ARIC Manuscript Proposal # 1473

PC Reviewed: 02/10/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Prevalence and Risk Factors for Gout in Women in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): gout prevalence in women

2. Writing Group:

Writing group members: Janet Maynard, Mara McAdams, Anna Kottgen, Alan Baer, Allan Gelber, Josef Coresh, Others welcome.

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

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3. Timeline : Data analysis to start after approval of this manuscript proposal, first draft available by April 2009

4. **Rationale:**

Gout is the most common type of inflammatory arthritis and its incidence and prevalence are increasing worldwide (1). In the United States, 6.1 million adults have a diagnosis of

gout (1) and data from NHANES indicate that the prevalence of gout is 5.6% in women 80 years and older (2).

Hyperuricemia can lead to the deposition of monosodium urate crystals in joints and surrounding tissues. Acute attacks of gout are thought to be triggered by the release of monosodium urate crystals into the joint space from deposits in the synovium and cartilage, inciting an intense inflammatory response. Chronic deposition of monosodium urate crystals can lead to erosion of juxta-articular bone and cartilage, leading to progressive joint damage. However, this joint damage is preventable with available chronic therapies that correct hyperuricemia when such therapy is implemented early in the disease course.

Male sex has been considered a strong risk factor for the development of gout. Therefore, gout has been considered a disease of men and most studies have focused on the prevalence and characterization of male gout patients. However, the number of female gout patients is rising in the US (3). This may be due in part to changes in the prevalence of obesity and metabolic syndrome in women and the increasing number of older women in the general population, both of which are associated with the development of gout. Additionally, post-menopausal women were observed in one study to have an increased risk for gout due to an increase in serum uric acid levels after menopause (4). However, this cross-sectional study focused on women with hyperuricemia, rather than women who had developed gout.

The epidemiology of gout in women has been evaluated in only one study. This study compared the evaluation and treatment of female and male gout patients in a group of US managed care plans with pharmacy benefits (HMO Research Network). Female gout patients were noted to be older at first diagnosis, and had more comorbidities and were more likely to be taking a diuretic as compared with males (5). However, this study was limited by the lack of clinical information available on the patients and was unable to evaluate the effect of menopausal status, BMI, or socioeconomic status on gout risk. Importantly, information on serum uric acid levels, the most important predictor of gout, was lacking as well.

Understanding the risk factors for the development of gout in women is critical given the high prevalence of gout, its increasing prevalence in women, and the availability of inexpensive therapies for patients with a correct diagnosis. The Atherosclerosis Risk in Communities Study (ARIC) provides a valuable sample of 400 women with gout. This population-based study includes detailed clinical information about patients, which has been lacking from previous studies.

We propose to test the hypothesis that women with gout differ in their frequency of obesity, in their diuretic use profile, and have different reproductive histories than women without gout. Additionally, we propose to determine whether the risk factors for gout differ in women compared to men with this disease process.

5. Main Hypothesis/Study Questions:

Primary study questions:

1. In the ARIC study, what is the prevalence of gout in women by age and menopausal status and how does this compare to the prevalence of gout in men?
2. What are the risk factors for prevalent gout in women?
3. Are the traditional risk factors for gout the same in men and women?

Secondary study questions:

5. Is there an association between reproductive factors (such as parity, age at menarche, age at menopause) and gout in women?
6. Does use of hormone replacement therapy change the risk of gout in post-menopausal women?
7. Does menopausal status affect serum uric acid levels?
8. What is the length of time between self-reported menopause and the development of gout?
9. Is there an association between change in adult weight and the reported development of gout in women?

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 methodologic limitations or challenges if present).

Study design:

1. We will compare the prevalence of gout among women and men in the ARIC study, with gout status ascertained at visit 4. We will use a cross-sectional study design of prevalent gout cases stratified by gender to evaluate the association of the following demographic and clinical variables as possible risk factors for gout: estimated glomerular filtration rate (GFR), race, body mass index, change in adult weight, smoking status, diuretic and hypertensive medication use, education, and alcohol intake.

