ARIC Manuscript Proposal # 1518

PC Reviewed: 5/12/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title: Prevalence of kidney stones and incidence of kidney stone hospitalization in a middle aged, biracial population of men and women: ARIC

b. Abbreviated Title (Length 26 characters): Prevalence and incidence of kidney stones

2. Writing Group:
Writing group members: Saloua Akoudad, Anna Kottgen, Moyses Szklo, Tibor Fulop Linda Kao, Josef Coresh, others are welcome…

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SA **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Data to be used in this proposal are already available. Analyses will begin immediately upon approval of the proposal and manuscript preparation will be performed over the next 3 months.

4. Rationale:

Nephrolithiasis has been noted to be a common disease especially in industrialized countries. Multiple studies have shown a lifetime risk of stone formation in the U.S population exceeding 12% in men and 6% in women [1-3]. Prevalence of kidney stones is highest in older white males and lowest in younger black females [3]. Kidney stone disease has been associated with reduced kidney function and CKD [4,5]. Andrew et al showed in a population based cohort study that stone formers have 50-67% higher risk of a clinical diagnosis of CKD [5] In addition, the postulated increase in prevalence of kidney stones has been attributed to an increasing prevalence of some well known risk factors for kidney stones such as changes in diet, obesity and type 2 diabetes. Along with other factors, these risk factors give rise to the so-called metabolic syndrome, which seems to be an independent risk factor for kidney stones [6]. These new insights have therefore led to the idea that nephrolithiasis may be a systemic disorder [7].

Thus far, studies addressing kidney stones prevalence or incidence have focused on either a predominately male or a female study population, or mainly on one ethnic group. Using data from the ARIC Study provides an excellent opportunity to investigate the prevalence of self-reported kidney stones as well as the incidence of kidney-stone related hospitalizations in a middle aged, biracial population of men and women.

An interesting angle for exploration is the different levels of uric acid in stone vs. non-stone formers. Studies have suggested that patients with gout are more likely to suffer from kidney stones as well [6-11]. Regarding this association, Kramer and Curhan found that, in a probability sample of the general US population from the NHANES 3 survey, patients with gout are almost 3 times more likely to develop kidney stones. Approximating 0.7 million individuals in the US have both gout and kidney stone disease.[9] Moreover, a large prospective study of men (The Health Professionals Follow-up Study) found that gout patients had a 2 fold increased risk of incident kidney stones. On the other hand, patients with kidney stones did not seem to have an increased risk of incident gout.[10]

The objectives of this proposal are: i. to generate estimates of prevalence and incidence of hospitalizations for kidney stones in a large, biracial study of middle-aged adults; ii. to identify risk factors for kidney stones in this population and evaluate their association in men and women, and in Caucasians and African Americans; and iii. to evaluate the association between the presence of kidney stones and gout, as well as the role of hyperuricemia in this association.

5. Main Hypothesis/Study Questions:

1. What is the prevalence of kidney stone disease and the incidence of kidney stone hospitalization in subjects enrolled in the ARIC study?
2. What are the risk factors for kidney stones in this biracial middle aged population of men and women?
3. Is there an association between kidney stones and gout, and what role does hyperuricemia play in this association?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).

All analyses will be conducted locally at Johns Hopkins by Saloua Akoudad and Anna Kottgen.

Main Exposure:
Risk factors for kidney stone disease as well as their prevalence in the population will be explored. Based on previous literature and biological plausibility, we will investigate demographical factors (age, race, sex, education, study center), anthropometric data (waist circumference, BMI), co-morbid conditions (blood pressure, hypertension, diabetes status, prevalent coronary heart disease (CHD), laboratory measurements such as glucose and serum lipids, and lifestyle conditions (smoking status, alcohol intake and medication use [especially diuretics]). For the assessment of kidney function, we will look at glomerular filtration rate estimated from serum creatinine (eGFRcreatinine) and cystatin C (eGFRcystatin), as well as CKD at visit 4. Finally, we will investigate uric acid (assessed at visit 1 and 2) and gout (assessed at visit 4) and their association with kidney stones. More details on the exposures are provided in the covariate section.

