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Physical activity, energy intake, and the risk of incident kidney stones

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Abstract

Purpose—Recent data suggest higher physical activity (PA) and lower energy intake (EI) may be associated with a lower risk of kidney stones. Whether these associations can be reproduced in other study populations after accounting for lifestyle and dietary factors is not known.

Materials and methods—We analyzed data from three large prospective cohorts, the Health Professionals Follow-up Study (HPFS) and Nurses' Health Studies (NHS) I and II. Information was collected through validated biennial questionnaires. The hazard ratio (HR) of incident stones among participants within different categories of PA and EI was assessed with Cox proportion hazards regression adjusted for age, BMI, race, comorbidities, medications, calcium supplement use, fluid and nutrient intakes.

Results—The analysis included 215,133 participants. After up to 20 years of follow-up, 5,355 incident cases of kidney stones occurred. In age-adjusted analyses, higher levels of PA were associated with a lower risk of incident kidney stones in women (NHS I and II) but not men. However, after multivariate adjustment, there was no significant association between PA and risk of kidney stones (HPFS: HR for highest vs lowest category 1.00, 95% confidence interval [CI] 0.87, 1.14, p for trend=0.94; NHS I: HR 1.01, 95% CI 0.85, 1.19, p for trend = 0.88; NHS II: HR 1.03, 95% CI 0.90, 1.18, p for trend = 0.64). EI was not associated with stone risk (multivariate-adjusted p for trend ≥ 0.49).

Conclusions—In three large prospective cohorts, there were no independent associations between PA, EI, and incidence of symptomatic kidney stones.

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Keywords

body mass index; energy intake; exercise; urolithiasis

Introduction

Kidney stone disease is a common condition, with a prevalence of about 10% in the general population,[1, 2] and is associated with high morbidity and cost.[3] Numerous potentially modifiable risk factors for kidney stones have been identified, including higher body mass index, lower intake of fluid, and intakes of a wide variety of specific nutrients and beverages.[4–8]

It is not known whether reduced levels of physical activity increase the risk of developing kidney stones, especially since lower activity is highly correlated with known risk factors for kidney stones such as higher body mass index. A recent observational study reported that among postmenopausal women, increased levels of physical activity and lower energy intake were associated with a significant reduction in the risk of kidney stones, even after taking into account body mass index (BMI), history of diabetes, and intakes of fluid, dietary calcium, sodium, and animal protein.[9] However, it is not clear whether these associations might be due to other comorbidities or dietary factors associated with physical activity, energy intake, and kidney stone risk. It is also unknown whether such associations would hold for other populations such as men or younger women. We analyzed the independent associations between physical activity, energy intake, and 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 population

The HPFS enrolled 51,529 male health professionals between the ages of 40 and 75 years in 1986. The NHS I enrolled 121,700 female nurses between the ages of 30 and 55 years in 1976, and the NHS II enrolled 116,430 female nurses between the ages of 25 and 42 years in 1989. Participants in all three cohorts complete biennial questionnaires reporting information on medical history, lifestyle, and medications; information was updated every 2 years or every 4 years (for food frequency questionnaires). Participants with a history of kidney stones or cancer (except for nonmelanoma skin cancer) at baseline were excluded from the analysis, whereas those who developed cancer during follow-up were censored.

Assessment of physical activity

The questionnaires assessed every two years the average time per week spent in the previous year on recreational and outdoor activities, including walking, jogging (slower than 10 min/mile), running (10 min/mile or faster), bicycling, calisthenics or exercise machines, tennis, racquetball or squash, lap swimming, weight lifting and outdoor work. A metabolic equivalent (MET) score was assigned for each activity, which is the metabolic rate associated with that particular exercise in comparison with the resting rate. MET scores for each activity were multiplied by the reported hours spent per week and summed to obtain a MET-hour score, with one MET corresponding to about 1 kcal per kilogram of body weight per hour. MET scores obtained from the questionnaires have been previously validated in two of the three cohorts included in our analysis.[10, 11]

