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ORIGINAL ARTICLE

Factors associated with sex differences in the risk of kidney stones

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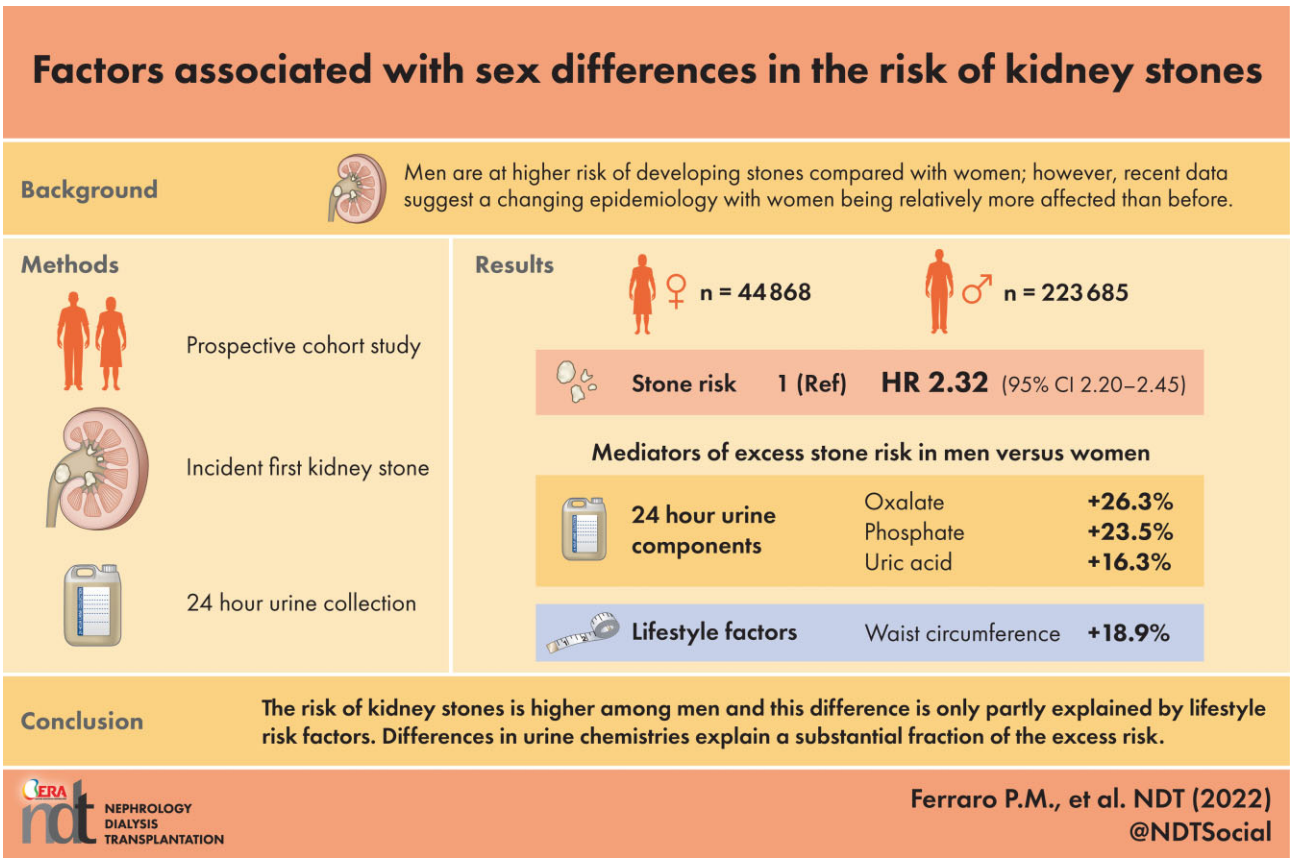
GRAPHICAL ABSTRACT



ABSTRACT

Background. Men are at higher risk of developing stones compared with women; however, recent data suggest a changing epidemiology, with women being relatively more affected than before.

Methods. To estimate the proportion of excess risk among men, we analysed data from large cohorts (Health Professionals Follow-up Study and Nurses' Health Study I and II). Kidney stone incidence rates were computed and hazard ratios (HRs) and 95% confidence intervals (CIs) generated with

KEY LEARNING POINTS

What is already known about this subject?

