

ARIC Manuscript Proposal # 3215

PC Reviewed: 8/14/18
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Priority: 2
Priority: _____

1.a. Full Title: Traditional and Novel Risk Factors for Peripheral Neuropathy in the ARIC Study

b. Abbreviated Title (Length 26 characters): Risk factors for peripheral neuropathy

2. Writing Group:

Writing group members: Caitlin W. Hicks, Dan Wang, Natalie Daya, B. Gwen Windham, Christie M. Ballantyne, Kunihiro Matsushita; 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 (PN) is estimated to affect between 2% and 7% of the general population^{1,2}. The prevalence increases substantially in older adults (>55 years of age), and among patients with diabetes mellitus¹. Based on data from the Pittsburgh Epidemiology of Diabetes Complications Study, the prevalence of PN is 34% among patients with type I insulin-dependent diabetes in general, and 58% if ≥ 30 years of age³.

Peripheral neuropathy is one of the most common neurologic conditions encountered by physicians in the outpatient setting⁴. It is usually symmetric and starts distally, gradually spreading in a stocking-like distribution up the feet⁵. The presentation occurs on a spectrum; some patients are asymptomatic, some patients complain of painful neuropathy, and others may present with foot ulcers requiring inpatient hospital admission and multiple costly procedures to promote healing⁶. Symptomatic PN has been shown to significantly impact health status, function, and work productivity, and associated annual average direct costs are estimated to be \$8,055 per patient⁷. Within the diabetic population, the costs are even higher, with annual direct medical costs estimated to be between \$12,492 to \$30,755 based on the severity of disease⁸.

Unfortunately, therapeutic options for PN are limited. Once present, PN is not reversible and, apart from maintaining strict glycemic control and providing supportive treatment of patient symptoms, there are no effective treatment strategies for the disease^{5,9}. As a result, the mainstay of PN management is preventative. Patients considered to be at-risk for PN are generally recommended to control standard cardiovascular risk factors and practice lifestyle modifications such as wearing closed-toes shoes, clean socks, and performing regular foot examinations to check for ulcer formation⁴. Among diabetic patients, intensive glucose control is also recommended.

Due to the cost associated with PN and its complications, preventive care is necessary. As such, there has been a recent interest in research focused on identifying patients who may be at the highest risk for PN¹⁰. Duration of diabetes, independent of diabetes control, has been shown to be associated with both the development and severity of disease¹¹. In a cross-sectional study of 563 patients with diabetes, both mean hemoglobin A1c (HbA1c) and HbA1c variability over time was associated with PN¹². Most recently, Andersen et al. demonstrated that the rate of HbA1c increase over time affected the development of PN independent of mean HbA1c levels among participants in the Anglo-Danish-Dutch Study of Intensive Treatment of Diabetes in Primary Care (ADDITION) study¹³.

We have previously shown that high-sensitivity cardiac troponin T (hs-cTnT) is associated with incident diabetes in the ARIC cohort¹⁴, and that non-traditional blood-based biomarkers are associated with major diabetic complications¹⁵⁻¹⁷. However, there are currently limited data on the association of non-traditional biomarkers with PN in the diabetic population, and there are minimal reports about the association of any laboratory measures with PN in non-diabetic patients, particularly in a community-based population.

5. Main Hypothesis/Study Questions:

The aim of this study is to assess the association of traditional and non-traditional risk factors - particularly blood-based biomarkers - with PN in diabetic and non-diabetic patients in the ARIC study. Because hs-cTnT and N-terminal prohormone brain natriuretic peptide (NTproBNP) have been shown to distinguish between high diabetes risk *versus* low diabetes risk

for cardiovascular disease risk¹⁶; elevated high-sensitivity C-reactive protein (hs-CRP) is associated with increased risk of diabetes and CVD¹⁵; and β -2 microglobulin, creatinine-based estimated glomerular filtration rate (eGFR), and cystatin C-based eGFR are strongly associated with CVD and long-term complications among patients with diabetes¹⁷; we anticipate that some or all of these biomarkers will be associated with PN. We also predict that there may be a difference in risk factors associated with PN among diabetic *versus* non-diabetic participants.

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 at visit 6 and had nontraditional biomarkers (hs-cTnT, pro-BNP, hs-CRP, β -2 microglobulin, creatinine-based eGFR, and cystatin C-based eGFR) measured at ARIC visits 2, 4, and 5. Participants with self-reported ethnicities other than black or white and those with missing PN or biomarker data will be excluded.

