ARIC Manuscript Proposal #4216

PC Reviewed: 3/18/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

a. Full Title: Associations between Peripheral Neuropathy and Gait Characteristics in Community-Dwelling Older Adults: the Atherosclerosis Risk in Communities (ARIC) Study
b. Abbreviated Title (Length 26 characters): Gait characteristics in PN

2. Writing Group
Writing group members: Katherine McDermott, Dan Wang, Yein Jeon, Laura Skow, B. Gwen Windham, Jennifer Schrack, Elizabeth Selvin, Caitlin Hicks, others welcome

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

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3. Timeline
First Analysis: 4 months. Manuscript: 4 months.
Second Analysis: 6 months. Manuscript: 4 months.

4. Rationale

Peripheral neuropathy (PN) is common among older adults, with a prevalence near 50% in adults >70 years of age with diabetes (1) and at least 25% to 32% in adults >70 years of age without diabetes (1,2). Loss of proprioception and protective pain and temperature sensations, decreased joint mobility, and asymmetric muscle atrophy leading to foot deformities are characteristic of PN. Together, these factors predispose to gait abnormalities, foot ulceration, and

increased risk of falls in adults with diabetes, but the associations of non-diabetic PN with gait changes and clinical outcomes are not well described (1,3–7).

Slow gait speed in persons with PN, and in older adults regardless of PN status, is associated with increased risk of falls, loss of independence, and mortality (8–10). Other gait aberrations that suggest poor balance or instability (e.g., changes in step and gait phase patterns, increased gait variability) have been observed in PN populations and are proposed as early markers of fall risk, though the existing literature on these characteristics is limited by small sample sizes and a paucity of data on non-diabetes populations (8,9,11). These changes are often subtle and are not easily recognized in a standard clinical evaluation, thus objective methods for measuring gait are required to identify and quantify these changes (6).

The assessment of gait in both clinical and research practice is highly variable. Gait measurements range in complexity from simple visual observation to conventional measures of speed and distance (e.g., cadence, gait speed) to video and sensor-based biomechanical analysis (7). Gait mat technology is increasingly used as an objective, non-examiner dependent measurement of traditional gait measures as well as additional mat-derived gait characteristics (e.g., stride, step, and pressure distribution characteristics), which is unique from other modalities. Data evaluating the association between PN and gait features, both overall and specifically using gait mat technology, is lacking.

Examining the associations of PN with gait abnormalities is important for understanding the functional sequelae of PN and, further, potential mechanisms of increased fall risk (4,8,10,12). If PN is associated with unique gait mapping signatures, this technology may be an important tool to stratify the risk of falls, facilitate patient education, prompt more frequent provider foot exams, and evaluate of the effectiveness of interventions to correct gait in adults with PN (12). The aim of our study is to characterize the associations of PN with a comprehensive set of gait features measured using gait map technology (Zeno^{TM} Walkway) in a community-based sample of older adults.

5. Main Hypothesis/Study Questions

We hypothesize that:

1. PN will be associated with slow gait speed (defined as gait speed <1m/s) and with slower gait speed (meeting the minimum clinically meaningful difference of >=0.05m/s) compared to no PN.
    a. These associations will persist after adjusting for age, sex, race (black vs. white), diabetes (yes vs. no), prevalent CVD, cognitive status (normal vs. MCI or dementia), and low weight.
2. PN will be associated with gait changes traditionally considered to be markers of instability: shorter step and stride length, wider stride width, and greater variability in stride length and width variability (“step” features); shorter time in swing phase/single-support, longer time in stance phase/double-support and grater variability in phase length (“gait phase” features); greater footfall length percent, less center of pressure path efficiency, and greater center of pressure path efficiency variability.
3. PN will be associated with differences in gait phase gait mat measurements in exploratory analyses.

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).

Our initial analysis will include ARIC participants who completed standardized monofilament testing for PN at V6 and completed 1) at least one 4-meter walk test at V6 and/or 2) the ProtoKinetics Zeno^{TM} Walkway gait map testing at V8 for at least one usual pace walk. Zeno^{TM} Walkway gait map testing data comprise the majority of our outcome measures; 4-meter walk test gait speed at V6 will be used for sensitivity analysis of gait speed and to objectively assess for selection bias in the V8 sample, which represents a subgroup of ARIC participants due to site closures related to COVID-19. This represents a mixed cross-sectional and non-concurrent cross-sectional analysis.

We plan to repeat this analysis using V10 study visit data for a concurrent cross-sectional analysis. We will similarly assess the association of PN with a variety of gait map measurements, but the definition of PN will be modified to align with the Michigan Neuropathy Screening Instrument (MNSI), which includes a 15-item symptom inventory and a lower extremity examination (inspection, reflex testing, vibratory sensation testing and monofilament testing). The MNSI data is being collected concurrently with gait mat assessments using the same ProtoKinetics Zeno^{TM} Walkway gait map as used at V8.