- The higher prevalence of kidney stones among men compared with women has been previously reported, but there is limited evidence on why men are at higher risk.

What this study adds?

- This study investigated three large cohorts with detailed and updated information on dietary habits and other conditions that might impact the risk of forming stones and found that men are overall at higher risk of stones compared with women.
- Several factors, including differences in waist circumference, fluid intake and especially urine composition, explained a meaningful proportion of the excess risk among men.

What impact this may have on practice or policy?

- Since lifestyle risk factors play a role in the excess risk of kidney stones among men, we can expect that vigorously tackling those factors would result in a reduction in the rate of stone formation.

age-adjusted Cox proportional regression models. Mediation analysis estimated the excess risk for men explained by risk factors, including waist circumference, high blood pressure, diabetes, use of thiazides and dietary intake. The 24-h urine composition was also examined.

Results. The analysis included 268 553 participants, contributing 5 872 249 person-years of follow-up. A total of 10 302 incident stones were confirmed and the overall incidence rate was 271 and 159 per 100 000 person-years for men and women, respectively. The age-adjusted HR was 2.32 (95% CI 2.20, 2.45) and the risk of stones was consistently higher across categories of age (HRs ranging from 2.02 to 2.76) for men compared with women. The risk remained higher among men, but tended to decrease over time (48.1%), while it increased among women. Urine supersaturations for calcium oxalate and uric acid were higher among men, primarily because of higher oxalate (26.3%), uric acid (16.3%), phosphate (23.5%) and lower pH.

Conclusions. The risk of kidney stones is higher among men and this difference is only partly explained by lifestyle risk factors; differences in urine chemistries explain a substantial fraction of the excess risk.

Keywords: cohort studies, kidney stones, nephrolithiasis, risk factors, sex

INTRODUCTION

Kidney stone disease is common in the general population, with a prevalence higher than 10% in the most recent National Health and Nutrition Examination Survey [1]; it is also characterized by high recurrence rates [2]. A number of genetic [3] and environmental [4] factors are thought to play a role in its pathogenesis, including fluid intake, [5, 6] dietary calcium [7–9], animal protein [10] and adherence to a Dietary Approach to Stop Hypertension-style diet [11]. Men are more than twice as likely to be affected as women, although this gap seems to be decreasing [1]. The reasons for the sex difference and for the apparent change over time have not been thoroughly investigated. It is possible that some factors carry a differential risk in men compared with women, as suggested for example in different magnitudes of relative risks by sex for waist circumference [12] and intake of phytate [9], vitamin C [13] and vitamin D [14]. The aims of this study were to analyse data from three large, longitudinal cohorts to (i) compare incidence rates of kidney stones by sex overall and over categories of age and calendar time, (ii) define to what extent differences in incidence rates are explained by different risk factors and (iii) explore differences in 24-h urine composition relevant to kidney stones between men and women. The findings could provide insight into potential pathophysiologic differences in stone formation between men and women.

MATERIALS AND METHODS

Study cohorts

The Health Professionals Follow-up Study (HPFS) cohort was started in 1986 with the enrolment of 51 529 male health professionals (dentists, optometrists, osteopaths, pharmacists, podiatrists and veterinarians) aged 40–75 years; the Nurses' Health Study (NHS) I cohort was started in 1976 with the enrolment of 121 700 female nurses aged 30–55 years; the NHS II cohort was started in 1989 with the enrolment of 116 429 female nurses aged 25–42 years. For all the cohorts, participants completed a detailed baseline questionnaire with information on lifestyle, medical history and medications. Questionnaires were subsequently mailed every 2 years to update information. These studies were approved by the Partners HealthCare Institutional Review Board and adhered to the principles of the declaration of Helsinki. The return of completed questionnaires was accepted by the institutional review board as implied informed consent.

Assessment of exposure

The primary exposure of interest was self-reported sex. In secondary analyses, we examined differences in sex-specific incidence rates by age and calendar time.

Assessment of outcome

The outcome of interest was time for a first, symptomatic kidney stone. Participants reporting an incident kidney stone were asked to complete a supplementary questionnaire with information about the date of occurrence and accompanying symptoms. A symptomatic kidney stone was defined as the presence of pain and/or haematuria. Self-reported

diagnosis was found to be highly reliable by medical record review of a sample (confirmed in ≥95% who completed the supplementary questionnaire) [11]. 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 cohorts [11].

