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ORIGINAL ARTICLE

Heritability of dietary traits that contribute to nephrolithiasis in a cohort of adult sibships

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Abstract
Background Kidney stones and their risk factors aggregate in families, yet few studies have estimated the heritability of known risk factors.
Objective Estimate the heritability of dietary risk factors for kidney stones.
Methods Dietary intakes were assessed using the Viocare Food Frequency Questionnaire in sibships enrolled in the Rochester, MN cohort of the Genetic Epidemiology Network of Arteriopathy. Measures of urinary supersaturation were determined using 24 h urine samples. Heritabilities and genetic correlations were estimated using variance components methods.
Results Samples were available from 620 individuals (262 men, 358 women, mean (SD) age 65 (9) years). Dietary intakes of protein, sucrose, and calcium had strong evidence for heritability ($p < 0.01$) after adjustment for age, sex, height and weight. Among the significantly heritable dietary intakes ($p < 0.05$), genetic factors explained 22–50 % of the inter-individual variation. Significant genetic correlations were observed among dietary protein, dietary sucrose, and dietary calcium intakes ($p < 0.001$).
Conclusions Evidence from this relatively large cohort suggests a strong heritable component to dietary intakes of protein, sucrose and calcium that contributes to nephrolithiasis risk. Further efforts to understand the interplay of genetic and environmental risk factors in kidney stone pathogenesis are warranted.

Keywords Diet · Heritability · Nephrolithiasis · Supersaturation

Introduction

Kidney stones are common, affecting approximately one in ten persons during lifetime [1]. Human urine is often supersaturated for the crystals that constitute kidney stones [2], and diet is thought to be a key determinant of the urinary composition. Indeed, many components of diet can influence kidney stone risk such as fluid, calcium, and protein intakes. Relatively little is known about the heritability of risk factors for kidney stone disease, although our recent study suggested that variability in several urinary traits including calcium, magnesium and citrate have heritable components [3].

A recent study [4] added to older evidence [5–7] that suggested dietary preferences might have a heritable component. Therefore, the objective of the present study was to estimate the heritabilities and genetic correlations of dietary nephrolithiasis risk factors in a population not selected for stone disease. Heritability provides an overall estimate of additive genetic influences, reflecting the sum of the contribution of all genome-wide allelic variation shared by sibs on trait variation. Genetic correlations between different traits reflect the extent to which common underlying genetic factors affect both traits i.e., pleiotropy [8]. We took advantage of sibships in the Rochester, MN cohort of the Genetic Epidemiology Network of

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Arteriopathy (GENOA), for whom detailed phenotypes and family structures are available [9, 10]. Adult sibships are ideal for studying the overall contributions of genes and environments to urinary and dietary nephrolithiasis risk factors and their correlations because the influence of shared household environment is minimized and dietary patterns have stabilized. Our results suggest that dietary nephrolithiasis risk factors have significant heritable components and that there is evidence of genetic correlation, i.e., pleiotropy, among these factors.

Methods

This study was approved by the Mayo Clinic Institutional Review Board.

GENOA cohort

The Genetic Epidemiology Network of Arteriopathy (GENOA), a member of the Family Blood Pressure Program (FBPP), recruited non-Hispanic white hypertensive sibships from Rochester, Minnesota for linkage and association studies to investigate the genetic underpinnings of hypertension and target organ damage related to hypertension between 1996–2001 during Phase I [10]. In Phase II (2000–2004), 1241 Rochester participants were successfully re-recruited to measure potential target organ damage due to hypertension. The Genetic Determinants of Urinary Lithogenicity (GDUL) study (2006–2012) is an ancillary study of the Phase III GENOA Genetics of Chronic Kidney Disease (CKD) Study. GDUL was initially funded by a Mayo Foundation Grant and timed with a CKD visit and subsequently by a separate NIH grant R01 DK073537 (GDUL visit). All participants in the Rochester, MN GENOA cohort were invited to participate in this study which consisted of one to three study visits (CKD and GDUL), one to three 24 h urine collections, and a diet questionnaire. Having a history of kidney stones was not a criterion nor exclusion for study participation. Participants were excluded from this study if they were in endstage renal failure (stage 5 CKD). The analysis sample for this report comprised 620 participants in 387 sibships.