Measures of Peripheral Neuropathy
For our initial analysis, PN will be defined for V8 study participants as peripheral sensory deficits based on Semmes-Weinstein monofilament testing collected at V6, as previously described (2). Briefly, a monofilament instrument (5.07 Semmes–Weinstein nylon monofilament mounted on a plastic handle), was applied with gentle pressure to the sole of each foot at the plantar-first metatarsal head, the plantar-fifth metatarsal head, and the plantar-hallux. Sites were evaluated separately. For each site, if the participant was able to identify pressure, then sensation at that site was deemed intact and the test was not repeated at that site. If the participant was unable to identify pressure, the test was repeated up to three times total until two similar responses were obtained. A site was defined as insensate if the participant was unable to determine when pressure was applied on two tests at that site (either two out of two tests, or two out of three tests). PN was defined as having at least one insensate site on any foot (2).

For our second analysis, PN will be defined based on previously established MNSI criteria of $\geq$7 items (13,14), with additional sensitivity analysis for $\geq$4 items, which has been suggested as a more sensitive cutoff for the diagnosis of PN in persons with diabetes (13).

Gait Measurement & Gait Features
All gait measurements will be assessed using ProtoKinetics Zeno^{TM} Walkway gait mat systems and calculated by ProtoKinetics PKMAS gait analysis software (V8). The Zeno^{TM} Walkway gait mat is a padded, flat sensor mat with a 5-meter sensor distance. Participants are asked to walk in a straight line from one side of the mat to the other at a comfortable pace, referred to as a “usual pace” walk trial. All participants with at least one completed usual pace walk trial will be included; for participants who completed two, the faster of these trials will be used for all analysis in keeping with standard gait analysis methodology.

Gait speed
The primary outcome of our analysis is usual pace gait speed (m/s). Gait speed will be evaluated continuously and as a binary variable categorized as normal (≥1m/s) or slow gait (<1m/s), a commonly used cutoff to define slow gait and a predictor of fall risk in older adult populations (10,15). We will evaluate both V6 4-meter walk gait speed and V8 gait mat-derived gait speed. Additional gait mat-derived features of interest in several categories below will be evaluated as secondary outcomes, described below.

Step
We plan to evaluate step length (cm), stride length (cm), and stride width using linear regression. Step length is a measure of initial contact distance between one foot and the other within the same stride; stride length is a measure of initial contact distance between the same foot from one stride to the next; stride width is a measure of the distance between the forward vector of one foot stride and the initial contact point of the opposite foot (**Table 1**). We will additionally evaluate the coefficient of variation of these measures to evaluate for within-person variability. Shorter step and stride lengths and wider stride width have been previously associated with PN in persons with diabetes and are proposed to measure poor balance and gait instability (6).

Gait Phase
Gait phase describes the division of a gait cycle based on whether one or both feet are on the ground. The portion of the gait cycle in which both feet are on the ground is described as stance phase (also represented by double-support time), and in normal gait this comprises approximately 60% of the gait cycle. The complementary portion of the gait cycle in which only one foot is on the ground is described as swing phase (also represented by single-support time), and in normal gait comprises the remaining 40% of the gait cycle. More time, or higher proportion of time, in stance phase/double-support is associated with poor balance and gait instability. We plan to evaluate percent-of-time measures of stance phase, double-support, swing phase, and single-support (as opposed to raw times, which may be confounded by gait speed) (**Table 1**). We will further examine differences in within-patient variation in these measures (% CV), which have also been proposed to measure of gait instability (4,6).

Path distance and path efficiency
Both path distance and path efficiency measure the degree to which a person is effectively "rolling through" each step. Measures of length or distance assess the proportion of each foot, compared to the maximum foot length, that contacts the mat with each step, with high values indicating "flat-footed" gait, which can be associated with poor joint mobility in PN. Measures of pressure assess the degree to which a participant's center of mass deviates side-to-side during each step, with perfect efficiency suggesting stable forward propulsion in the direction of the footfall, and decreased efficiency suggesting instability. We plan to evaluate percent-of-distance measures of length parameters (rather than raw distance, to avoid confounding by foot size) and percent measures of path efficiency in both double-support and single-support gait phases (**Table 1)**.

Global measures of gait function

The functional ambulation performance (FAP) score is a calculated variable ranging from 0-100 that incorporates variability in step time, stride length, and stride width to provide a global assessment of the consistency of gait (16). Generally, 95 or higher is considered normal, less than 90 has been previously associated with falls (16,17). The Zeno^{TM} Walkway PKMAS software FAP score has not been extensively published but its component measures have been validated against other gait mat technologies, including in older adults (18). We plan to evaluate continuous FAP score and binary FAP score comparing <90 to ≥90, consistent with existing literature on clinically meaningful cutoffs.