2. To examine the potential association of reproductive history with gout, we will perform a cross-sectional study comparing the women with to those women without gout using prevalent gout ascertained at visit 4. We will evaluate the following variables as possible risk factors for gout by comparing women with gout to women without gout with regard to: menopausal status, age of menopause, cause of menopause, parity, age at menarche, use of oral contraceptive pill (OCP) and of hormone replacement therapy (HRT) .

3. We will examine the association of serum uric acid with gout status, using uric acid levels measured at visits 1 and 2, and will evaluate whether the previously mentioned risk factors affect uric acid levels, by comparing these values in 1) men with gout to women with gout, and 2) among women with gout to women without gout.

4. In the group of women who self-reported gout at visit 4, we will conduct a prospective analysis of the risk of gout in women at visit 4 as a function of menopausal status, HRT use, and other possible risk factor variables (listed above) at visit 1.

Inclusion/Exclusion: In the primary analysis, we will include all African-American and white patients evaluated at visit 1 to select cases and controls. Asian and Native American participants will not be included in this study due to the low prevalence of these groups in ARIC. Cases will be all women with gout (see gout definition under the Outcome section). These cases will be compared to women who do not meet the definition for gout. This female control group will be used in the analyses to identify possible risk factors for prevalent gout in women.

The second control group will be men who meet the gout definition. The male gout patient control group will be used to evaluate whether men and women possess the same risk factors for prevalent gout. In our third analysis using serum uric acid, we will include all patients with a uric acid measurement. We will exclude patients from the analysis of uric acid if they are taking medications known to influence uric acid levels (including losartan, thiazides, allopurinol, and probenecid) at either visit 1 or visit 2. If there are sufficient numbers of women with incident gout during follow-up, we will restrict the fourth analysis to those women whose age at first gout diagnosis is after the age of study enrollment.

Outcome: The primary outcome of interest is a diagnosis of gout if and when one of the following three circumstances is satisfied if: [a] an ARIC participant self-reported a gout diagnosis at visit 4, [b] if the surveillance of hospital discharge summaries reveals an ICD-9 code for gout (ICD-9 codes 274.0, 274.1, 274.8, and 274.9, Table 1), or [c] if a patient was taking a medication used exclusively to treat gout, including allopurinol, colchicine, or probenecid at any study visit.

Other variables of interest: Variables of interest include potential risk factors for gout, traditional risk factors for gout, and other potential risk factors. Female specific risk factors of interest include menopausal status, age of menopause, cause of menopause, parity, age at menarche, OCP use and length of time on HRT. Traditional risk factors include estimated GFR, race, body mass index, diuretic use, alcohol intake, sweetened beverage intake, purine intake, and seafood intake. Other potential risk factors include a history of smoking and education level.

Data analysis:
Primary analyses:
Cross-sectionally, the distribution of demographic and clinical characteristics of the study population according to gout status will be compared at visit 4. Logistic regression will be used to examine the association of covariates with gout, specifically sex, age, race, BMI, waist circumference, hypertension status, alcohol consumption, parity, age at menarche, HRT, as well as further covariates found to be significantly associated with both gout and uric acid levels in the exploratory data analyses. We will calculate

prevalence odds ratios. These analyses will then be repeated with linear regression, except rather than using gout, serum uric acid levels at visit 1 and 2.

Prospective analyses will be conducted among the subset of subjects who self-reported gout at visit 4, but had not developed gout at visit 1. These patients will be identified using age at onset of gout. For this subset, we will perform logistic regression of gout (present vs. absent) status. Risk factors will be those measured at baseline (visit 1 menopausal status, age of menopause, cause of menopause, parity, age at menarche, OCP use and length of time, HRT, estimated GFR, age, sex, race, body mass index, diuretics, alcohol intake, sweetened beverage intake, purine intake, seafood intake, and dairy intake).