Assessment of covariates

Information about age, waist circumference, history of diabetes and thiazide use was obtained from the biennial questionnaires. Starting in 1986 (for HPFS and NHS I) and 1991 (for NHS II), participants completed a food frequency questionnaire providing information on the average use of >130 foods and >20 beverages during 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 using capillary electrophoresis [15]. The food frequency questionnaire has been sent every 4 years and also queries the use of multivitamins, as well as individual supplements. Information for nutrients obtained using the food frequency questionnaire has been demonstrated to be valid [16, 17].

Urine collections

Twenty-four-hour urine samples were collected in three cycles. In the first cycle, which spanned from 1994 to 1999, participants were eligible if they were aged ≤70 years (HPFS) or ≤65 years (NHS I) and had no history of cancer or cardiovascular disease. In the second cycle, which began in 2003, participants were eligible if they were aged ≤75 years and had no history of cancer (other than non-melanoma skin cancer). In the third cycle, which spanned 2010–11, NHS II participants with no history of hypertension were enrolled. Urine samples were analysed with the system provided by Mission Pharmacal (San Antonio, TX, USA) for the first two cycles and by Litholink (Labcorp, Chicago, IL, USA) for the third cycle. Participants with a history of kidney stones were oversampled in the first two cycles. Participants with possible over- or under-collections (defined as urinary creatinine excretion in the top or bottom 1% of the non-stone formers distribution) were removed from the analysis. For participants who provided more than one collection, the first sample was analysed. Supersaturation (SS) values were computed with the EQUIL-2 software.

Statistical analysis

The study design was prospective; information on variables of interest was collected before the incident kidney stone except for the 24-h urine collections. Time at risk started from the date of return of the 1986 (HPFS, NHS I) or 1991 (NHS II) questionnaire and participants were followed up until the development of a symptomatic kidney stone, an asymptomatic kidney stone, cancer, death or end of follow-up (2012 for HPFS and NHS I, 2015 for NHS II), whichever occurred first. Participants with a history of cancer (except nonmelanoma skin cancer) or a history of kidney stones at baseline were excluded from the study.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). To explore how much of the exposure 'effect' (e.g. the excess risk of kidney stones among men) was explained by known risk factors for kidney stones, we implemented a mediation analysis by calculating the relative change in the coefficient for sex from a fully adjusted model to a model that did not include the given risk factor [18]. Models included age, waist circumference, history of high blood pressure, history of diabetes, use of thiazides, dietary intakes of animal protein, caffeine, fructose, potassium, sodium, oxalate and phytate, dietary and supplemental intakes of calcium, vitamin C and vitamin D and sugar-sweetened beverages, and total fluid intake. Percent changes of estimates were calculated using the non-exponentiated coefficients.

Linear regression models adjusted for age and kidney stone status were used for the analysis of urinary components. To determine the relative contribution of each urinary component to the excess risk of stones among men, we applied the mediation analysis approach described earlier by calculating the relative change in the coefficient for sex from a logistic regression model with kidney stone status as the dependent variable including the key lithogenic urinary components (calcium, oxalate, citrate, uric acid, magnesium, volume, pH) as well as age to a model that did not include the given urinary component.

A two-tailed P-value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

The analysis included 268 553 participants, contributing 5 872 249 person-years of follow-up, during which 10 302 incident stone events were confirmed. Baseline characteristics by sex are reported in Table 1 (baseline characteristics by cohort are reported in Supplementary data, Table S1). On average, men were older than women, had larger waist circumference, took less supplemental calcium and had higher intakes of animal protein, potassium, sodium, phytate and vitamins C and D.

The association between sex and risk of stones is reported in Table 2. The overall incidence rates of kidney stones were 271 and 159 per 100 000 person-years for men and women, respectively. The age-adjusted HR for kidney stones in men compared with women was 2.32 (95% CI 2.20, 2.45).

