ARIC Manuscript Proposal # 1343A

1.a. Full Title: Addendum to MP #1343: “Stage II of a Genome-Wide Association Study for Genetic Variants Associated with Uric Acid Levels and Gout”

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
   Writing group members: Anna Kottgen, Claudia Hundertmark, Eric Boerwinkle, Linda Kao, Josef Coresh

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Data analysis to start immediately, completion of data analysis and drafting of the manuscript over the next year.

4. Rationale: Recent evidence suggests that the number of genes discovered in genome-wide association studies of complex traits increases rapidly with the size of the initial study population,(1) and this has been true for association studies of serum urate concentrations and gout as well. (2, 3, Yang et al, in press) We would therefore like to request an addendum to ARIC MP #1343 (‘Stage II of a Genome-Wide Association
Study for Genetic Variants Associated with Uric Acid Levels and Gout” to conduct genome-wide association analyses for serum urate levels and gout, overall and sex-stratified, in the ARIC Study, and to combine summary statistics with results from other cohorts participating in the Global Urate Genetics Consortium.

5. Main Hypothesis/Study Questions:
Common SNP variants associated with serum urate levels and gout, and there are sex-specific differences. Novel loci will be identified through meta-analysis with a larger number of studies participating in the Global Urate Genetics Consortium.

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).

The design of the study is similar to the description in ARIC MP #1343. Briefly, we will estimate mean serum urate levels and the odds of gout as a function of age, sex, study center and SNP, iteratively for all SNPs, using linear and logistic regression. Associated regions identified in the meta-analysis will be re-imputed using data from the 1000 Genomes Project and HapMap3 as the reference for fine-mapping purposes. Regions of association identified in the meta-analysis of individuals of European ancestry in the Global Urate Genetics Consortium will be interrogated among African American ARIC participants.

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?  _X_ Yes  ____ 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”?  _X_ 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)?

#1343: “Stage II of a Genome-Wide Association Study for Genetic Variants Associated with Uric Acid Levels and Gout”

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

   __X   A. primarily the result of an ancillary study (list number* 2006.03, 2007.02)

   ___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*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.

References