ARIC Publication Admin Use Only: ARIC Manuscript Proposal # 4592

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1.a. Full Title: Prevalence of Peripheral Neuropathy defined by the Michigan Neuropathy Screening Instrument in Older Adults - an Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Peripheral Neuropathy by MNSI

2. Writing Group [please provide a middle name if available; EX: Adam Lee Williams]:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __YW___ **[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 6 month.

4. Rationale:

Peripheral neuropathy is a distal symmetric polyneuropathy that has been traditionally associated with diabetes. Previous studies have shown that peripheral neuropathy contributes to substantial morbidity, including pain, extremity complications, autonomic dysregulation, sensory/vision/hearing loss, falls, and trauma[1-3]. Peripheral neuropathy assessed by monofilament testing is associated with mortality among US adults, even in the absence of diabetes[4]. The risk of peripheral neuropathy increases with age, but studies focused on understanding its etiology and burden, in very old adults, especially those without diabetes, are limited.

In our previous work (MP#3125), we characterized peripheral neuropathy and its prevalence using standardized monofilament testing in two U.S. population-based cohorts: the National Health and Nutrition Examination Survey and ARIC (Atherosclerosis Risk in Communities) studies[5]. We demonstrated that peripheral neuropathy is common in adults aged 70 years and older, including adults without diabetes. However, monofilament testing is a screening tool for loss of protective sensation, which is a sign of a more advanced peripheral neuropathy in certain populations, particularly those with diabetes[6 7]. It is unclear whether monofilament alone can diagnose peripheral neuropathy in other populations. A more comprehensive screening tool is needed to accurately assess peripheral neuropathy, encompassing both sensory symptoms and physical examination findings, to detect a broader spectrum of neuropathic changes in older adults.

The Michigan Neuropathy Screening Instrument (MNSI) is a validated tool developed to detect peripheral neuropathy in adults with diabetes.[8] Current literature does not report MNSI assessment on adult older than 75 years old, and the burden of peripheral neuropathy in this population still needs to be defined. The estimated prevalence of less severe peripheral neuropathy (without loss

of protective sensation) in adults 80 years or older is likely much higher than 34% to 42% we previously reported[5], due to low awareness of the disease and lack of screening[9]. In the ARIC Study, we used the MNSI to evaluate peripheral neuropathy in older adults (median age 81) at Visit 10. In this proposed study, we aim to report the prevalence of, and risk factors associated with peripheral neuropathy identified by the MSNI in older adults with and without diabetes.

5. Main Hypothesis/Study Questions:

Aim 1: Determine the prevalence of peripheral neuropathy as assessed by the MNSI in participants with and without diabetes.
Hypothesis: Peripheral neuropathy as defined by the MNSI is highly prevalent among older adults regardless of diabetes status.

Aim 2: Compare the prevalence of peripheral neuropathy in older adults when peripheral neuropathy is defined by the MNSI vs. monofilament testing alone.
Hypothesis: Older adults will show a higher prevalence of peripheral neuropathy when peripheral neuropathy is detected using the validated MNSI tool, because a broader range of symptoms and signs are captured by the MNSI compared to monofilament testing.

Aim 3: Quantify risk factor associations with peripheral neuropathy in older adults with and without diabetes.
Hypothesis: Older adults with or without diabetes are more likely to have peripheral neuropathy if they have including lifestyle risk factors including lifetime smoking and drinking status, prevalent cardiovascular disease, taller heights and more advanced age.

Aim 4: Compare the prevalence of physical examination abnormalities captured by the MNSI in older adults with versus without diabetes.
Hypothesis: Physical examination abnormalities, specifically monofilament testing, identified by the MNSI will be more prevalent in older adults with diabetes compared to those without diabetes, reflecting a higher burden of advanced peripheral neuropathy in the DM population.

6. Design and analysis

a) Study Design

We will conduct a cross-sectional analysis among participants who completed the MNSI.

Outcomes: For the primary aim of this analysis, we will define peripheral neuropathy using the screening results of the MNSI at ARIC Visit 10. The MNSI involves a questionnaire and a physical assessment. The questionnaire is a staff-administered 15-item questionnaire. Responses to 13 of the 15 questions that indicate potential symptoms attributable to neuropathy are scored one point each. Questions 4 and 10 are measures of impaired circulation and general asthenia, respectively, and are not included in the scoring algorithm (Table 1). A score of ≥ 7 on the MNSI questionnaire is traditionally considered abnormal, although a recent analysis assessing the performance of the MNSI questionnaire demonstrated that a score ≥ 4 improves the sensitivity of the screening tool in adults with type 1 diabetes[8 10].