The associations between sex and incident kidney stones across categories of age and calendar time are reported in Figure 1, Tables 2 and 3, and Supplementary data, Table S2. The risk of stones was consistently higher across categories of age among men. Regarding calendar time, the risk remained higher among men, but tended to decrease over time, while it increased among women, resulting in a 48.1% decrease after 2009 compared with before 1990. All the previous analyses were repeated using cohort as the exposure of interest rather than sex (Supplementary data, Tables S3 and S4). Interestingly, while risk remained significantly higher among men (the HPFS

Table 1. Baseline characteristics of the study participants by sex

	Men ($n = 44\,868$)	Women ($n = 223\,685$)
Age, years[a]	54 (10)	44 (10)
Waist circumference (cm)	94 (9)	79 (12)
Dietary calcium (mg/day)	804 (300)	805 (290)
Calcium supplement (mg/day)	85 (244)	241 (373)
Caffeine (mg/day)	246 (255)	263 (224)
Animal protein (g/day)	67 (18)	60 (16)
Fructose (g/day)	25 (12)	22 (10)
Potassium (mg/day)	3360 (686)	3006 (582)
Sodium (mg/day)	3237 (1130)	2495 (837)
Oxalate (mg/day)	139 (129)	146 (107)
Phytate (mg/day)	925 (375)	749 (258)
Vitamin C (mg/day)	415 (472)	303 (349)
Vitamin D (IU/day)	383 (300)	368 (258)
Sugar-sweetened beverages (servings/day)	0.4 (0.7)	0.3 (0.7)
Fluid intake (mL/day)	1992 (825)	2079 (791)
Diabetes, %	1.8	2.6
High blood pressure, %	16.0	17.1
Thiazide use, %	5.9	6.9

Values are means (SD) for continuous variables, percentages for categorical variables and are standardized to the age distribution of the study population. [a]Value is not age-adjusted.

Table 2. Risk of incident kidney stones by sex overall and across categories of age

	Men	Women
Overall		
Cases	2392	7910
Person-years	883 224	4 989 025
Incidence rate[a]	271	159
HR (95% CI)	2.32 (2.20, 2.45)	1.00 (Ref.)
<50 years		
Cases	439	3291
Person-years	113 035	1 770 286
Incidence rate[a]	388	186
HR (95% CI)	2.76 (2.41, 3.15)	1.00 (Ref.)
50–54 years		
Cases	382	1314
Person-years	100 845	740 903
Incidence rate[a]	379	177
HR (95% CI)	2.55 (2.22, 2.91)	1.00 (Ref.)
55–59 years		
Cases	438	1305
Person-years	129 679	722 061
Incidence rate[a]	338	181
HR (95% CI)	2.18 (1.93, 2.47)	1.00 (Ref.)
60–64 years		
Cases	439	948
Person-years	148 886	656 760
Incidence rate[a]	295	144
HR (95% CI)	2.31 (2.04, 2.61)	1.00 (Ref.)
65–69 years		
Cases	325	595
Person-years	140 050	484 199
Incidence rate[a]	232	123
HR (95% CI)	2.02 (1.74, 2.33)	1.00 (Ref.)
≥70 years		
Cases	369	457
Person-years	250 730	614 816
Incidence rate[a]	147	74
HR (95% CI)	2.17 (1.87, 2.52)	1.00 (Ref.)

The estimates are age-adjusted as age is the time axis for the survival analysis. [a]Number of events per 100 000 person-years

cohort), women in the more recently started cohort (the NHS II) had a significantly higher risk compared with those in the less recently started cohort (the NHS I) across categories of age and calendar time. For instance, an NHS II participant in the age range 50–54 years had a 47% higher risk compared with an NHS I participant in the same age category, though from a different point in calendar time.

Results of the mediation analysis, aimed at investigating what characteristics explained the higher risk of stones among men, are reported in Table 4 for those factors for which the percent mediated effect was statistically significant. Taken together, the non-urinary risk factors considered explained part of the excess risk among men and most of the mediation was due to differences in waist circumference (percent mediated effect 18.9%).

Urine data were available for 6334 participants. Differences in 24-h urine composition between men and women are reported in Table 5. After adjustment for age and kidney stone status, men had significantly higher urinary excretion of potassium, oxalate, citrate, uric acid, sodium, magnesium and phosphate, and lower urinary volume and urine pH. Overall, the differences in urine composition resulted in significantly higher SS for calcium oxalate and uric acid among men. Interestingly, all SS values were higher among men compared with women in collections performed before 2000 as opposed to 2000 or after (differences between men and women pre- and post-2000 for SS CaOx: 2.15 versus 1.19; SS UA: 0.80 versus 0.61; SS CaP: 0.30 versus −0.06). After further adjustment for body weight, all the differences in urinary components remained statistically significant with the exception of citrate.