Secondary analyses: In sensitivity analyses, we will investigate whether the different definitions of the outcome affect the strength of the various examined associations by using self-reported gout only vs. self-reported gout as well as patients with ICD-9 codes for gout at hospital discharge vs. gout defined by use of gout-specific medication. Further, reported age at the diagnosis of gout will be examined as a function of the covariates.

Limitations: Limitations include the cross-sectional design of the collected data, as well as possible misclassification bias inasmuch as the case definition of gout was based on self-report, use of a medication of gout, or upon hospital a discharge diagnosis of gout, rather than being defined by the gold standard for the diagnosis of gout, which is aspiration of monosodium urate crystals from affected joint fluid.

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 ICTDER03 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 ICTDER03 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 ICTDER03 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)?

1. #759 - Serum uric acid and risk of stroke: the ARIC study; published
2. #1077r - Uric Acid and Hypertension; published
3. #1229 - Uric Acid & Metabolic Syndrome
4. #1311 - Serum uric acid, lung function and chronic obstructive pulmonary disease in adults
5. #525 1. Elevated uric acid as a risk factor for coronary heart disease: the ARIC study; published
6. #313 1. Association between serum uric acid and asymptomatic carotid atherosclerosis: the ARIC study; published

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

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)* albuminuria, AS#_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.

Table 1. Ambulatory diagnostic codes of interest used to identify gout cases

Diagnosis	**ICD-9 codes**
Gout	274
Gout with other specified manifestations	274.8x
Gouty nephropathy	274.1x
Gout, unspecified	274.9
Gouty arthropathy	274.0
Special screening for Gout	V77.5

Table 2. List of variables in ARIC

Variable	Visit	Form (File)	Variable Name	Coding	Notes
Gender	1	Derived	GENDER	M=Male F=Female	
Self-reported gout	4	Medical History	MHQA6A	Y=Yes N=No .=Missing	Only measured at visit 4
Age at 1st gout	4	Medical History	MHQZ6B	Continuous	Self-reported
Age	1	Derived	V1AGE01	Continuous	
Traditional Risk factors					
Baseline BMI	1	Derived	BMI01	Continuous	
BMI	4	Derived	BMI41	Continuous	
Race/Ethnicity	1	Derived	RACEGRP	A=Asian B=Black I=Am. Indian W=White	
Ethanol intake	1	Derived	ETHANL03	Continuous	
Total Kcal	1	Derived	TOTCAL03	Continuous	Used to calculate % of calories from purine-rich foods
Red meat	1	Dietary Intake	DTIA32 DTIA33	Continuous	Purine-rich diet
Organ meat (liver)	1	Dietary Intake	DTIA66	Continuous	
Shellfish	1	Dietary Intake	DTIA37	Continuous	
Uric acid (mg/dL)	1	Chemistry Analysis	CHMA15	Continuous	
	2	Chemistry Analysis	CHMB10	Continuous	
Prescription drugs	1	Medication Survey	CODE1--CODE17	See below	
	2	Medication Survey	CODE1--CODE17		
	3	Medication Survey	CODE1--CODE17		
	4	Medication Survey	CODE1--CODE17		
Coffee Intake	1	Dietary Intake	DTIA61	A=>6/day B=4-6/day C=2-3/day	

				D=1/day E=5-6/week F=2-4/week G=1/week H=1-3/month I=Almost never	
Hot or iced tea	1	Dietary Intake	DTIA62	See above	
Low-calorie soft drink	1	Dietary Intake	DTIA63	See above	
Regular soft drink	1	Dietary Intake	DTIA64	See above	
Fruit-flavored punch	1	Dietary Intake	DTIA65	See above	
Female-specific risk factors					
Current menopausal status	1	Reproductive History	RHXA07	Y=Yes N=No U=Unknown .=Missing	
	3	Reproductive History	RHXB6	Y=Yes N=No U=Unknown .=Missing	
	4	Reproductive History	RHXC6	Y=Yes N=No U=Unknown .=Missing	
Age at menopause	1	Reproductive History	RHXA08	Continuous	
	3	Reproductive History	RHXB7	Continuous	
	4	Reproductive History	RHXC7	Continuous	
Cause of menopause	1	Reproductive History	RHXA09	I=. N=Natural R=Radiation S=Surgery U=Unknown Y=.	
	3	Reproductive History	RHXB8	N=Natural R=Radiation S=Surgery U=Unknown	
	4	Reproductive History	RHXC8	N=Natural R=Radiation	