The physical assessment portion of the MNSI consists of evaluations of foot health and nerve function: foot inspection, vibration sensation, and muscle stretch reflexes. Monofilament testing tests for loss of protective sensation. Feet are inspected for dryness, callouses, ulcers, deformities, and signs of Charcot foot. Vibration sensation is tested with a 128 Hz tuning fork on the great toe, with results categorized as present, reduced, or absent based on the duration of sensation compared to the examiner's finger. Ankle reflexes are checked using a reflex hammer. The monofilament test assessed sensation by applying a 10-gram filament to the great toe[11].

Table 1. List and order of questionnaire in the Michigan Neuropathy Screening Instrument

Question Order	Reponses
1. Are your legs and/or feet numb?	Y/N
2. Do you ever have any burning pain in your legs and/or feet?	Y/N
3. Are your feet too sensitive to touch?	Y/N
4. Do you get muscle cramps in your legs and/or feet?	Y/N
5. Do you ever have any prickling feelings in your legs or feet?	Y/N
6. Does it hurt when the bed covers touch your skin?	Y/N
7. When you get into the tub or shower, are you able to tell the hot water from the cold water?	Y/N
8. Have you ever had an open sore on your foot?	Y/N
9. Has your doctor ever told you that you have neuropathy?	Y/N
10. Do you feel weak all over most of the time?	Y/N
11. Are your symptoms worse at night?	Y/N
12. Do your legs hurt when you walk?	Y/N
13. Are you able to sense your feet when you walk?	Y/N
14. Is the skin on your feet so dry that it cracks open?	Y/N
15. Have you ever had an amputation?	Y/N

A score of ≥7 on the MNSI questionnaire or a score of >2 in the physical examination portion is traditionally considered abnormal (i.e. positive for peripheral neuropathy; **Table 2**). We will perform a secondary analysis using an MNSI cutoff of ≥4 on the questionnaire portion of the MNSI based on data from the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) trial[10].

Table 2. Michigan Neuropathy Screening Instrument Assessment Components

Assessment	Definition of Abnormal
Questionnaire	
15-item about health	Score ≥ 7
Physical assessment	
Foot inspection	Dryness, callouses, ulcers, deformities, and signs of Charcot foot
Monofilament testing	2 or more insensate areas
128 Hz tuning fork	Present or reduced
Ankle reflexes	Present or absent
*Peripheral Neuropathy by MNSI = abnormal on questionnaire or 2 abnormalities on the physical assessment	

Exposures: We will evaluate risk factors that may be associated with peripheral neuropathy including demographic factors (age, sex), social determinants of health (race-center, education), the national Area Deprivation Index (ADI), body mass index (BMI) in sex-specific quartiles, physical functioning (Short Physical Performance Battery scores [SPPB]), lifetime lifestyle habits (smoking history, drinking status), frailty, and the presence of comorbidities including diabetes status, cardiovascular disease, hypertension, hypercholesterolemia, and chronic kidney disease.

The ADI will be calculated from existing participant zip codes. The SPPB (scored 0-12), a standardized tool assessing lower extremity function based on balance, gait speed, and repeated chair stand performance, will be categorized into three levels: low (0-6), fair (7-9), and good (10-12)[12 13]. Drinking status will be classified as never drinkers, former drinker, or current drinker based on participant self-report. Diabetes will be defined as either self-reported doctor-diagnosed diabetes, current use of glucose-lowering medication, or hemoglobin A1c (HbA1c) level of 6.5% or higher. Pre-diabetes will be defined as an HbA1c level between 5.7% and 6.4% in individuals without diabetes. Prevalent cardiovascular disease will be defined as history of myocardial infarction, heart disease, cardiac procedures, heart failure, or ischemic stroke. Hypertension will be defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking medication for blood pressure. Hypercholesterolemia will be defined as having plasma total cholesterol ≥ 240 mg/dL or taking medication for high cholesterol. Prevalent chronic kidney disease was identified by estimated glomerular filtration rate (eGFR) < 60 ml/min/1.72m2, where the eGFR will be calculated from on the CKD-Epi Creatinine-Cystatin Equation 2021[14].

b) Inclusion/Exclusion

We will include all ARIC participants who attended ARIC visit 10 and who completed the MNSI. Participants with missing monofilament testing or MNSI assessment from ARIC Visit 10 will be excluded. Participants with missing diabetes status information and main covariates of interest listed below in Section 6 (c) will be excluded.

c) Outcome and other variables of interest with specific reference to the time of their collection

Peripheral neuropathy will be defined using a validated screening tool, the MNSI, which was obtained from the participants at ARIC visit 10 during a single clinic visit. Monofilament insensitivity testing was performed as part of the MNSI at ARIC Visit 10.