Assessment of kidney stones

The primary outcome was an incident kidney stone accompanied by pain or hematuria. Biennial questionnaires asked about a history of kidney stones in each cohort in the previous 2 years. Participants reporting an incident kidney stone completed a supplementary questionnaire about the date of occurrence and related symptoms. In medical record validation studies, the self-reported diagnosis was confirmed in approximately 97% of participants who completed the supplementary questionnaire.[5, 7] Stone composition analyses were available in a subsample of the population and stone type was predominantly calcium oxalate in 86% of the HPFS participants, 77% of the NHS I participants and 79% of the NHS II participants.[12]

Assessment of other covariates

The following covariates were included in the analysis: age, race, geographic region (Midwest, Northeast, South, West), BMI, use of calcium supplements (yes vs no), use of postmenopausal hormones (for NHS I and NHS II cohorts), profession (HPFS), intakes of energy, dietary calcium, sodium, animal protein, caffeine, potassium, magnesium, total vitamin C, total fructose, oxalate, phytate and fluid (all quintiles), alcohol (7 categories), history of diabetes, history of hypertension, history of gout, and use of thiazide diuretics (yes vs. no).

Self-reported weight, from which BMI was calculated, was validated in the HPFS and NHS I cohorts.[13] Nutrient intakes were derived from a semiquantitative food-frequency questionnaire (FFQ) administered every 4 years. The baseline FFQ asked about average intake of more than 130 individual foods and 22 beverages during the previous year. Intake of nutrients was derived from the reported frequency of consumption of each item and from United States Department of Agriculture data on the content of the relevant nutrient in specified portions (except for oxalate, whose content in the foods reported in the food-frequency questionnaire was measured by capillary electrophoresis).[14, 15] The reproducibility and validity of the FFQs were previously documented in HPFS and NHS I.[16–19] Energy-adjusted nutrients were used for this analysis. The intake of mineral and vitamin supplements, such as calcium and vitamin D, in multivitamin or isolated form was determined by the brand, type, and frequency of reported use.

Statistical analysis

Categories of physical activity were created with cutpoints at 5, 10, 20, and 30 METs/week as previously reported.[9] Similarly, cutpoints for BMI were placed at 18.5, 25, 30, and 35 Kg/m^2 and for energy intake at 1,800, 2,000, 2,200, and 2,500 Kcal/day. Nutrients were included in the analysis as quintiles. Linear trends for categories of physical activity were assessed assigning the median value of METs/week to each category and analyzing the term as a continuous variable. Age- and multivariate adjusted hazard ratios (HRs) with 95%

confidence intervals (CIs) for the development of symptomatic kidney stones in categories of physical activity were computed by means of Cox regression models with update of exposure and covariate status, selecting the lowest category (0 to 4.9 METs/week) as the referent category. For this analysis, follow-up time started in 1986 for the HPFS and NHS I cohorts and 1991 for the NHS II cohort and went up to 2006 for the HPFS and NHS I cohorts and 2007 for the NHS II cohort.

All the analyses were performed with SAS version 9.3 (SAS Institute). The research protocol for this study was reviewed and approved by the institutional review board of Brigham and Women's Hospital.

Results

The analysis included 215,133 participants, providing 3,468,691 person-years of follow-up. Baseline characteristics of the study population are reported in Tables 1–3, divided by categories of physical activity. Across increasing categories of physical activity, there was a trend toward younger age in HPFS and NHS II, increased intakes of calcium (dietary and supplemental), vitamin C, potassium, magnesium, oxalate and fluid in all the cohorts, and lower prevalence of the following: hypertension in all cohorts, diabetes in HPFS and NHS I, gout in HPFS, and use of thiazides in HPFS and NHS I.

