

ARIC Manuscript Proposal #3496

PC Reviewed: 10/8/19
SC Reviewed: _____

Status: _____
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Priority: 2
Priority: _____

1.a. Full Title: Association of Peripheral Neuropathy with Mild Cognitive Impairment and Dementia and Brain MRI Findings

b. Abbreviated Title (Length 26 characters): Peripheral neuropathy and cognitive impairment

2. Writing Group:

Writing group members: Caitlin W. Hicks, Dan Wang, B. Gwen Windham, Kunihiro Matsushita, Josef Coresh, Rebecca Gottesman, Elizabeth Selvin; others welcome

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

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3. Timeline: Data to be used in this proposal are available. Analyses and manuscript preparation will be performed over the next 12 months.

4. Rationale:

Peripheral neuropathy contributes to substantial morbidity including pain, foot ulcers, and lower limb amputation. The risk of peripheral neuropathy increases with age, with a prevalence of 44% among adults with diabetes >70 years of age (1).

Peripheral neuropathy is thought to be caused by microvascular damage, which leads to a length-dependent “dying back” axonopathy that primarily involves the distal portions of the longest sensory axons (2). More proximally, sensory ganglia may also be affected by microangiopathy, inflammation, and hyperglycemia-induced oxidative stress (3; 4). Similarly, oxidative stress and inflammation have been implicated in neurodegenerative disorders including Alzheimer’s disease and vascular dementia (5). Type 2 diabetes is also a robust risk factor for cognitive decline and dementia in older adults (6-10), and has been associated with smaller brain volumes and an increased burden of brain vascular pathology in the ARIC study (11). Despite having apparently similar etiologies, the association of peripheral neuropathy in adults with and without diabetes with cognitive impairment or dementia is not well characterized.

ARIC is one of the only US population-based studies to formally test for peripheral neuropathy using 10-g monofilament testing. Peripheral neuropathy testing was performed in all ARIC participants at visit 6 (2016-2017), when the mean age was 79 years (range 71-94 years). At this visit, 32% (N = 1,071) of the study population had diabetes. Notably, the ARIC-Neurocognitive Study (ARIC-NCS) began at ARIC visit 5 and is currently ongoing. ARIC participants who attended visit 5 and onward underwent a comprehensive battery of cognitive, neurologic, and behavioral assessments as part of ARIC-NCS (12). Brain MRIs were obtained at visit 5 and visit 6 or 7 for the dual purposes of obtaining quantitative imaging features for analysis and documenting cerebrovascular lesions such as infarcts and white matter hyperintensities (13). These data offer the unique opportunity to examine the association of peripheral neuropathy with mild cognitive impairment, dementia, and MRI findings in older adults.

5. Main Hypothesis/Study Questions:

The aim of this study is to assess the association of peripheral neuropathy with mild cognitive impairment, dementia, and brain MRI parameters. We hypothesize that older adults with peripheral neuropathy have a higher prevalence of cognitive impairment and markers of subclinical cerebrovascular disease (lobar microhemorrhages, subcortical microhemorrhages, cortical infarcts, and lacunar infarcts) measured on brain MRI than older adults without peripheral neuropathy. We also hypothesize that these associations will be observed in older adults with diabetes and also among those without diabetes independent of risk factors.

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).

Inclusion/Exclusion

We will include all black or white ARIC participants who underwent peripheral neuropathy testing and cognitive testing at visit 6. Participants with self-reported ethnicities other than black or white and those with missing peripheral neuropathy or cognitive data will be excluded.

Exposures of Interest:

Our primary exposure of interest is the presence of PN, which was assessed at ARIC visit 6. Peripheral neuropathy data were collected via Semmes-Weinstein 10 g monofilament testing of three sites on each foot: the plantar-hallux, the plantar-first metatarsal head, and the plantar-fifth metatarsal head. Each site was tested three times by certified technicians and modeled after the NHANES protocol (14). If two of three responses for a site were incorrect or indeterminate, the response was considered insensate at that site. PN was defined as having at least one insensate site.

