95% CI	ref	0.65, 1.42	0.57, 1.20	0.62, 1.28	0.59, 1.23	0.53, 1.10	0.51, 1.10	0.43, 0.96	0.45, 1.10	—
NHS II										
Cases	74	269	477	515	535	458	370	214	102	—
Person-years	26,321	106,978	189,458	241,233	256,746	237,592	188,673	121,780	59,582	—
Age-adjusted HR	1.00	0.90	0.90	0.76	0.75	0.70	0.70	0.63	0.61	<0.001
95% CI	ref	0.69, 1.16	0.70, 1.15	0.60, 0.97	0.59, 0.96	0.54, 0.89	0.54, 0.90	0.48, 0.82	0.45, 0.82	—
Multivariable HR	1.00	0.94	0.96	0.84	0.85	0.81	0.84	0.78	0.80	0.003
95% CI	ref	0.72, 1.21	0.75, 1.23	0.66, 1.07	0.67, 1.09	0.63, 1.04	0.65, 1.08	0.59, 1.01	0.59, 1.08	—
Pooled										
Cases	148	536	938	1166	1224	1035	835	477	217	—
Person-years	55,780	224,267	417,439	554,336	606,828	570,473	454,894	291,244	141,372	—
Age-adjusted HR	1.00	0.90	0.86	0.80	0.77	0.70	0.70	0.62	0.58	<0.001
95% CI	ref	0.72, 1.08	0.68, 1.02	0.65, 0.95	0.59, 0.92	0.59, 0.83	0.52, 0.83	0.47, 0.75	0.37, 0.72	—
Multivariable HR	1.00	0.94	0.93	0.89	0.86	0.84	0.78	0.79	0.72	<0.001
95% CI	ref	0.93, 0.95	0.77, 1.11	0.75, 1.06	0.72, 1.02	0.71, 1.00	0.65, 0.93	0.66, 0.94	0.59, 0.87	—

Multivariable models were adjusted for age, BMI, history of high blood pressure, history of diabetes, use of thiazides, intake of supplemental calcium, supplemental vitamin C, total vitamin D, fluid, and caffeine. aMED: alternate Mediterranean Diet Score; HPFS, Health Professionals Follow-up Study; NHS I, Nurses' Health Study I; NHS II, Nurses' Health Study II; Ref, reference group.

In general, participants with the highest aMED score had lower BMI, lower prevalence of high blood pressure, lower caffeine intake, and higher intakes of vitamin C supplements, Ca supplements, and total vitamin D.

The association between the aMED score and risk of kidney stones is shown in **Table 2**. In age-adjusted analyses, a higher adherence to the Mediterranean diet was associated with a lower risk of incident kidney stones (*P* value for trend <0.001 in the 3 cohorts). The association remained significant after adjusting for potential confounders (*P* value for trend <0.001, 0.001, and 0.003 for HPFS, NHS I, and NHS II, respectively). The multivariable-adjusted risk of developing a stone in participants in the highest category (aMED score 8 or 9) compared with those in the lowest category was 43% lower in HPFS, 29% lower in NHS I, and 20% lower in NHS II . After pooling (Table 2), the highest category had a 28% (95% CI 13%, 41%) lower risk of stones compared with the lowest category. The relation between aMED and the risk of kidney stones did not vary across age or BMI categories (*P* value for interaction >0.05).

The association of each of the 9 components of the aMED score with incident kidney stones is shown in **Figure 1**. A higher consumption of whole grains and fruit, and moderate alcohol consumption, were associated with a lower risk of kidney stone formation in the 3 cohorts. A higher consumption of legumes and nuts was associated with a lower risk of kidney stones only in men (HPFS cohort), whereas a higher consumption of meat was associated with a lower risk of kidney stones in women (NHS I and II) but not in men.

The association between the aMED score and 24-h urinary composition is reported in **Table 3**. The higher adherence to a Mediterranean diet was associated with higher Ox, citrate (Cit), magnesium (Mg), phosphate, UA, K, urinary volume (V), and pH, and was associated with lower sodium excretion. There was no difference observed in Ca excretion across the aMED categories. Overall, higher aMED categories were associated with a lower RSS for CaOx, UA, and CaP. In this last case, RSS was only statistically significant when measured by Mission Pharmacal, but not when measured by Litholink.