During follow-up, 5,355 participants developed symptomatic kidney stones. Estimates of association for the age-adjusted and multivariate-adjusted models are reported in Table 4. The age-adjusted association between physical activity and incident kidney stones was not statistically significant in the HPFS cohort (HR for the highest vs lowest category 0.92, 95% CI 0.80, 1.04; p-value for trend = 0.26), whereas there was a significant trend toward reduced risk in the NHS I cohort (HR for the highest vs lowest category 0.81, 95% CI 0.69, 0.95; p-value for trend = 0.003) and in the NHS II cohort (HR for the highest vs lowest category 0.81, 95% CI 0.71, 0.92; p-value for trend = 0.001). However, after adjustment for total energy intake, intakes of dietary calcium, sodium, animal protein and total fluid, diabetes, race, use of calcium supplements, postmenopausal hormones and region of living, the association became non-significant in both the NHS I cohort (HR for the highest vs lowest category 0.94, 95% CI 0.80, 1.10; p-value for trend = 0.27) and the NHS II cohort (HR for the highest vs lowest category 0.99, 95% CI 0.87, 1.12; p-value for trend = 0.81) and remained non-significant in the HPFS cohort (HR for the highest vs lowest category 0.93, 95% CI 0.81, 1.06; p-value for trend = 0.38). Additional adjustment for other nutrients and comorbidities further increased the HR for kidney stone risk to 1.00 (95% CI 0.87, 1.14) for HPFS, to 1.01 (95% CI 0.85, 1.19) for NHS I, and to 1.03 (95% CI 0.90, 1.18) for NHS II.

The main factors that changed the stone risk estimates associated with physical activity from inverse toward the null in age-adjusted compared with multivariate adjusted analyses in the NHS I and II cohorts were BMI and potassium intake. In NHS II, alcohol and fluid intake also attenuated the inverse association between physical activity and stone risk. In HPFS, the main factors attenuating the inverse association were calcium, potassium and alcohol intake.

Total energy intake was not associated with risk of kidney stones in any cohort: among HPFS participants, the multivariate-adjusted HR for the highest category compared with the lowest was 1.05 (95% CI 0.89, 1.24; p-value for trend = 0.49). Among NHS I participants, the multivariate-adjusted HR for the highest category compared with the lowest was 1.05 (95% CI 0.85, 1.30; p-value for trend = 0.55). Among NHS II participants, the multivariate-adjusted HR for the highest category compared with the lowest was 1.01 (95% CI 0.85, 1.18; p-value for trend = 0.55).

We performed a number of sub-analyses. Using different cutpoints for physical activity, including dividing the lowest category in two categories of “0 to 0.9” and “1 to 4.9” METs/week and the highest category in “30 to 34.9” and “35+” METs/week did not significantly change the magnitude of the associations. We also restricted the analysis to postmenopausal women in the NHS I cohort, and the results did not change. In addition, including calcium supplements in categories instead of as a binary variable did not change the results. We also repeated the analyses without updating exposure and covariate status and the results were unchanged. Finally, we repeated the analyses without supplemental questionnaire verification of incident kidney stones. In these analyses, the results for NHS II were unchanged. However, in HPFS the HR for the highest vs lowest category of physical activity (adjusted for the covariates in the “first” multivariate model in Table 4) decreased from 0.93 to 0.89 (95% CI 0.79, 1.00) and in NHS I decreased from 0.94 to 0.82 (95% CI 0.67, 1.00).

Discussion

In our study, we analyzed the relation between physical activity and incidence of kidney stones in three large prospective cohorts; in age-adjusted analyses, we found a significant inverse association between physical activity and risk of developing stones in two of the three cohorts (NHS I and NHS II), whereas the association was null in the HPFS. However, after adjusting for additional covariates, the association between physical activity and kidney stones was null in all three cohorts. Changing the cutpoints for categories of physical activity and restricting the analysis to post-menopausal women did not change these findings. We also did not find any significant associations between total energy intake and risk of developing stones in age-adjusted and multivariate-adjusted analyses.

