ARIC Manuscript Proposal #2508

PC Reviewed: 3/10/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Serum Vitamin D and Risk of Parkinson's Disease in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): vitamin D and PD in ARIC

2. Writing Group:

Writing group members: Srishti Shrestha (NIEHS postdoc), Honglei Chen (NIEHS, PI), Thomas Mosley, Alvaro Alonso, Pamela Lutsey, Xuemei Huang

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

First author: Honglei Chen
Address: 111 T.W. Alexander Dr. RTP, NC 27709

Phone: 919-541-3782 Fax:
E-mail: chenh2@niehs.nih.gov

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).
Name: Thomas H. Mosely
Address: 2500 North State Street, Jackson, Mississippi 39216-4505

Phone: 601-984-2763 Fax: 601-815-3422
E-mail: tmosley@umc.edu

3. Timeline: Manuscript submitted by December 2015

4. Rationale:

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease and its causes are largely unknown. Recent experimental data suggest that vitamin D may protect against PD mostly due to its antioxidative and immunomodulatory properties.

Several case-control studies have demonstrated that PD patients had substantially lower levels of circulating vitamin D than controls [1 2 3 4]. But these cross-sectional comparisons did not address the direction and nature of this association. We therefore propose to prospectively evaluate serum vitamin D in relation to the risk of PD in the ARIC study.

5. Main Hypothesis/Study Questions:

Higher levels of serum 25-hydroxyvitamin D is associated with a lower risk for PD.

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).

We propose to examine serum 25-hydroxyvitamin D measured at ARIC study visit 2 (1990-1992) in relation to future risk of PD (1992-2008). In ARIC, potential PD cases though 2008 were identified from multiple sources at and a total of 106 PD cases were adjudicated. For this specific analysis, we will exclude ARIC participants who 1) did not have 25(OH)D measurements at visit 2; 2) are neither Black nor White; 3) consented only to cardiovascular research; 4) had prevalent PD at visit 2; or 5) were missing/undetermined on PD status. We plan to use Cox proportional models to derive hazard ratios and 95% confidence interval. Follow-up will be defined as age at PD diagnosis, death, loss to follow-up, or December 31 2008 whichever came first. Vitamin D level will be defined as quartile or tertile depending on the sample size or according to meaningful clinical cutoffs (e.g. <20, 20-30, and >30 ng/mL). All analyses will adjust for age at visit 2, gender, and race. Additional potential confounders (such as smoking, caffeine intake, plasma urate level, and estimated glomerular filtration rate) will be evaluated individually and adjusted if they meaningfully change the risk estimates. Despite the small sample size, we will also evaluate interactions by race, and by key vitamin D binding protein SNPs rs7041 and rs4588. Regardless of whether a statistically significant race-interaction is observed, race-stratified results will be reported, given inherent interest. As PD may have a long prodromal period, we plan to conduct additional analyses by examining the relationship separately for the first half and second half of the follow-up or by excluding cases identified in the first 5 years of follow-up. The main limitations of the current study are the relatively small sample size and the lack of cohort-wide systematic case ascertainment.

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 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? __X__ Yes ____ No

(This file ICTDER 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 __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"?
__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)?
The PD group had two recent publications (HRV and PD on *Annals of Neurology* and cholesterol and PD on *Movement Disorders*). Dr. Lutsey who leads the vitamin D project (2009.17) has approved this proposal, and confirmed that there was no overlap with other vitamin D proposals.

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* 2009.19**)**
___ 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/

12a. 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. Understood.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from

http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central. Understood.

References:

1. Evatt ML, DeLong MR, Khazai N, Rosen A, Triche S, Tangpricha V. Prevalence of Vitamin D Insufficiency in Patients With Parkinson Disease and Alzheimer Disease 10.1001/archneur.65.10.1348. Arch Neurol 2008;65:1348-1352.
2. Wang L, Evatt ML, Maldonado LG, et al. Vitamin D from different sources is inversely associated with Parkinson disease. Mov Disord 2014.
3. Ding H, Dhima K, Lockhart KC, et al. Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study. Neurology 2013;81:1531-1537.
4. Evatt ML, DeLong MR, Kumari M, Auinger P, McDermott MP, Tangpricha V. High prevalence of hypovitaminosis D status in patients with early Parkinson disease. Arch Neurol 2011;68:314-319.