Discussion

In this longitudinal study of 3 large cohorts, a higher adherence to a Mediterranean dietary pattern, calculated as the aMED score, was associated with a markedly lower risk of incident kidney stones. This association was consistent in all 3 cohorts and independent of potential confounders including age, BMI, history

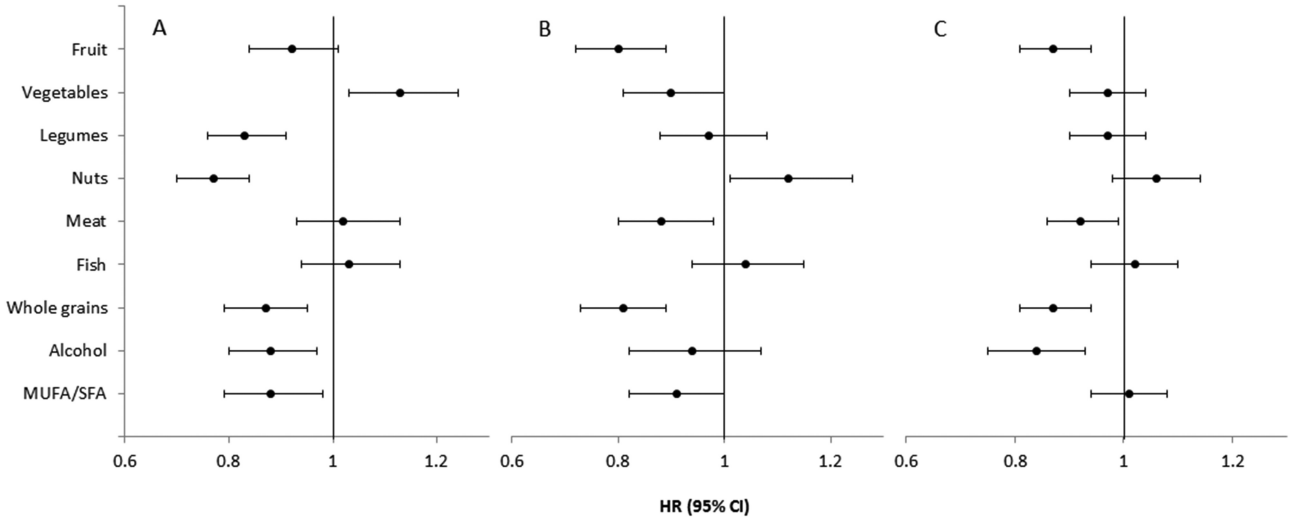

FIGURE 1. HRs for kidney stones associated with each component of the aMED score in (A) HPFS cohort ($n = 42,902$), (B) NHS I cohort ($n = 59,994$), and (C) NHS II cohort ($n = 90,631$). Results are reported as adjusted HRs (95% CI) for the 9 components of the aMED separately, simultaneously adjusted for all the other aMED components, as well as for age, BMI, history of high blood pressure, history of diabetes, use of thiazides, and intake of supplemental calcium, supplemental vitamin C, total vitamin D, fluid, and caffeine. aMED, alternate Mediterranean diet score; HPFS, Health Professionals Follow-up Study; NHS I, Nurses' Health Study I; NHS II, Nurses' Health Study II.

of high blood pressure, history of diabetes, thiazide use, and the intake of supplemental Ca, vitamin C, vitamin D, fluid, and caffeine.

To our knowledge, this is the first longitudinal cohort study in which the aMED score has been associated with a lower risk of kidney stone formation. However, 2 other dietary patterns have been already studied: the MDS (11) and DASH (12). Both MDS and DASH were associated with a lower risk of nephrolithiasis. In the case of the DASH score, it was also examined in the HPFS, NHS I, and NHS II cohorts. Participants in the highest quintile of the DASH score showed a 40–45% lower risk of developing a kidney stone compared with the lowest quintile (12). In the SUN cohort ("Seguimiento University of Navarra"), participants in the highest categories of the MDS (7–9) showed a 36% lower risk of stone formation, when compared with the lowest MDS categories (0–3) (11).