Our results differ from those of a recent study that examined the association between physical activity and risk of developing kidney stones in a cohort of 84,225 post-menopausal women in the Women’s Health Initiative (WHI).[9] The authors found that, after adjusting for age, race, history of diabetes, use of calcium supplement, hormone replacement therapy, income, region, intake of water, sodium, animal protein, and dietary calcium, those with a level of physical activity > 10 METs/week had a significant 30% lower risk of kidney stones, taking into account levels of energy intake and BMI. The authors also found that increased energy intake was associated with a significantly higher risk of developing stones, taking into account levels of physical activity and BMI.

The reasons for the discrepancy between our results and those obtained in the WHI cohort[9] may be due to several factors. As in WHI, higher BMI independently associates with increased risk of kidney stones in the HPFS, NHS I, and NHS II cohorts,[4] and higher levels of physical activity in our study were associated with lower risk in unadjusted analyses. However, after replicating the set of covariates used in the multivariate-adjusted WHI models, the inverse associations between physical activity and kidney stones in our study were attenuated and statistically non-significant. Further adjustment for a number of comorbid conditions and nutrient intakes not accounted for in the WHI analysis confirmed our finding that there was no independent association between physical activity and kidney stones. Taken together, these findings suggest that the relation between physical activity and kidney stones is confounded by other factors associated with both. This hypothesis is corroborated by our finding that the main contributors of the association between physical activity and kidney stones were BMI and intake of potassium.

There are several potentially important differences between our study and the WHI study. First, self-reported kidney stones have not been validated in WHI. Of note, the stone risk hazard ratios associated with physical activity in our study became more inverse in HPFS and NHS I when we included self-reported kidney stones without supplemental questionnaire verification. Second, our study included both males and females of various ages, whereas the WHI study only included post-menopausal women. However, restriction of our study sample to post-menopausal women did not modify the results. Third, we updated the values of exposures and covariates throughout the course of the study. However, repeating our analyses without updating exposure and covariate status did not change the findings. Fourth, our study population had only a small number of participants with extremely low levels of physical activity. Thus, we did not use a physically “inactive” group (< 0.1 METs/wk) as our referent category. However, sub-analyses with different cutpoints for lower physical activity did not change our results. Fifth, we could not include income in our analysis as this information was not available in our cohorts. However, this is unlikely to have influenced our results since income is not a risk factor for incident kidney stones per se but rather as a proxy of – mainly dietary – lifestyle factors that could entail a risk of stones and that have been taken into account in our analysis. Furthermore, given that our cohorts are composed of participants with the same profession, a significant disparity of income within cohorts would be unlikely.

Our study has limitations. Because our study is observational, it is possible that our results are confounded by unmeasured or unknown variables. We also do not have stone composition reports for the majority of incident kidney stones in our study. It is possible that physical activity is independently associated with some types of kidney stones but not others. Finally, our study population is predominantly white and includes no men < 40 years of age. Thus, our results may not be generalizable to other races or to younger men.

Conclusions

In conclusion, physical activity and total energy intake are not independent risk factors for kidney stones.

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Abbreviations

BMI	body mass index
CI	confidence interval
EI	energy intake
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
MET	metabolic equivalent
NHS	Nurses' Health Study
PA	physical activity
WHI	Women's Health Initiative

Table 1

Age-standardized baseline characteristics by categories of physical activity. Health Professionals Follow-up Study (n=44,964)

	Physical activity, METs/week				
	0–4.9 (n=13,644)	**5–9.9 (n=6,525)**	**10–19.9 (n=8,750)**	**20–29.9 (n=5,443)**	**30+ (n=10,602)**
Age, years*	55.3(9.9)	54.9(9.9)	54.2(9.8)	55.0(10.0)	53.0(9.7)
BMI, kg/m^2	25(6)	25(5)	25(5)	25(5)	24(5)
Caucasian, %	94	95	95	95	95
Diabetes, %	4	3	3	3	2
Hypertension, %	24	22	22	21	19
Gout, %	6	5	5	5	4
Thiazide use, %	11	10	9	8	7
Calcium supplement use, %	14	15	17	17	19
Caffeine, mg/day	270(274)	251(252)	229(240)	229(241)	218(234)
Dietary calcium, mg/day	786(320)	802(304)	804(295)	815(297)	810(302)
Potassium, mg/day	3,324(715)	3,412(706)	3,469(705)	3,538(715)	3,585(744)
Magnesium, mg/day	338(80)	350(82)	358(80)	364(82)	372(89)
Total vitamin C, mg/day	373(435)	410(460)	451(488)	460(487)	489(505)
Fructose, g/day	24(12)	25(11)	25(11)	26(11)	27(12)
Oxalate, mg/day	134(116)	142(179)	148(130)	150(126)	153(130)
Phytate, mg/day	879(365)	916(376)	963(397)	972(383)	1,009(430)
Alcohol intake, g/day	11(16)	11(16)	11(15)	11(15)	12(15)
Fluid, mL/day	1,924(846)	1,944(791)	1,913(784)	1,949(787)	2,011(828)