Table 1. Gait measures by the category of gait characteristics they describe

Category	Gait measures (units)
Stride information	**gait speed (m/s)** cadence (steps/min) stride velocity (m/s)
Step information	*step length (cm)* *stride length (cm)* *stride width (cm)* number of steps toe in/out angle (degrees)
Gait phase	gait cycle time (s) single-support time (s) double-support time (s) initial double-support time (s) terminal double-support time (s) *stance phase (%)* *double-support time (%)* *initial double-support time (%)* *terminal double-support time (%)* *swing phase (%)* *single support time (%)*
Path distance	stance center of pressure distance (cm) single-support center of pressure distance (cm) double-support center of pressure distance (cm) *stance center of pressure distance (%)* *single-support center of pressure distance (%)* *double-support center of pressure distance (%)*) right, left, and both feet pressure (standard deviation)
Path efficiency	*stance center of pressure path efficiency (%)* *double-support center of pressure path efficiency (%)* *single-support center of pressure path efficiency (%)* *foot length percent (%)* *integrated pressure* pressure asymmetry index (0-100)
Global measures of gait function	*Functional ambulation performance (FAP)*
primary outcome; *secondary outcomes;* potential exploratory outcomes	

Demographic and clinical factors

We will report age (years), sex, and race (white, Black) in the initial analysis. We will plan to report and adjust for race-center in the subsequent analysis, but in-person V8 sample size will not allow for this adjustment. We will report and adjust for BMI [categorical BMI defined as "low or normal weight" (< 25kg/m^2), "overweight" (25 - <30 kg/m^2), or "obesity" ($\geq$30 kg/m^2)]; the sample size and prevalence of underweight in our initial analysis will not allow further adjustment for low weight. We will consider separating the "low or normal weight" category into "underweight" (BMI < 18.5 kg/m^2) and normal weight (18.5 - <25 kg/m^2) in our second analysis, sample size permitting. We will report diabetes status (yes vs no), defined as the composite of self-reported doctor diagnosis, current use of antihyperglycemic medication, or HbA1c >6.5%; we will also consider time of diabetes (for adults with diabetes), and HbA1c. Prevalent cardiovascular disease will be defined as prior occurrence of myocardial infarction, coronary heart disease, or cardiac procedural intervention, evidence of myocardial infarction on ARIC study electrocardiogram, hospitalization for heart failure, and/or definite or probable ischemic stroke. Cognitive status will be defined using the ARIC Neurocognitive Study global cognition evaluation, categorized as normal, mild cognitive impairment, or dementia. All demographic and clinical factors will be collected at the study visit of interest for the gait analysis whenever possible (i.e., V8 for the initial analysis, V10 for the second analysis). For the initial analysis, PN will be characterized according to the V6 monofilament testing as described above.

Statistical Analysis

We will report measures of central tendency and variance for individual gait features comparing adults with vs. without PN for all gait measures in Table 1. We will conduct logistic and linear regression analysis assessing the associations of PN with our primary outcomes using a sequential model approach. Model 1 will be unadjusted. Model 2 will adjust for age, sex, and race. Model 3 will adjust for all covariates in Model 2 plus low weight (BMI < 18.5 and/or recent >10% weight loss), diabetes status, prevalent cardiovascular disease, cognitive status. Model 4 will adjust for the same covariates in Model 3 but with HbA1c substituted for diabetes status. We will also evaluate the association of PN with continuous gait speed variables using splines models. We will perform sensitivity analyses stratified by diabetes status and cognitive impairment, sample size permitting.

Limitations

The use monofilament testing to define PN captures loss of protective sensation (i.e., severe PN), but likely underestimates the prevalence of mild or moderate PN. This limitation, as well as the non-concurrent nature of PN and gait assessments in our initial analysis, may misclassify participants who truly have PN as not having PN. Small sample size of the ARIC V8 in-person cohort due to COVID-19 may limit our power to evaluate associations between PN and the gait features we propose to assess and will negatively impact the precision of our subgroup analyses. We plan to collect more granular, concurrent data on PN and gait at V10 to address these limitations. Finally, multiple comparisons will make our findings exploratory, particularly in the initial analysis. Despite these limitations, investigating potential associations of PN with gait mat parameters are necessary to direct future research and clinical use of gait mat technologies in adults with PN.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ___ Yes ___X_ 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

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 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: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html
__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)?

ARIC Manuscript Proposal #3914 - Gait Characteristics in Older Adults using the ProtoKinetics Zeno^{TM} Walkway: the Atherosclerosis Risk in Communities (ARIC) Study
ARIC Manuscript Proposal #3928 - Association of Peripheral Neuropathy with Falls and Fractures in the ARIC Study
ARIC Manuscript Proposal #3215 - Traditional and Novel Risk Factors for Peripheral Neuropathy in the ARIC Study

The lead authors of each of these proposals (Drs. Skow and Hicks) are members of the current proposal's writing group.

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
___A. primarily the result of an ancillary study (list number* 2008.06)
_X_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __ **2008.06** ____ _____ _____)
*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/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. **Yes**

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. **Policy reviewed and acknowledged.**

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