Study visit

Subjects were instructed by the recruiter via phone and written materials prior to their study visit. After signing a consent form, the participants completed a food frequency questionnaire (Viocare Technologies, Princeton, NJ, USA) [11].

At the time of the visit, subjects completed one (CKD) or preferably two (GDUL) 24-h urine collections for determination of quantitative urinary lithogenic factors, including supersaturation (SS). A total of 142, 295, and 183 participants had a total of one, two, or three urine collections, respectively. For individuals with two or three urine collections, values were used averaged. The mean time between the earliest (CKD) and last (GDUL) urine collections was 1.73 years (range 0.9–3.6 years). The average time between the two GDUL collections was 22 days. Intraclass correlation coefficients (ICCs) for urine factors across collections revealed that the majority of urine measures were relatively stable across time. Of the urine factors, chloride had the lowest ICC (0.41) and calcium had the highest (0.73). All subjects completed the detailed Kidney Stone Questionnaire (which provided data on kidney stone status of the subject), and data from a recently administered GENOA Chronic Kidney Disease Questionnaire was also available (not used for the current analysis). The current study focuses on six diet variables previously correlated with stone risk (calcium, oxalate, total protein, animal protein, sucrose and fructose intake) and three urine variables that directly reflect diet intake of three others (sodium, potassium, and total volume).

Descriptive statistics

Data management and statistical analyses were conducted in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and R version 12.1.2 (R Core Development Team) [12]. Most dietary measures appeared to have relatively normal distributions; thus, no variable transformations were applied. Values that were $\geq$4 standard deviations from the mean of any dietary measure were removed. The number of values excluded was small and varied from 36 (protein and calcium) to 45 (oxalate).

Linear mixed effects (LME) models were used to test whether there were significant differences between men and women for dietary measures. We also conducted LME models that included age, sex, height, and weight as predictor variables to explore the relationships between these variables and each dietary measure. LME modeling with family as a random intercept was used to account for the sibship structure among GENOA participants while retaining a valid type I error rate [13]. R^2 values for the LME models were calculated based on the likelihood ratio [14].

Biometrical genetic modeling

We used variance components modeling to estimate the heritability of dietary factors, both before and after accounting for covariates (age, sex, height, and weight). After accounting for phenotypic variation due to the covariates, the phenotypic covariance between sib pairs was partitioned into additive genetic covariance and variance not

explained by additive genetic effects (error covariance), as follows: $\Omega = 2\Phi\sigma_g^2 + I\sigma_e^2$, where σ_g^2 represents the genetic variance due to additive genetic factors and σ_e^2 is the error variance. The kinship matrix, Φ, represents the Mendelian expectation that sibling pairs share one half of their genetic variation. SOLAR (Sequential Oligogenic Linkage Analysis Routines) [15] was used to implement the variance component modeling based on maximum likelihood estimation. Heritability ($h^2 = \sigma_g^2/\sigma_p^2$), the proportion of total phenotypic variance that is attributable to genetic variance, was tested for significance by comparing the log-likelihood of the model in which heritability is estimated to that of the model in which heritability is fixed to 0. All GENOA participants (N = 620) were included in the SOLAR modeling. While the 228 singletons are not used by SOLAR to estimate the genetic contribution to trait variation, they are used for estimation of overall trait variation.

We also used SOLAR to perform bivariate analysis for pairs of traits that had strongly significant heritabilities ($p < 0.01$) after accounting for age, sex, height, and weight. In this bivariate modeling framework, the phenotypic covariance between two traits is decomposed into genetic correlation due to additive genetic effects influencing both traits and correlation due to environmental effects influencing both traits, according to the following model:

$$\Omega_{12} = 2\Phi\rho_g\sigma_{g1}^2\sigma_{g2}^2 + \rho_e\sigma_{e1}^2\sigma_{e2}^2$$

where 1 and 2 are the two traits of interest, ρ_g is the additive genetic correlation between the traits and ρ_e is the correlation due to unmeasured environmental effects. The genetic correlation provides an estimate of the proportion of genetic effects shared between the two traits. SOLAR estimates phenotypic correlation using family relationships among the participants. The formula for calculating total phenotypic correlation is as follows:

$$\rho_p = \rho_g\sqrt{h_1^2h_2^2}s + \rho_e\sqrt{(1-h_1^2)(1-h_2^2)}$$

where ρ_p is the phenotypic correlation between traits 1 and 2, h_1^2 is the heritability of trait 1, and h_2^2 is the heritability of trait 2. The genetic and environmental correlations between the traits estimated in SOLAR, ρ_g and ρ_e, were tested for significance by comparing the log-likelihood of the model in which the parameter of interest is estimated to the log-likelihood of the model in which the parameter is fixed to 0.

Results

A total of 620 individuals from 387 sibships participated in this study and had FFQ data available for analysis. The sibship structure of the sample was as follows: 228 singletons, 116 sibpairs, 26 sibships with 3 siblings, and 17 sibships with 4 or more siblings. Mean age (SD) was 65 (9) years, and 57.7 % of participants were female. All of the measured dietary intakes are summarized in Table 1 and indicate that men and women are significantly different for total protein and animal protein. Many key dietary measures were influenced by demographic factors (Table 2). Increasing age was associated with decreased intake of all dietary components measured, while larger body weight was generally associated with higher intake of some components (animal protein) and lower intake of others (oxalate, sucrose). Women ate less animal and total protein than men.

The calculated dietary heritabilities are summarized in Table 3. Heritabilities for dietary protein, animal protein, calcium, oxalate, sucrose and fructose were statistically significant ($p < 0.05$) and substantial in magnitude ($h^2 = 0.25$–0.56). Covariates (age, sex, height, and weight) explained only 2.2–12.3 % of the variance in dietary components, and in adjusted models heritabilities all remained significant ($h^2 = 0.22$–0.50; $p < 0.01$ for protein, calcium and sucrose intake). Heritabilities for urine sodium ($h^2 = 0.07$, $p = 0.23$) and potassium ($h^2 = 0.005$, $p = 0.47$) were not significant, while urine volume (reflecting fluid intake) was significant ($h^2 = 0.24$, $p = 0.01$).

Genetic and environmental correlations were examined for dietary intakes with highly significant heritabilities ($p < 0.01$) after accounting for covariates. Genetic correlation between two traits indicates that common genetic factors influence both traits, i.e., there is evidence of pleiotropy. Strongly positive genetic correlations were observed among three dietary components: total protein, calcium, and sucrose (Table 4, $\rho_g = 0.84$–0.95; $p < 0.001$). Positive environmental correlations were also observed between total protein and calcium ($\rho_e = 0.65$; $p < 0.001$) and between total protein and sucrose ($\rho_e = 0.38$; $p < 0.01$).

Discussion

The current study represented a unique opportunity to examine heritability of dietary intakes that have been associated with kidney stone risk. Results demonstrate that many key dietary intakes previously linked to kidney stone risk [16–19] have a strong heritable component. These observations suggest that efforts to understand the genetics underlying dietary preference could help identify new stone prevention targets.

Nephrolithiasis has long been associated with affluence [20], and dietary factors associated with higher socioeconomic status [21]. More recently, two large prospective studies containing both men [22, 23] and women [22, 23]