Demographic Variables:

Sex, Age:

Time of Collection: Baseline demographic information from participant interviews at Visit 1

Social Determinants of Health:

Race-Center, Education Level:

Time of Collection: Baseline demographic information from participant interviews and medical records, during Visit 1

Area Deprivation Index (ADI):

Definition: Derived from participant zip code data linked to ADI from Visit 1 to 7.

Physical Measures:

Height and BMI:

Time of Collection: Weight was measured during Visit 10 and Height was captured on Visit 5 (for those with missing height at V5, height from V1 was used). Height will be categorized into sex-specific quartiles for analysis.

Comorbidities:

Diabetes Status:

Definition: Based on self-reported doctor diagnosis or glucose-lowering medication use from Visit 7 to 10, or HbA1c $\geq$ 6.5% at Visit 10.

Time of Collection: HbA1c levels measured via blood sample at 10.

Pre-diabetes:

Definition: HbA1c between 5.7% and 6.4%.

Time of Collection: Blood samples taken during Visit 10.

Cardiovascular Disease (CVD):

Definition: History of myocardial infarction, heart disease, cardiac procedures, heart failure, or ischemic stroke

Time of Collection: Medical records and participant reports over follow-up until 2022

Chronic Kidney Disease (CKD):

Definition: eGFR < 60 ml/min/1.73m² based on the CKD-Epi 2021 equation.

Time of Collection: Blood tests during Visit 10.

Hypertension:

Definition: SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or use of antihypertensive medication.

Time of Collection: Visit 10.

Hypercholesterolemia: Total cholesterol ≥ 240 mg/dL or use of lipid-lowering medication.

Time of Collection: Visit 10.

Frailty, Physical Function and Lifestyle Variables:

Frailty:

Definition: Using frailty construct previously constructed and validated in ARIC based on characteristics of unintentional weight loss >10% or BMI < 18 kg/m2, $<20^{th}$ percentile in sex=specific Bake leisure sport activity index, $< 20^{th}$ percentile in sex and height adjusted walking speed, fatigue or exhaustion identified on the Center for Epidemiologic Studies Depression Scale (CES-D), and $<20^{th}$ percentile in sex and BMI specific dominant hand grip strength.

Time of Collection: Visit 5, 6, and 7

Short Physical Performance Battery (SPPB):

Definition: Assesses balance, gait speed, and chair stands; scores range from 0–12.

Time of Collection: Visit 9.

Alcohol Use and Smoking Status:

Definition: Self-reported as never, former, or current collected via questionnaire.

Time of Collection: most recent available date (from Visit 5 to 7) or listed as unknown for missing information.

d) Summary of data analysis

We will estimate the adjusted prevalence of MNSI-defined peripheral neuropathy overall and by participant risk factors, using predictive margins from logistic regression with adjustment of age, sex and field center. We will also use logistic regression models to evaluate the age, sex- and field center-adjusted associations of risk factors with MNSI-defined peripheral neuropathy. Percentage and standard error will be reported for prevalence estimates, and odds ratio and 95% confidence interval will be reported for associations of risk factors with peripheral neuropathy. We will then repeat the above analyses for monofilament testing-defined peripheral neuropathy. The prevalence of peripheral neuropathy defined by MNSI and the monofilament test alone will be compared using chi-squared tests. All analyses results will be reported overall and stratified by diabetes status.

e) Any anticipated methodologic limitations or challenges if present

The gold standard test for peripheral neuropathy involves nerve conduction studies and/or electromyography, which were not performed in the ARIC study. This limitation prevents a direct comparison of the diagnostic performance of the MNSI and monofilament testing in diagnosing peripheral neuropathy.

Given the observational, cross-sectional design, there may be residual confounding, and we will not be able to establish temporality of any observed associations. There is a concern for survival bias given that the analysis focuses on older adults. Nonetheless, our goal is to examine epidemiologic associations, and we are focused on covariates that are well-established risk factors for peripheral neuropathy and related conditions.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed. ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic,

Geocoded, and Proteomics/Somalogic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ☐ Yes ☒ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ☐ Yes ☐ No

(The file ICTDER is distributed to ARIC PIs annually, 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 current derived consent file ICTDER05 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: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website→Publications→Proposal Search]

☒ 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 the ARIC study that define peripheral neuropathy using the Michigan Neuropathy Screening Instrument. This manuscript proposal is directly related to ARIC Ancillary Study #AS **2021.04** which is led by Dr. Hicks (senior author of this proposal). Manuscript proposal #3215 evaluates the traditional and novel risk factors for peripheral neuropathy in the ARIC study, in which peripheral neuropathy was defined using monofilament testing only (Drs. Hicks and Selvin were the first and senior investigators of that study, respectively).

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 (AS 2021.04)**

☐ **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 https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website→Ancillary Studies→Approved Ancillary Studies]

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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC WebsiteàPublicationsàPublication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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