Results of the mediation analysis on urine components are reported in Table 6. Taken together, urinary components explained a meaningful proportion of the excess risk among men. Urine volume, oxalate, pH and citrate were all significant contributors, with each factor being responsible for 6.8–28.0% of the higher risk of stones among men.

DISCUSSION

In our study, we report several findings of interest. First, while it is well-known that kidney stone disease manifests more frequently among men compared with women, with almost double the risk of developing a first symptomatic kidney stone among men, the excess risk remained across the span of ages included in our study. Known lifestyle risk factors for kidney stone disease explained only a fraction of the observed excess risk in men, demonstrating that other factors such as genetic or hormonal causes play a role. Post-menopausal women have a higher risk of forming stones compared with pre-menopausal women, indirectly suggesting a role of hormonal status in the risk of kidney stones [19]. In animal models, testosterone promoted the activity of glycolate oxidase and increased urinary excretion of oxalate [20]; furthermore, testosterone replacement therapy in men with hypogonadism was associated with an increased risk of stone formation [21].

Although in our study men remained more affected than women across the time periods considered, this difference tended to attenuate over time, resulting in a ∼50% relative risk

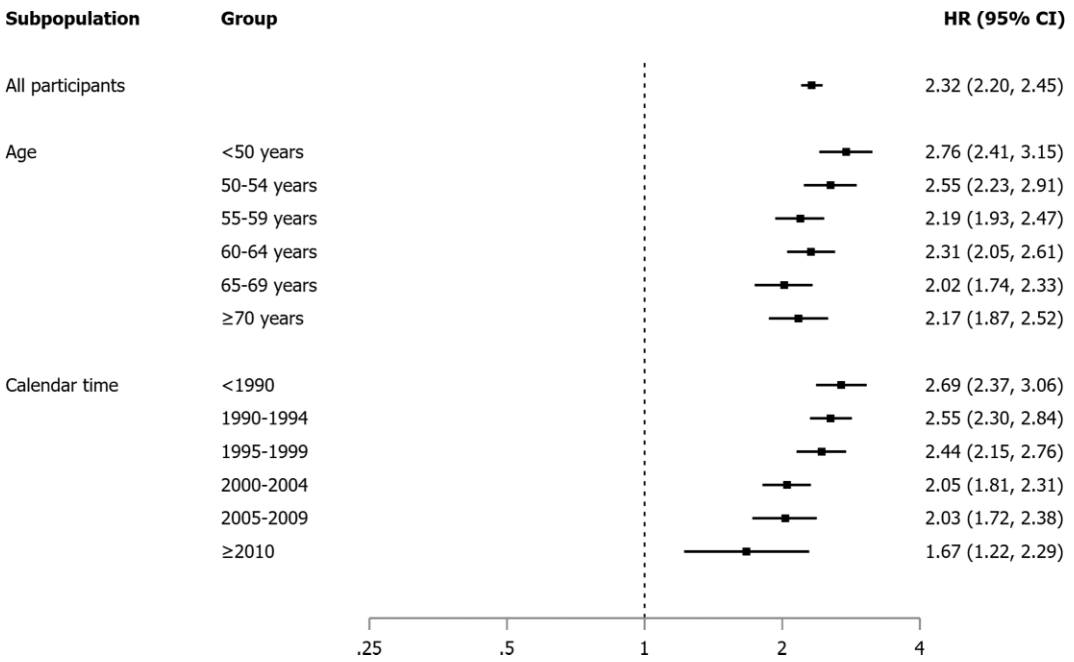


FIGURE 1: Association between sex and incident kidney stones across categories of age and calendar time.

Table 3. Risk of incident kidney stones by sex across categories of calendar time

	Men	Women
<1990		
Cases	498	520
Person-years	167 577	450 711
Incidence rate[a]	297	115
HR (95% CI)	2.69 (2.37, 3.06)	1.00 (Ref.)
1990–1994		
Cases	691	1520
Person-years	233 742	1 055,81
Incidence rate[a]	296	144
HR (95% CI)	2.55 (2.30, 2.84)	1.00 (Ref.)
1995–1999		
Cases	443	1707
Person-years	151 573	1 034 935
Incidence rate[a]	292	165
HR (95% CI)	2.44 (2.15, 2.76)	1.00 (Ref.)
2000–2004		
Cases	462	1610
Person-years	184 830	957 218
Incidence rate[a]	250	168
HR (95% CI)	2.05 (1.81, 2.31)	1.00 (Ref.)
2005–2009		
Cases	239	1421
Person-years	108 120	886 403
Incidence rate[a]	221	160
HR (95% CI)	2.02 (1.72, 2.38)	1.00 (Ref.)
≥2010		
Cases	59	1132
Person-years	37 382	604 377
Incidence rate[a]	158	187
HR (95% CI)	1.67 (1.22, 2.29)	1.00 (Ref.)