Main outcomes:
The overall prevalence of self-reported kidney stones assessed at visit 3 will be examined. Additionally, incidence of kidney stones will be determined using hospitalization discharge records through December 31, 2005. Hospitalization records with the following ICD-9 codes will be used to define a kidney stone-related hospitalization: 592 (calculus of the kidney and ureter), 592.0 (calculus of kidney), 592.1 (calculus of ureter), 592.9 (urinary calculus, unspecified), 274.11 (uric acid nephrolithiasis), and 275.49 (nephrocalcinosis). Incident kidney stone disease will be defined as a kidney-stone related hospitalization among individuals who did not report ever having kidney stones at visit 3.

Exclusions:
Participants missing information on self-reported kidney stones at visit 3 will be excluded. For the analyses of incident kidney stone disease, participants with prevalent kidney stone disease at visit 3 will be excluded. In secondary analysis, individuals reporting intake of medication that influences the uric acid levels (e.g. thiazides) will be excluded.

Covariates:
The exposure variables, as mentioned above and examined in univariate analyses, will be included as covariates in multivariable adjusted models to assess their independent contribution. Information on potential covariates was obtained at visit 3, when data on kidney stones were collected, with the exception of gout (visit 4) and uric acid (visits 1, 2).

Data analysis:

Primary analyses: Cross-sectionally, the distribution of risk factors in the study population among individuals with and without kidney stone disease will be computed using a t-test for continuous variables and a Chi-square test for categorical variables. Logistic and prevalence ratio regression will be used to examine the multivariate association of risk factors with kidney stones disease. We will evaluate two regression models: 1. Adjusted for age and sex; and 2. multivariate-adjusted for significant risk factors identified in univariate analysis.

Important risk factors will be evaluated in detail by conducting stratified analyses, as well as evaluating interactions.
Prevalence of kidney stones will be reported overall, by gender, by ethnicity (white or black) and by age (categorized into 5-year age interval).
Prospectively, individuals will be followed from visit 3 until the first date of hospitalization, December 31st, 2005 (end of follow up) or loss to follow up, whichever occurred first. Kidney stone hospitalization incidence rates will be calculated using person-time methods. If there are enough cases of incident kidney stone hospitalization, the relative hazard of incident kidney stone will be evaluated using Cox proportional hazards models.
Secondary analysis: Depending on the number of participants with incident kidney stones as well as incident gout, we will aim to investigate the temporality of the association. This will be done by investigating the incidence rates of kidney stones after visit 4 among those without gout compared to those with gout, as well as the incidence of gout after visit 3 comparing those with to those without kidney stone disease. We realize that the number of incident gout cases among those with the kidney stones will likely be small.

Limitations:

One limitation of this study lies in the self-report of kidney stones for the overall prevalence estimates with the potential for misclassification and under-ascertainment of asymptomatic kidney stone disease. Another limitation arises from the lack of data on types of kidney stones. Specific kidney stone types are thought to be associated with different risk factors, which we will not be able to distinguish. Moreover, we do not have data on the onset of kidney stone disease, complicating temporal inference. Finally, some exposures may have changed over the course of follow-up.

7.a. Will the data be used for non-CVD analysis in this manuscript?__ Yes _X_ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?__Yes ___No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X_ No
8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___X Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X_ Yes ____ No

No manuscript proposal on kidney stones were found.

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

__X B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* ____2002.02_)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

Literature:

[1] Johnson CM, Wilson DM. renal stone epidemiology. 1979
[2] Stamatelou KK, Time trends in reported prevalence of kidney stones in the US 2003
[3] Curhan Gary C. Epidemiology of stone disease. 2007
[4] Decreased renal function among adults with a history of nephrolithiasis NHANES 3. 2004
[5[Andrew D. Rule Kidney stones and the risk for chronic kidney disease 2009
[6] Metabolic syndrome and self-reported history of kidney stones: the National Health and Nutrition
Examination Survey (NHANES III) 1988-1994.
[7] Khashayer Sakhaee. Nephrolithiasis as a systemic disorder. 2008
[8] Yu T, Gutman AB: Uric acid nephrolithiasis in gout
[9] Pak CYC: Etiology and treatment of urolithiasis.
[10] The association between gout and nephrolithiasis NHANES 3. july 2002
[11] The association between gout & nephrolithiasis in men: The health professionals follow up study
[12] Fessel WJ: Renal outcomes of gout and hyperuricemia