TABLE 3 Pooled adjusted mean (SE) of 24-h urine components, by categories of the aMED

	aMED score									*P* value for trend
	0	1	2	3	4	5	6	7	8–9	
Ca, mg	190 (10)	188 (5)	197 (4)	200 (4)	191 (4)	195 (4)	196 (4)	198 (4)	188 (6)	0.99
Ox, mg	31.1 (1.1)	30.3 (0.6)	31.4 (0.5)	32.4 (0.4)	33.0 (0.4)	32.8 (0.4)	33.4 (0.4)	34.5 (0.5)	35.7 (0.7)	<0.001
Cit, mg	626 (29)	664 (16)	665 (12)	686 (11)	687 (10)	698 (11)	710 (11)	707 (13)	741 (17)	<0.001
UA, mg	524 (14)	516 (8)	519 (6)	529 (5)	526 (5)	538 (5)	536 (6)	533 (6)	549 (8)	<0.001
Na, mmol	158 (6)	151 (3)	154 (2)	155 (2)	152 (2)	149 (2)	152 (2)	152 (3)	143 (3)	<0.001
K, mmol	56.4 (2.1)	57.6 (1.1)	58.8 (0.8)	61.4 (0.7)	62.8 (0.7)	64.8 (0.7)	66.6 (0.8)	68.9 (0.9)	71.8 (1.2)	<0.001
Mg, mg	96 (4)	99 (2)	104 (2)	102 (1)	107 (1)	109 (1)	110 (2)	114 (2)	114 (2)	<0.001
P, mg	734 (32)	674 (17)	720 (13)	706 (12)	732 (11)	715 (12)	738 (13)	754 (15)	750 (19)	<0.001
pH	5.90 (0.05)	5.98 (0.03)	5.94 (0.02)	5.99 (0.02)	5.98 (0.02)	6.01 (0.02)	6.06 (0.02)	6.02 (0.02)	6.06 (0.03)	<0.001
V, L	1.55 (0.08)	1.58 (0.04)	1.64 (0.03)	1.69 (0.03)	1.72 (0.03)	1.81 (0.03)	1.85 (0.03)	1.89 (0.03)	1.89 (0.05)	<0.001
Creat, mg	1309 (25)	1330 (13)	1315 (10)	1332 (9)	1335 (9)	1339 (9)	1326 (10)	1322 (11)	1345 (15)	0.33
RSS,[1] CaOx	1.80 (0.14)	1.70 (0.07)	1.76 (0.06)	1.72 (0.05)	1.63 (0.05)	1.64 (0.05)	1.55 (0.05)	1.61 (0.06)	1.47 (0.08)	<0.001
SS,[2] CaOx	5.76 (0.55)	5.77 (0.28)	5.93 (0.23)	5.74 (0.21)	5.63 (0.20)	5.22 (0.20)	5.35 (0.22)	5.33 (0.25)	5.61 (0.31)	0.007
RSS,[1] CaP	1.49 (0.15)	1.35 (0.08)	1.37 (0.06)	1.39 (0.05)	1.29 (0.05)	1.35 (0.05)	1.33 (0.06)	1.20 (0.07)	1.19 (0.09)	0.011
SS,[2] CaP	1.05 (0.16)	1.32 (0.08)	1.15 (0.07)	1.16 (0.06)	1.14 (0.06)	1.07 (0.06)	1.12 (0.06)	1.12 (0.07)	1.18 (0.09)	0.16
RSS,[1] UA	2.15 (0.21)	2.05 (0.11)	2.12 (0.08)	1.95 (0.07)	1.87 (0.07)	1.85 (0.08)	1.61 (0.08)	1.85 (0.09)	1.56 (0.13)	<0.001
SS,[2] UA	0.94 (0.13)	0.75 (0.06)	0.76 (0.05)	0.72 (0.05)	0.70 (0.05)	0.60 (0.05)	0.60 (0.06)	0.57 (0.06)	0.59 (0.07)	<0.001

Models were adjusted for age, BMI, urinary creatinine, history of kidney stones, and study cohort (HPFS, NHS I, or NHS II).

aMED, alternate Mediterranean diet score; Ca, calcium; CaOx, calcium oxalate; CaP, calcium phosphate; Cit, citrate; Creat, creatinine; HPFS, Health Professionals Follow-up Study; K, potassium; Mg, magnesium; Na, sodium; NHS I, Nurses' Health Study I; NHS II, Nurses' Health Study II; Ox, oxalate; P, phosphorous; RSS, relative supersaturation; SS, supersaturation; UA, uric acid; V, urinary volume.

[1]Measured by Mission Pharmacal.

[2]Measured by Litholink.