The estimates are age-adjusted as age is the time axis for the survival analysis. [a]Number of events per 100 000 person-years

Table 4. Non-urinary contributors to the difference in risk of incident kidney stones between men and women

Contributor	Percent mediated effect (95% CI)
Waist circumference	18.9 (15.6, 22.2)
Fluid intake	5.7 (4.5, 6.9)
Sugar-sweetened beverages	3.9 (2.9, 5.0)
Thiazides	1.8 (1.0, 2.7)
Dietary oxalate	0.7 (0.2, 1.2)
Dietary calcium	0.7 (0, 1.4)

This table shows the relative contribution of each non-urinary factor to the excess risk of incident kidney stones among men

reduction from earlier to later time periods. This phenomenon could be explained by changes in dietary habits and/or body composition over time, as well as the ageing of the male cohort. Interestingly, when we repeated our set of analyses using cohort rather than sex as the exposure, we found that women enrolled in NHS II, the more recently established female cohort, had a significantly higher risk of stones compared with women enrolled in NHS I, even within strata defined by age. Considering that the design and methodology of the two cohorts are almost identical, this could be taken as indirect evidence that women are more exposed to lithogenic factors in recent years than in the past. Our data also show an apparent reduction of kidney stone rates over time among both men and women. This phenomenon is likely due to ageing of the study population.

Our finding of a higher risk of kidney stones among men was corroborated by our urine studies, showing significantly higher supersaturation values for calcium oxalate and uric acid, emphasizing the tendency for a more lithogenic urinary profile in men. Also consistent with our hypothesis of a shift towards a more lithogenic environment for women, we showed that sex differences for supersaturations of each crystal type, a measure of the likelihood of urine to become saturated with certain chemical species, tended to attenuate over time. Our analysis showed that differences in urinary composition explain a substantial fraction of the excess risk of kidney stones found in men. In particular, lower urine

Table 5. Twenty-four-hour urine components by sex

	Mean (SD)					
	Men ($n = 1145$)	Women ($n = 5189$)	Adjusted Difference (95% CI)	P-value	Adjusted Difference (95% CI)[a]	P-value[a]
Creatinine (g)	1.65 (0.37)	1.18 (0.25)	0.56 (0.54, 0.58)	<0.001	0.47 (0.45, 0.48)	<0.001
Potassium (mEq)	76.4 (25.1)	61.2 (21.1)	16.1 (14.6, 17.6)	<0.001	14.5 (12.9, 16.0)	<0.001
Calcium (mg)	197 (106)	201 (98)	4.4 (−2.4, 11.2)	0.21	−1.8 (−8.8, 5.2)	0.62
Oxalate (mg)	40.3 (13.0)	29.7 (10.9)	11.3 (10.5, 12.0)	<0.001	9.4 (8.6, 10.2)	<0.001
Citrate (mg)	696 (308)	741 (306)	29.1 (8.5, 49.8)	0.006	2.5 (−18.8, 23.8)	0.82
Uric acid (mg)	618 (229)	517 (157)	153 (142, 165)	<0.001	118 (106, 129)	<0.001
Sodium (mEq)	183 (70)	142 (59)	45.7 (41.5, 49.9)	<0.001	30.4 (26.3, 34.6)	<0.001
Magnesium (mg)	124 (44)	104 (39)	23.2 (20.5, 26.0)	<0.001	20.4 (17.5, 23.2)	<0.001
Phosphate (mg)	1067 (323)	816 (262)	301 (282, 319)	<0.001	237 (218, 255)	<0.001
pH (U)	5.86 (0.46)	6.10 (0.51)	−0.19 (−0.23, −0.16)	<0.001	−0.12 (−0.16, −0.09)	<0.001
Volume (mL)	1690 (650)	1930 (810)	−143 (−196, −91)	<0.001	−180 (−235, −126)	<0.001
SS CaOx	8.57 (5.08)	6.26 (4.00)	2.12 (1.85, 2.40)	<0.001	2.00 (1.71, 2.29)	<0.001
SS CaP	1.90 (1.63)	1.57 (1.43)	0.26 (0.17, 0.36)	<0.001	0.34 (0.24, 0.44)	<0.001
SS UA	2.09 (1.59)	1.05 (1.16)	0.94 (0.86, 1.03)	<0.001	0.76 (0.68, 0.85)	<0.001

