ARIC Manuscript Proposal # 1299

PC Reviewed: _10 / _09 _/07 **Status: _A___** **Priority: __2_**

SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

Uric acid and Parkinson 's Disease in Atherosclerosis Risk in Community Cohort

b. Abbreviated Title (Length 26 characters): Urate and Parkinson

2. Writing Group:

(Currently in alphabetical order): Chen, Honglei; Huang, Xuemei; Mailman, Richard; Mosley, Thomas H; Post-doc (TBA)

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

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3. Timeline:

From approval to finish data analysis: 3-6 months.

From approval to submission of manuscript (6-9 months).

4. Rationale:

Parkinson's disease (PD) is a common age-related neurodegenerative disorder. In rare cases, PD could be caused by genetic mutations; but for most of the typical PD, the causes are not known. It has been long hypothesized that oxidative stress contributes to the loss of dopaminergic neurons in PD pathogenesis. Urate is a potent antioxidant that effectively scavenges reactive nitrogen and oxygen radicals, and has been hypothesized to be protective against PD. This hypothesis was recently examined in three small prospective studies, each with fewer than 100 PD cases(1-3); all found that individuals with high plasma urate have a lower risk of developing PD. Further, among patients with early PD, higher plasma or

CSF urate concentration predicts a slower clinical PD progression in men, but, not in women (Ascherio and Schwarzschild, abstracts presented at 10th International Congress of Parkinson's Disease and Movement Disorders and Society for Neuroscience Annual Meeting respectively). Interestingly, women in general have lower plasma urate than men but also a lower risk of PD. While these preliminary data suggest that urate may be a novel and tractable target for neuronprotective therapies in a gender specific manner, more research is needed to further characterize the relationship between urate and PD.

These previous studies (1-3) also could not address the potential influence of gender and race on the relationship because two studies include men only and the third one very few women. The ARIC study, with urate measurements for all study participants, offers us a good opportunity to further look into this relationship by gender and race. In addition, ARIC also assessed urate levels at the 2nd visit; with this repeated measurements, we would be able to assess whether urate level is modified by disease status. Furthermore, with the dietary data, we will able to examine potential roles of dietary factors that modulate urate level and their impacts on PD occurrence as has been done in another cohort (Neurology, In press). This dietary analysis will be pursued in a related paper.

Previously, we have obtained some data from ARIC with the permission to examine potential associations between apolipoprotein E and plasma cholesterol levels and PD risk (Manuscript #1176). Urate was included in this dataset as a potential confounder. A preliminary analysis showed that urate level predicted PD risk in this study population. We therefore plan to expand the analysis and prepare a manuscript on this topic.

5. Main Hypothesis/Study Questions:

Higher plasma level of urate is associated with a lower occurrence of PD.

6. Design and analysis

Study Design:

Study participants will be selected from ARIC study, a prospective investigation of ARIC involving 15,792 persons aged 45-64 years at recruitment of 1987-1989 from four US communities: Forsyth County, NC; Jackson, MI, the northwestern suburb of Minneapolis, MN; and Washington County, MD. Approximately 27% (4,000) of the participants are African Americans. A comprehensive survey on dietary and lifestyle factors was conducted in 1987-1989 and most participants also provided a blood sample. The cohort has since been followed by similar surveys about every three years with additional blood collections; a brief annual phone interview to update health status. Urate levels were available from the first and second surveys for nearly all participants. Medication data was collected during home visits and hospitalization data are available from routine ARIC data collection. Suspected PD patients will be identified from multiple sources (see below).

Inclusion criteria:

1) participants with plasma urate measurements or dietary data

Exclusion criteria:

1) When applicable, we will exclude participants without urate information or invalid dietary data

Outcome measures.

1) Potential PD cases were identified from multiple sources: hospital discharge record, medication data from follow-up surveys, death certificates, as well as self-reports at visit 4 (1996 -1998) when a question "Have you ever been told by an MD that you have PD?" was asked. In this way, 172 suspected PD cases were identified and 111 of them were confirmed to be PD cases by review all these information by Dr. Xuemei Huang, blinded to the exposure status.

4) **Potential confounders:** age, sex, race will be adjusted throughout the analysis. Other potential confounders (BMI, alcohol intake, caffeine intake, plasma creatinine, histories of several chronic diseases, cancer therapy information) will be considered individually and adjusted as appropriate. We have obtained information on most of these covariates as part of the data request for cholesterol and PD analysis. Variables not yet available will be requested as part of this analysis.

Summary of Data analysis

Logistic regressions will be conducted, adjusting for age, sex and race throughout the analysis and for other potential confounders as appropriate. Plasma urate will be classified into quartiles, either according to the overall distribution of the cohort or by gender. Subgroup analysis will then be conducted according to race and gender. The average change of plasma urate level between visit one and two will be compared between PD patients and those without PD. Dietary urate index will be created using regression analysis of urate level on relevant dietary intakes.

Limitations/Challenges:

A major limitation of this study is the ascertainment of incident PD cases, which primarily relies on hospital discharge records and other indirect sources. This case-finding procedure may not be as sensitive and specific as conducting clinical PD diagnostic examinations on all participants. Nevertheless, PD cases have been identified by hospital discharge records and self-report of clinical diagnosis in other studies (4, 5) In addition, our preliminary analysis showed that all known risk factors of PD seemed to be related to the risk of PD in the expected direction: risk increases with age, higher in men and lower among smokers and coffee drinkers.

Another limitation is that we were unable to differentiate incident from prevalent cases. However, as the PD is rarely diagnosed before age 60, most of the cases should be incident. Further, the number of cases is small and we may not have sufficient power in subgroup analysis. We will explicitly acknowledge these limitations in our publications.

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

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 X __ 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)?

We are aware of no other manuscripts on this topic in ARIC.

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

11.b. If yes, is the proposal

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

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

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.

Understand

References:

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2. de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum uric acid levels and the risk of Parkinson disease. Ann Neurol 2005;58:797-800.
3. Weisskopf M, O'Reilly E, Chen H, Schwarzschild M, Ascherio A. Plasma Urate and Risk of Parkinson's Disease
10.1093/aje/kwm127. Am. J. Epidemiol. 2007:kwm127.
4. Kamel F, Tanner C, Umbach D, et al. Pesticide Exposure and Self-reported Parkinson's Disease in the Agricultural Health Study
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