Values are means(SD) or percentages and are standardized to the age distribution of the study population. Dietary intakes are energy-adjusted except for alcohol and fluid.

* Value is not age adjusted

Table 2

Age-standardized baseline characteristics by categories of physical activity. Nurses' Health Study I (n=74,551)

	Physical activity, METs/week				
	0–4.9 (n=30,804)	**5–9.9 (n=12,276)**	**10–19.9 (n=13,933)**	**20–29.9 (n=7,765)**	**30+ (n=9,773)**
Age, years*	52.9(7.1)	52.9(7.2)	52.9(7.2)	53.0(7.2)	52.9(7.2)
BMI, kg/m^2	26(5)	25(5)	25(4)	25(4)	24(4)
Caucasian, %	94	95	95	94	94
Diabetes, %	4	4	3	3	3
Hypertension, %	27	26	24	23	22
Gout, %	2	2	2	2	2
Thiazide use, %	14	14	13	12	11
Calcium supplement use, %	42	48	51	52	54
Postmenopausal hormone use, %	14	14	14	14	14
Caffeine, mg/day	302(240)	281(224)	271(219)	261(213)	263(218)
Dietary calcium, mg/day	699(257)	721(245)	735(252)	743(249)	749(259)
Total potassium, mg/day	2,960(619)	3,053(595)	3,116(606)	3,158(609)	3,242(655)
Magnesium, mg/day	287(66)	299(66)	308(68)	314(71)	320(72)
Total vitamin C, mg/day	311(356)	342(365)	364(376)	371(379)	410(409)
Fructose, g/day	21(9)	22(9)	22(9)	22(9)	23(9)
Oxalate, mg/day	108(83)	119(90)	124(92)	129(96)	140(120)
Phytate, mg/day	673(252)	706(259)	732(277)	745(281)	752(311)
Alcohol intake, g/day	6(11)	6(10)	6(10)	7(11)	7(11)
Fluid, mL/day	1,423(709)	1,401(677)	1,386(658)	1,362(658)	1,395(704)

Values are means(SD) or percentages and are standardized to the age distribution of the study population. Dietary intakes are energy-adjusted except for alcohol and fluid.

*Value is not age adjusted

Table 3

Age-standardized baseline characteristics by categories of physical activity. Nurses' Health Study II (n=95,618)

	Physical activity, METs/week				
	0–4.9	**5–9.9**	**10–19.9**	**20–29.9**	**30+**
	(n=23,839)	**(n=16,962)**	**(n=21,595)**	**(n=12,372)**	**(n=20,850)**
Age, years*	37.1(4.6)	36.7(4.6)	36.5(4.6)	36.4(4.7)	36.0(4.7)
BMI, kg/m^2	26(6)	25(6)	24(5)	24(5)	23(4)
Caucasian, %	92	94	94	95	93
Diabetes, %	1	1	1	1	1
Hypertension, %	7	7	6	6	6
Gout, %	0	0	0	0	0
Thiazide use, %	2	2	2	2	2
Calcium supplement use, %	14	16	18	18	19
Postmenopausal hormone use, %	5	4	5	4	4
Caffeine, mg/day	251(232)	243(221)	240(218)	236(217)	244(223)
Dietary calcium, mg/day	847(313)	874(301)	896(301)	910(295)	916(304)
Total potassium, mg/day	2,783(525)	2,880(503)	2,945(515)	3,015(533)	3,104(568)
Magnesium, mg/day	296(70)	308(70)	318(72)	327(75)	338(81)
Total vitamin C, mg/day	219(287)	238(298)	260(319)	277(332)	305(362)
Fructose, g/day	22(12)	22(11)	23(10)	23(10)	24(11)
Oxalate, mg/day	117(98)	126(101)	134(110)	144(122)	158(139)
Phytate, mg/day	739(218)	767(225)	789(235)	806(249)	827(266)
Alcohol intake, g/day	3(6)	3(6)	3(6)	3(6)	4(6)
Fluid, mL/day	2,022(851)	2,084(840)	2,130(828)	2,180(833)	2,278(910)