Differences are reported with women as referent category and adjusted for age and kidney stone status. [a]Further adjustment for body weight. CaOx, calcium oxalate; CaP, calcium phosphate; SD, standard deviation; SS, supersaturation; UA, uric acid.

Table 6. Urinary contributors to the difference in risk of kidney stones between men and women

Contributor	Percent mediated effect (95% CI)
Volume	26.0 (20.0, 32.3)
Oxalate	17.0 (10.9, 23.0)
pH	8.4 (4.0, 12.8)
Citrate	6.8 (2.5, 11.1)

This table shows the relative contribution of each urinary factor to the excess risk of incident kidney stones among men

volume, pH and urinary excretion of citrate and higher levels of sodium and oxalate explained a substantial proportion of the excess risk. Unfortunately, it is not methodologically feasible to compute sum estimates of the percent mediated effect, due to the potential interplay between factors [22]. However, the individual estimates of percent mediated effect convey information on the weight of each parameter on the difference between men and women.

Although previous studies reported a difference in kidney stone disease by sex, they were mostly cross-sectional in design and thus focussed on prevalence rather than incidence: sex-specific estimates from longitudinal cohort studies are very rare [23]. Prevalence figures could be affected by other elements such as disease duration, which in turn might reflect patterns of treatment and access to care. Furthermore, previous studies used only self-reported information about kidney stones (without demonstration of the validity of the self-report), whereas in our study we confirmed the outcome of interest. We previously showed that lack of validation could have a significant impact on results [24]. Censoring of asymptomatic kidney stone events, as implemented in our study, further improved the robustness of our findings by reducing the risk of misclassifying the passage or discovery of a previously present kidney stone as a new stone event. Most importantly, no previous studies could rely on the combination of confirmed data on incident kidney stones, detailed and validated data on nutrient intakes repeated over time and extensive data on urine composition to explore the potential mechanisms underlying the epidemiology of kidney stones in men and women. A further strength of our study is the identical study design and procedures for information collection for the three cohorts analysed.

Our study also has limitations. First, participants were in large majority White, thus potentially limiting the generalizability of the findings to other races. We did not have information on younger age groups in men; however, since in our study we excluded those participants with a history of kidney stones at baseline, this limitation is unlikely to have influenced our estimates. Another potential limitation of our study is related to urine analysis being performed by different laboratories over time. Finally, we did not have information on stone composition for a significant number of participants, which would have been useful to further explore potential mechanisms of stone formation in men and women, but our previous work suggests that the majority are primarily calcium oxalate [11].

In conclusion, men have a higher risk of forming kidney stones compared with women. Such difference is explained by lifestyle and urinary risk factors, in particular a significantly more lithogenic urinary profile in men. Lifestyle risk factors for kidney stones could be changing over time, giving rise to trends toward increased incidence of kidney stones among women. Future studies should explore the mechanisms by which these factors result in a higher risk of stone formation in men.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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CONFLICT OF INTEREST STATEMENT

P.M.F. received consultant fees and grant support from Allena Pharmaceuticals, Alnylam, AstraZeneca, BioHealth Italia and

Vifor Fresenius, and royalties as an author for UpToDate. G.C.C. is an employee of OM1, Inc., has received consulting fees from Allena Pharmaceuticals and receives royalties as a Section Editor and author for UpToDate. The other authors have nothing to disclose. The results presented in this paper have not been published previously in whole or part, except in abstract format.

AUTHORS' CONTRIBUTIONS

Funding acquisition was carried out by E.N.T. and G.C.C.; data curation was performed by E.N.T. and G.C.C.; conceptualization was by G.C.C. and P.M.F.; formal analysis was carried out by P.M.F.; visualization was by P.M.F.; writing of the original draft was done by P.M.F.; and writing—review and editing was done by E.N.T. and G.C.C.

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