ARIC Manuscript Proposal #3928

PC Reviewed: 9/14/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association of Peripheral Neuropathy with Falls and Fractures in the ARIC Study

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

2. Writing Group:

Writing group members: Caitlin W. Hicks, Dan Wang, Natalie Daya, B. Gwen Windham, Stephen Juraschek, 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 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).

We have previously shown that peripheral neuropathy is associated with all-cause and cardiovascular mortality in the US population (2). We have also demonstrated strong associations of peripheral neuropathy with vision and hearing impairment using data from the National Health and Nutrition Examination Surveys (NHANES) (*Hicks et al., Under review*). There is some evidence that diabetic peripheral neuropathy is associated with gait imbalance and fall risk (3,4). Peripheral neuropathy has been associated with self-reported falls in adults with diabetes (3-5). Preliminary analysis of NHANES data also suggests there is an association of peripheral neuropathy with a self-reported history of falls in adults ≥ 40 years of age among adults with and without diabetes (unpublished data). However, the association of peripheral neuropathy with incident falls and fractures has not been investigated, especially in adults without a diagnosis of diabetes.

5. Main Hypothesis/Study Questions:

The aim of this study is to assess the association of peripheral neuropathy (assessed by monofilament testing) with incident falls and fractures. We hypothesize that older adults with evidence of decreased sensation of the foot suggestive of peripheral neuropathy will have a higher risk of incident falls and fractures than older adults without evidence of decreased sensation. We also hypothesize that these associations will be observed in older adults both with and without diabetes independent of other 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 monofilament testing at visit 6. Participants with self-reported races/ethnicities other than black or white and those with missing monofilament testing will be excluded.

Exposures of Interest:

Our primary exposure of interest is decreased lower extremity sensation, which was assessed at ARIC visit 6. Peripheral neuropathy data were collected at visit 6 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 (6). 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 covariates of interest include sociodemographics (age, race-center, sex, education), physical information (blood pressure, body mass index [BMI]), lifestyle (smoking status/amount,

alcohol consumption, difficulty in any activity of daily living [(eating, dressing, walking between rooms, standing from an armless chair, and getting out of bed]), diabetes (presence/absence, duration, insulin-dependency), cognitive status (normal/mild cognitive impairment/dementia), prevalent cardiovascular disease (CVD) (prevalent coronary heart disease, heart failure, and/or stroke), prevalent peripheral artery disease, prevalent chronic kidney disease, and prevalent cancer. We will also include data on hypertension medication use, diuretic use, and psychotropic medications (antidepressants, sedatives, hypnotics, antipsychotic medications, anti-epileptic medications, and anticholinergic medications) as these medications are associated with fall risk.

Outcomes:

The primary outcome of interest will be any fall or fracture captured in ARIC hospitalization records or Medicare claims after visit 6. We will identify falls using ICD-9-Clinical Modification E codes E880.x–E886.x or E888.x (7; 8). We will identify fractures using any fall with an additional ICD-9 diagnosis codes for fracture (fractures from injury: 800.x–829.x; pathologic or stress fractures: 733.1, 733.93, 733.94, 733.95, 733.96, 733.97, and 733.98; and late effect of fractures: 905.0, 905.1, 905.2, 905.3, 905.4, and 905.5). ICD-9 codes will be mapped to ICD-10 codes for claims after 2014. We will perform an internal validation of ICD-10 codes for falls by comparing self-reported falls to falls using ICD-10 codes that were identified in the corresponding 6-month period (7).

Table 1: ICD-9 and ICD-10 and E codes used to identify falls.

Outcome	E codes	ICD-9 codes
Falls	E880.x-E886.x, E888.x	
Falls with fracture	E880.x-E886.x, E888.x	820.x-829.x 733.1x, 733.93, 733.94, 733.95, 733.96, 733.97, 733.98 905.0x, 905.1x, 905.2x, 905.3x, 905.4x, 905.5x

Analysis Plan:

We will compare baseline characteristics of participants with and without falls using chi-squared tests and t-tests as appropriate. We will calculate incidence rates of falls for adults with vs. without peripheral neuropathy, overall and stratified by diabetes status. We will also model incidence rate ratios for falls using Poisson regression to adjust for age, sex, and race-center, as well as psychotropic medications.

We will use Cox proportional hazards models to assess the association of peripheral neuropathy with incident falls. Model 1 will include age, sex, and race-center. Model 2 will include covariates in Model 1 as well as hypertension medication use, diuretic use, psychotropic medication use, and cognitive status. Model 3 will additionally adjust for BMI, education level, smoking status, drinking status, physical activity, prevalent cardiovascular disease, prevalent peripheral artery disease, chronic kidney disease, and cancer. We will conduct analyses overall and stratified by diabetes status. The overall fit of all final models in our analysis will be assessed through standard likelihood methods and the Hosmer-Lemeshow test (9).

For our secondary outcome, we will assess the association of peripheral neuropathy with falls with fractures by calculating incidence rate ratios and the same Cox proportional hazards

models above. Finally, given the potential impact of the competing risk of death for estimating the risk of falls, we will run Fine and Gray's proportional subhazards models (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 visit 6 onward. Visit 6 will serve as the baseline for all exposure variables described above. Peripheral neuropathy testing is limited to monofilament testing, whereas nerve conduction studies are the gold standard. However, monofilament testing is diagnostic for loss of protective sensation, which is an advanced form of peripheral neuropathy, and is used in clinical practice. We do not have additional exam data or patient symptom data to expand on the diagnosis of peripheral neuropathy beyond loss of sensation. In addition, falls and fractures will be identified based on administrative codes, and have not been adjudicated. 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? __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? ____ 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"? ____ 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)?

There are currently no manuscript proposals in ARIC that evaluate the association of peripheral neuropathy with falls. 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. Dr. Selvin is also the senior author on MP #3082 evaluating the association of severe hypogylcemia with falls. Manuscript proposal #2381 evaluates falls prevalence in older black and white ARIC participants; Dr. Windham is the senior author on the proposal and included as a co-author for this proposal as well. Dr. Juraschek is the author of several manuscript proposals looking at falls risk associated with cardiovascular disease (MP #3221) and orthostatic hypotension (MP #2611), and is included as a co-author for this proposal as well.

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* _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.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.

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.

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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