Values are means(SD) or percentages and are standardized to the age distribution of the study population. Dietary intakes are energy-adjusted except for alcohol and fluid.

*Value is not age adjusted

Table 4

Hazard ratios and 95% confidence intervals of incident kidney stones by categories of physical activity in the Health Professional Follow-Up Study, Nurses' Health Study I and Nurses' Health Study II cohorts

	Physical activity (METs/week)					p-value for trend
	< 5	**5 – 9.9**	**10 – 19.9**	**20 – 29.9**	**≥30**	
HPFS						
cases	367	205	356	250	663	
person-years	136,789	79,675	130,804	99,102	263,469	
age-adjusted HR	1.00	0.94 (0.79, 1.12)	0.99 (0.86, 1.15)	0.93 (0.79, 1.09)	0.92 (0.80, 1.04)	0.26
first multivariate HR	1.00	0.94 (0.79, 1.12)	0.99 (0.85, 1.14)	0.92 (0.78, 1.08)	0.93 (0.81, 1.06)	0.38
second multivariate HR	1.00	0.96 (0.81, 1.15)	1.03 (0.88, 1.19)	0.97 (0.82, 1.15)	1.00 (0.87, 1.14)	0.94
NHS I						
cases	563	243	275	141	217	
person-years	456,604	213,348	264,921	153,582	218,050	
age-adjusted HR	1.00	0.92 (0.79, 1.07)	0.84 (0.73, 0.98)	0.75 (0.62, 0.90)	0.81 (0.69, 0.95)	0.003
first multivariate HR	1.00	0.96 (0.82, 1.11)	0.91 (0.79, 1.05)	0.84 (0.69, 1.01)	0.94 (0.80, 1.10)	0.27
second multivariate HR	1.00	0.99 (0.85, 1.15)	0.95 (0.82, 1.10)	0.89 (0.74, 1.08)	1.01 (0.85, 1.19)	0.88
NHS II						
cases	600	382	441	245	407	
person-years	383,275	251,592	321,629	185,592	310,258	
age-adjusted HR	1.00	0.94 (0.82, 1.07)	0.85 (0.75, 0.96)	0.82 (0.71, 0.95)	0.81 (0.71, 0.92)	0.001
first multivariate HR	1.00	1.00 (0.88, 1.13)	0.95 (0.84, 1.07)	0.95 (0.81, 1.10)	0.99 (0.87, 1.12)	0.81
second multivariate HR	1.00	1.01 (0.89, 1.15)	0.97 (0.86, 1.10)	0.98 (0.84, 1.14)	1.03 (0.90, 1.18)	0.64

First multivariate model adjusted for age, race, BMI, diabetes, calcium supplement use (yes vs no), postmenopausal hormone use (NHS I and NHS II), geographic region (Midwest, Northeast, South, West), and dietary intakes of total energy (4 categories), calcium, sodium, animal protein and fluids (all quintiles). Second multivariate model further adjusted for intakes of caffeine, potassium, magnesium, vitamin C, fructose, oxalate and phytate (all quintiles), alcohol (7 categories), diabetes, high blood pressure, gout, profession (HPFS), and use of thiazides.