Exposures of Interest:

Traditional exposures of interest will include sociodemographics (age, race-center, sex, education), physical information (blood pressure, height, weight, body mass index [BMI], waist circumference), lifestyle (smoking status/amount, alcohol consumption), diabetes (presence/absence, duration, insulin-dependency), prevalent cardiovascular disease (CVD) (prior history of coronary heart disease, heart failure, and/or stroke), prevalent peripheral artery disease, clinical variables (LDL-c, HDL-c, triglycerides, systolic blood pressure), prevalent thyroid disease (TSH levels, thyroid medications), prevalent liver disease (AST, ALT, GGT), prevalent cancer, and traditional markers of hyperglycemia (fasting glucose, HbA1c [assessed as visit 1 baseline and as rate of increase over time]).

The nontraditional biomarkers we plan to study include hs-cTnT, pro-BNP, hs-CRP, β -2 microglobulin, creatinine-based eGFR, cystatin C-based eGFR, urine-to-creatinine ratio, fructosamine, glycated albumin, 1,5-anhydroglucitol, and galectin-3. Each of these biomarkers was measured in ARIC participants at visits 2, 4, and 5. The assays used to measure these biomarkers have been previously described in detail¹⁸ and have been applied to multiple different populations including the ARIC cohort^{15-17,19-22}.

Outcomes:

The primary outcome of interest is the presence of PN, which was assessed at ARIC visit 6. Peripheral neuropathy data was collected via Semmes-Weinstein 10 g monofilament testing of four sites on each foot: the hallux, the first metatarsal head, and the third metatarsal head, and the fifth metatarsal head. Each site was tested three times by certified technicians and modeled after the NHANES protocol²³. If two of three responses for a site were incorrect or indeterminate, the response was considered insensate at that site. Peripheral neuropathy was defined as having at least one insensate site.

The initial PN testing was performed using the AliMed reusable nylon Semmes-Weinstein Monofilament, 5.07 instrument. There was a change in protocol to a disposable monofilament instrument (Medical Monofilaments used with a permanent “monogripper”

handle) mid-way through visit 6 because the original instrument was discontinued by the manufacturer. The effect of this change was assessed in an 80-participant crossover study (20 participants from each site), where participants underwent standard PN testing as well as 2 additional rounds of testing (one with each instrument). There was no significant difference in the incidence of PN diagnosis with the original monofilament instrument compared to the new instrument.

Analysis Plan:

This analysis will be a cross-sectional analysis examining the association of traditional and non-traditional risk factors with PN at visit 6. Univariate and multivariable logistic regression modeling will be used to assess the association between each of the biomarkers and the presence of PN. We will use a multi-staged approach to assess the association of various risk factors with PN. Model 1 will be a crude (unadjusted) model. Model 2 will adjust for sociodemographic, physical, and lifestyle variables. Model 3 will adjust for diabetes, CVD, and clinical variables. Model 4 will include HbA1c and each of the non-traditional biomarkers of interest. Biomarker values will be measured as both mean values overall (visits 2, 4, and 5) as well as biomarker value change over time (slope between visit 2, 4, and 5).

Model discrimination will be assessed using receiver operating characteristic (ROC) curves. We will evaluate whether the addition of each of the biomarkers improves the accuracy of Model 4+biomarkers compared to Model 4 with HbA1c alone using a Wald test of the coefficient and a comparison of the C-statistic before *vs.* after addition of each biomarker. We will also calculate the net reclassification improvement²⁴ to assess whether the addition of nontraditional biomarkers improves the model's strength of association with PN above traditional risk factors.

In addition, we will conduct sensitivity analyses by stratifying the study sample into key clinical subgroups to assess whether the associations identified above are consistent for participants with diabetes *versus* those without diabetes. Specifically, we will analyze the interaction between any significant biomarker-PN associations identified in Model 5 according to diabetes status using the likelihood ratio test.

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 not truly prospective because we cannot exclude prevalent PN at earlier time points. Our analysis will identify factors associated with the presence of PN; whether these factors will be predictive of PN would require a prospectively collected cohort with regular PN assessments.

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 arrangements to validate our final model in an external cohort. We will explore the possibility of validating any associations that we identify in a clinical cohort of diabetic patients enrolled in cohorts through Johns Hopkins University School of Medicine, or possibly using NHANES data depending on the availability of data for identified covariates.

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 peripheral neuropathy as an outcome. Manuscript Proposal #1968 (The association of cardiac troponin T measured by a highly sensitive assay and incident diabetes), Manuscript Proposal #3158 (Advanced glycation end product biomarkers in association with diabetes and diabetes-related traits), and Manuscript Proposal #2207 (Associations of C-reactive protein over six years with incident diabetes, cardiovascular events, and mortality) are the most closely related manuscript proposals with the proposed study. Dr. Selvin is the senior investigator for all three projects, as well as the current project, and thus has extensive experience with the use of biomarkers for predicting clinical outcomes in ARIC.

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* 2009.16)

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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