Table 1 Descriptive statistics

	Total		Males		Females		p value[a]
	N = 620		N = 262 (42.2 %)		N = 358 (57.8 %)		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Age (years)	620	65 (9)	262	67 (9)	358	64 (9)	0.007
Height (cm)	620	168 (9)	262	176 (7)	358	163 (6)	<0.001
Weight (kg)	620	88 (20)	262	98 (18)	358	81 (18)	<0.001
History of kidney stone (N, %)	600	13 %	45	18 %	35	10 %	0.006
Urine measures							
Calcium (mg/day)	618	160 (89)	262	164 (95)	356	157 (84)	0.15
Oxalate (mg/day)	615	0.30 (0.09)	260	0.34 (0.09)	355	0.27 (0.08)	<0.001
Citrate (mg/day)	617	564 (313)	262	617 (347)	355	526 (280)	<0.001
Sulfate (mmol/day)	620	19 (7)	262	23 (8)	358	16 (6)	<0.001
Sodium (mmol/day)	619	135 (56)	261	164 (56)	358	113 (45)	<0.001
Renal function							
Serum Cr (mg/dl)	456	0.84 (0.21)	191	0.97 (0.20)	265	0.75 (0.17)	<0.001
eGFR (ml/min/1.73 m^2)	460	83 (16)	269	85 (16)	191	81 (15)	0.120
eGFR >60 ml/min/1.73 m^2 (N, %)	420	91 %	172	90 %	248	92 %	0.56[b]
eGFR 45–59 ml/min/1.73 m^2 (N, %)	32	7 %	15	8 %	17	6 %	
eGFR 30–44 ml/min/1.73 m^2 (N, %)	7	2 %	4	2 %	3	1 %	
eGFR 15–29 ml/min/1.73 m^2 (N, %)	1	0 %	0	0 %	1	0 %	
Dietary measures							
Total protein (g)	619	81 (35)	261	89 (38)	358	76 (31)	<0.001
Animal protein (g)	619	53 (26)	261	60 (30)	358	49 (22)	<0.001
Calcium (mg)	619	1073 (560)	261	1081 (596)	358	1067 (533)	0.66
Oxalate (mg)	610	219 (130)	261	218 (138)	349	220 (124)	0.76
Fructose (g)	615	21 (12)	259	21 (12)	356	21 (12)	0.68
Sucrose (g)	616	38 (22)	259	37 (23)	357	39 (22)	0.34

cm centimeter, *Cr* creatinine, *dl* deciliter, *eGFR* estimated GFR (CKD-EPI equation), *g* grams, *kg* kilograms, *m* meter, *mg* milligrams, *min* minute, *mmol* millimol, *ml* milliliter

[a] p value for difference of means between males and females, from a linear mixed effects model accounting for sibship

[b] p value for a global test of differences in frequency distribution of CKD stages between males and females, from a linear mixed effects model accounting for sibhip

Table 2 Linear Mixed Effects Modeling for Dietary Measures

	Beta coefficients				R^2	p value[a]
	Age	Sex	Height	Weight		
Total protein (g)	−0.87***	−11.53**	0.16	0.12	0.145	<0.001
Animal protein (g)	−0.68***	−10.70***	−0.01	0.14*	0.146	<0.001
Calcium (mg)	−7.06**	4.94	5.57	−2.21	0.118	0.001
Oxalate (mg)	−1.93**	4.79	1.25	−0.63*	0.059	0.002
Fructose (g)	−0.20***	0.46	0.05	−0.01	0.020	0.002
Sucrose (g)	−0.21*	1.90	0.23	−0.15**	0.038	0.008

Statistical significance of the beta coefficients were assessed using a Wald test

R^2 calculated based on likelihood ratio

* 0.01 < p value < 0.05, ** 0.001 < p value < 0.01, *** p value < 0.001

[a] p value for full model (including age, sex, height, and weight as predictors)

Table 3 Heritabilities of dietary measures

	h^2 unadjusted	h^2 unadjusted p value	Proportion of variance of measure explained by covariates (%)	h^2 adjusted for age, gender, height, weight	h^2 adjusted for age, gender, height, weight p value
FFQ dietary intake					
Total protein (g)	0.45	<0.001	10.8	0.37	<0.001
Animal protein (g)	0.31	0.002	12.3	0.24	0.013
Calcium (mg)	0.56	<0.001	2.7	0.50	<0.001
Oxalate (mg)	0.25	0.011	2.7	0.22	0.021
Fructose (g)	0.26	0.007	2.6	0.23	0.016
Sucrose (g)	0.37	<0.001	2.2	0.38	<0.001
Urine variables that reflect diet intake					
Sodium (mmol/day)	0.00	0.50	16.5	0.07	0.23
Potassium (mmol/day)	0.00	0.50	16.2	0.005	0.47
Volume (ml/day)	0.30	0.002	1.9	0.24	0.01

Adjusted models included age, sex, height, and weight

Table 4 Genetic and environmental correlations among pairs of traits with significant heritabilities