The aMED score and MDS are 2 different ways of assessing adherence to a Mediterranean dietary pattern (14, 15). Compared with the aMED, the MDS also includes low dairy product intake in the score; fruits and nuts are calculated together as the same component; the values for moderate alcohol consumption are higher (5–25 mg/d for women and 10–50 mg/d for men); instead of whole grains, all cereals are considered; and instead of red and processed meat, all meat is considered. Even using a different score, our results are in accordance with the previously reported findings and reinforce the hypothesis that adherence to a Mediterranean diet would decrease the risk of stone formation.

When we studied the components of the aMED score separately, we found some consistencies among the 3 cohorts. Higher fruit and whole grains intake and moderate alcohol consumption were associated with a lower risk of nephrolithiasis in all 3 cohorts. A high fruit intake has been previously described as a protective factor for kidney stone formation (1, 3), probably because it can increase urinary pH, Cit, and volume. On the other hand, whole grains contain phytate, which is a CaOx crystallization inhibitor and may explain the observed lower risk (22). For alcohol intake, results are more difficult to interpret, since the score only counts for participants with a moderate consumption (5–15 g in women and 10–25 g in men). Thus, those with no alcohol consumption, and those with higher alcohol consumption are both given a zero in the score. However, these results are also in accordance with a previous study, in which we found that the intake of beer and wine was associated with a lower risk of stones (23).

Regarding red and processed meat, we found that women with high consumption had a lower risk of nephrolithiasis, but these differences were not observed in men. Differences in individual dietary factors between the cohorts of men and women were already found in the 3 cohorts. For example, a higher intake of phytate was associated with a lower risk of nephrolithiasis in women (22) but not in men (24). On the other hand, the intake of animal protein has been associated with a higher risk of nephrolithiasis in men (25) but not in women (22, 26), However, it has previously been demonstrated that the risk of kidney stones may vary by the type of protein intake: dairy protein is associated with a lower risk of stones in the NHS II cohort, whereas nondairy protein intake is associated with a slightly higher risk of stones in NHS I and HPFS (3). Finally, we cannot exclude that those findings were due to chance.

An unexpected finding was that the higher consumption of vegetables seems to be associated with a higher risk of nephrolithiasis in men. Our finding may be due to the fact that the comparison performed was between participants below and above the median consumption. Tendencies across quintiles of vegetable consumption would probably be a better approach to analyze such an association. Another possible explanation is that the analysis did not take into account effect modification by Ca intake, which would be relevant since some vegetables are a source of Ox: when we stratified the HPFS population based on dietary Ca intake (below or above 600 mg/d), the direct association between vegetable consumption and stones remained significant only among those with a lower Ca intake, confirming our previous findings (8).

The 24-h urinary excretion of some solutes involved in kidney stone formation may partially explain the results described above. For example, the higher adherence to a Mediterranean diet is associated with a higher excretion of Cit and Mg and higher V, which are all protective factors for kidney stone formation. On the other hand, it was also associated with higher Ox excretion, and higher UA and phosphate excretion, which can increase the risk. All these changes in the urinary excretion may modify the urinary SS of CaOx, CaP, or UA. In our cohorts, a higher aMED score was associated with significantly lower values for all 3 SSs, suggesting that the adherence to a Mediterranean dietary pattern is associated with overall protective urinary milieu.

Our study has several strengths. To our knowledge, this is the first study evaluating the association between the aMED and the risk of kidney stones. Furthermore, the association was examined in 3 different cohorts, and the results are consistent across those cohorts. Other strengths are the prospective design, the large sample size and follow-up, and the use of a validated FFQ. In addition, the analysis of the 24-h urine data from >6000 participants allowed a better understanding of the potential role of the Mediterranean diet in the formation of kidney stones.

Our study also has some limitations. First, there is a lack of information on kidney stone composition. Second, the cohorts are predominantly white, so these findings may not extrapolate to the general population. Furthermore, we do not have information on young men (<40 y). Last, as this is an observational study, residual confounding cannot be ruled out, despite the extensive control for a large number of key variables.

In conclusion, the consumption of a Mediterranean dietary pattern was independently associated with a lower risk of incident kidney stone formation. The lower urinary SS of CaOx, CaP, and UA likely accounts for the observed lower risk. Given the consistency of these results and others found in the literature, following a Mediterranean dietary pattern may reduce the burden of kidney stones.

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