				S=Surgery U=Unknown	
Oopherectomy	1	Reproductive History	RHXA48	B=Both N=No O=Yes, one U=Unknown	
	3	Reproductive History	RHXB40	B=Both N=No O=Yes, one U=Unknown	
	4	Reproductive History	RHXC40	B=Both N=No O=Yes, one U=Unknown	
Age at oopherectomy	1	Reproductive History	RHXA49	Continuous	
	3	Reproductive History	RHXB41	Continuous	
	4	Reproductive History	RHXC41	Continuous	
Oral contraceptives	1	Reproductive History	RHXA11	Y=Yes N=No .=Missing	Ever use of oral contraceptive
Number of years of OC use	1	Reproductive History	RHXA15	Continuous	
Age at first menarche	1	Reproductive History	RHXA01	Continuous	
Ever given birth	1	Medical History	AMHA14	Y=Yes N=No .=Missing	
Parity	1	Reproductive History	RHXA02	Continuous	Number of pregnancies
Ever used HRT	1	Reproductive History	RHXA16	Y=Yes N=No U=Unknown .=Missing	"Ever taken female hormones?"
HRT since last visit	3	Reproductive History	RHXB10	Y=Yes N=No U=Unknown .=Missing	
HRT since last visit	4	Reproductive History	RHXC10	Y=Yes N=No U=Unknown .=Missing	
Years of HRT use	1	Reproductive History	RHXA22	Continuous	

Other Risk Factors					
Education	1	Derived	ELEVEL02	1=Basic level 2=Intermediate 3=Advanced	
Wt at age 25	1	Dietary intake	DTIA101	Continuous	Coded in lbs
eGFR/creatinine	1	Chemistry	CHMA09	Continuous	Calculated using MDRD equation
eGFR/creatinine	2	Chemistry	CHMB08	Continuous	
Smoking	1	Derived	CIGT01	1=Current 2=Former 3=Never 4=Unknown	
Triceps skinfold mean measurement	1	Derived	MNTRCP01	Continuous	Coded in mm
Subscapular skinfold mean measurement	1	Derived	MNSSCP01	Continuous	Coded in mm
Waist to hip ratio	1	Derived	WSTHPR01	Continuous	No units

Table 3. Prescription drug codes

Drug	**Visit**	**Codes**
Gout drugs	1-4	"680000"="GOUT" "681000"="URICOSURICS" "689900"="COMBINATION GOUT DRUGS"
HRT	1-4	"240000"="ESTROGENS" "249900"="ESTROGEN COMBINATIONS" "249910"="ESTROGEN-ANDROGEN" "249920"="ESTROGEN-ANTIANXIETY AGENT" "249930"="ESTROGEN-PROGESTIN" "249940"="ESTROGEN-ANDROGEN-PROGESTIN" "260000"="PROGESTINS"
Diuretics	1	"370000"="DIURETICS" "372000"="LOOP DIURETICS" "373000"="MERCURIAL DIURETICS" "374000"="OSMOTIC DIURETICS" "375000"="POTASSIUM SPARING DIURETICS" "376000"="THIAZIDES" "379000"="MISC. DIURETICS" "379900"="COMBINATION DIURETICS" "379910"="DIURETICS & POTASSIUM"

		"379920"="NON-PRESCRIPTION DIURETICS"

References:

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