	Total protein	Calcium (mg)	Sucrose (g)
Dietary total protein	0.37	0.65^{***}	0.38^{**}
Dietary calcium (mg)	0.95^{***}	0.50	0.24
Dietary sucrose (g)	0.84^{***}	0.86^{***}	0.38

Above diagonal (shaded): environmental correlations, ρ_e

Below diagonal (white): genetic correlations, ρ_g

Diagonal (boxed cells): heritabilities from univariate polygenic analysis, h^2

All biometric models included age, sex, height, and weight

* 0.01 < p value < 0.05, ** 0.001 < p value < 0.01, *** p value < 0.001

identified specific dietary components that correlated with subsequent stone events [16]. Previous studies have demonstrated significant heritabilities in dietary intake patterns in children [24] and adults [5–7, 24]. Recently in a large cross-sectional cohort of 1410 individuals, fruit, vegetable and protein consumption also exhibited significant heritability (h^2 0.21–0.32) [4]. Fruit and vegetable consumption also exhibited genetic correlation with BMI. The authors concluded that individuals genetically predisposed to low fruit and vegetable intake could be at higher risk for a larger BMI. In our study, key diet components also appeared to be under heritable influence, including protein, calcium, sucrose and fructose intakes. Our previous study demonstrated that individual dietary components influenced many urinary traits [3]. For example, dietary protein intake moderately correlated with urinary calcium, magnesium, sodium, sulfate, oxalate, citrate and uric acid [3]. Net alkali absorption had an even stronger correlation with all of these, and with urine pH, while dietary calcium moderately influenced urine calcium. Thus, heritability of key dietary traits can ultimately influence the urine composition, and hence kidney stone risk.

While both shared genetic and environmental influences can be estimated in twin studies, shared environmental influences cannot be estimated in sibship studies because the impact of shared home environments is identical for each non-twin sib in a household. Consequently, this source of sib–sib covariability contributes to the environmental component of variance. Only environments that follow a sibship's genomic pattern of sharing would spuriously contribute to the estimated genetic component of variance used to estimate heritability [25]. Additionally, one study of the heritability of children's eating habits found no influence of shared environment (though significant heritability) between monozygotic and dizygotic twins, where it is possible to model differences in shared environment [26]. Thus, although we were studying adult siblings that were not living in the same household, our estimate of genetic heritability could still contain some influence from a shared environment at an earlier age.

The current study supports the hypothesis that the line between genetics and environment may be more blurred than previously appreciated, and that certain individuals may be predisposed to dietary preferences that increase stone risk. However, our study was not designed to identify the specific environmental and genetic factors contributing to the heritability of dietary patterns or how they simultaneously influence nephrolithiasis risk represented in the genetic correlations.

The sibship structure of our sample also allowed us to mathematically estimate the portion of the correlation between dietary traits that was due to shared genetic effects, with the remainder assumed to be shared environmental effects (Table 4). The strong genetic correlations between dietary protein, calcium, and sucrose (ρ_g from 0.84–0.95, p values <0.001) could represent the complex result of taste preferences which are known to be genetic [27–29] and to influence eating behaviors. Another plausible hypothesis is that genetic factors could influence consumption of foods rich in calcium, protein and sucrose, for example due to lactose intolerance causing an aversion to milk [30].

Limitations of this study include its cross sectional nature and lack of geographic or ethnic diversity. Thus it is not clear if results can be translated to all ethnicities or locales. Furthermore, diet intake was not confirmed by biomarkers. Nevertheless, complete dietary data assessed via a validated food frequency questionnaire was available from a relatively large cohort of adult sibships for our analysis, which can be validated in other future cohorts.

In conclusion, evidence from this relatively large cohort suggests a strong heritable component to dietary intake of key elements. Thus this study supports an underlying genetic component of nephrolithiasis risk factors typically considered to be purely environmental risk factors, such as diet.

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Conflict of interest No authors declare a conflict of interest.

Ethical standard This study was approved by the Mayo Clinic Institutional Review Board.

Informed consent All participants provided informed consent prior to enrolling and participating in the study.

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