Other exposures of interest include sociodemographics (age, race-center, sex, education), physical information (blood pressure, height, weight, body mass index [BMI]), lifestyle (smoking status/amount, alcohol consumption), diabetes (presence/absence, duration, insulin-dependency), prevalent cardiovascular disease (CVD) (prevalent coronary heart disease, heart failure, and/or stroke), prevalent peripheral artery disease, clinical variables (LDL-c, HDL-c, triglycerides, systolic blood pressure), prevalent cancer, traditional markers of hyperglycemia (fasting glucose, HbA1c), and APOE status.

Outcomes:

The primary outcome of interest will be the presence of mild cognitive impairment or dementia at visit 6. Participants were classified by an adjudication committee as cognitively normal or having mild cognitive impairment or dementia based on the National Institute on Aging–Alzheimer’s Association (NIA-AA) workgroup criteria (15; 16) and Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (17) after completing a comprehensive battery of cognitive, neurologic, and behavioral assessments, as previously describe in ARIC (12).

Secondary outcomes of interest will be markers of subclinical cerebrovascular disease on brain MRI as measured by the ARIC Brain MRI Study. We will assess the association of PN with white matter hyperintensities, lobar microhemorrhages, subcortical microhemorrhages, cortical infarcts, and lacunar infarcts on brain MRI performed at visit 5, 6, or 7 (11).

Analysis Plan:

We will use logistic regression to assess the cross-sectional association of peripheral neuropathy with mild cognitive impairment and dementia using cognitive function data from visit 6. Model 1 will include age, sex, education, APOE, and race-site. Model 2 will include covariates in Model 1 as well as BMI, smoking status, drinking status, hypertension and hypercholesterolemia. Model 3 will additionally adjust for prevalent cardiovascular disease, and prevalent peripheral artery disease. We will conduct analyses overall and stratified by race and diabetes status. We will also test for interactions by diabetes status and duration and conduct a stratified analysis based on duration of diabetes (<10 years vs. \geq 10 years, the median duration at visit 6).

For our secondary outcomes, we will assess the association of peripheral neuropathy with each of the subclinical markers of cerebrovascular disease using the same Models and sub-analyses described above. The overall fit of all final models in our analysis will be assessed through standard likelihood methods and the Hosmer-Lemeshow test (18).

To account for participant dropout across visits (and thereby reduce potential attrition bias due to missing data), we will use methods developed by the ARIC-NCS Analysis Working Group employing multiple imputation by chained equations to impute cognitive scores of persons who did not attend study visits (10).

Limitations:

Limitations to our study include the lack of monofilament testing and PN assessment at ARIC visits prior to visit 6, which means our study design is limited to a cross-sectional analysis. However, because data collection in the ARIC study is ongoing, we will have the opportunity to assess the association of peripheral neuropathy at visit 6 with incident mild cognitive impairment or dementia events at subsequent visits.

In addition, not all patients underwent MRI evaluation at visit 6. We will use MRI results from visit 6 whenever possible, but may also include MRI evaluations from visit 5 or visit 7 depending on sample size.

Finally, we may also have limited power to evaluate associations in subgroups of interest (i.e. age, sex, race-center, history of CVD), and we do not currently have the ability to validate our results in external cohort.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? 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? 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"? 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.csc.unc.edu/ARIC/search.php>

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)?

There are currently no manuscript proposals in ARIC that evaluate the association of peripheral neuropathy with cognitive impairment. Manuscript proposal #3215 evaluates the traditional and novel risk factors for peripheral neuropathy in the ARIC study. Dr. Hicks is the first author and Dr. Selvin is the senior investigator on that manuscript proposal as well as the current project, so we will avoid overlap in our analysis.

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

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 1999.01; 2008.06)

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.csc.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.

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.csc.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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript Yes No.

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