Longitudinal patient-oriented outcomes in neuropathy

Importance of early detection and falls

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ABSTRACT

Objective: To evaluate longitudinal patient-oriented outcomes in peripheral neuropathy over a 14-year time period including time before and after diagnosis.

Methods: The 1996–2007 Health and Retirement Study (HRS)–Medicare Claims linked database identified incident peripheral neuropathy cases (*ICD-9* codes) in patients ≥ 65 years. Using detailed demographic information from the HRS and Medicare claims, a propensity score method identified a matched control group without neuropathy. Patient-oriented outcomes, with an emphasis on self-reported falls, pain, and self-rated health (HRS interview), were determined before and after neuropathy diagnosis. Generalized estimating equations were used to assess differences in longitudinal outcomes between cases and controls.

Results: We identified 953 peripheral neuropathy cases and 953 propensity-matched controls. The mean (SD) age was 77.4 (6.7) years for cases, 76.9 (6.6) years for controls, and 42.1% had diabetes. Differences were detected in falls 3.0 years before neuropathy diagnosis (case vs control; 32% vs 25%, $p = 0.008$), 5.0 years for pain (36% vs 27%, $p = 0.002$), and 5.0 years for good to excellent self-rated health (61% vs 74%, $p < 0.0001$). Over time, the proportion of fallers increased more rapidly in neuropathy cases compared to controls ($p = 0.002$), but no differences in pain ($p = 0.08$) or self-rated health ($p = 0.9$) were observed.

Conclusions: In older persons, differences in falls, pain, and self-rated health can be detected 3–5 years prior to peripheral neuropathy diagnosis, but only falls deteriorates more rapidly over time in neuropathy cases compared to controls. Interventions to improve early peripheral neuropathy detection are needed, and future clinical trials should incorporate falls as a key patient-oriented outcome. *Neurology*® 2015;85:71–79

GLOSSARY

ADL = activities of daily living; **CI** = confidence interval; **GEE** = generalized estimating equations; **HRS** = Health and Retirement Study; **IADL** = instrumental activities of daily living; **ICD-9** = *International Classification of Diseases-9*; **OR** = odds ratio.

Peripheral neuropathy is a highly prevalent disease, particularly in older persons, with more than 15% of those over age 40 years affected.¹ While improved glucose control decreases the incidence of neuropathy in type 1 diabetes, the effect is much smaller in type 2 diabetes.² Similarly, no effective treatments exist for idiopathic peripheral neuropathy (20%–30% of cases).^{3–5} As new disease-modifying therapeutics are developed for the treatment and prevention of neuropathy, there is a need to better understand the natural history of how peripheral neuropathy affects patient-oriented outcomes over time.

Previous cross-sectional studies have shown that neuropathy is associated with worse quality of life, more pain, and increased number of falls.^{6–11} However, limited longitudinal data are available to provide stronger epidemiologic support for neuropathy as the prime mediator of these outcomes. Of the longitudinal studies that have been performed, Ahroni and Boyko¹² demonstrated that veterans with diabetes who develop neuropathy have a greater decline in quality of life than those who do not develop neuropathy over a 3-year time period. Similarly, DiBonaventura et al.¹³ reported that a physical quality of life measure in patients with painful

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Table 1 Demographic and clinical variables in the population of patients with peripheral neuropathy compared to propensity score-matched controls

Measure	Cases (n = 953), n (%) unless otherwise indicated ^a	Controls (n = 953), n (%) unless otherwise indicated ^a	p Value
Age at index date, y, mean (SD)	77.44 (6.72)	76.94 (6.55)	0.088
Male sex	422 (44.28)	441 (46.27)	0.368
Race/ethnicity			
Hispanic	75 (7.87)	63 (6.61)	0.550
Non-Hispanic white/other	756 (79.33)	769 (80.69)	
Non-Hispanic black	122 (12.80)	121 (12.70)	
Education, grade level			
0-11	312 (32.74)	311 (32.63)	0.775
12	318 (33.37)	310 (32.53)	
13+	323 (33.89)	332 (34.84)	
Body mass index			
<25	322 (34.18)	295 (31.15)	0.303
25-29.9	367 (38.96)	398 (42.03)	
30-34.9	181 (19.21)	180 (19.01)	
≥35	72 (7.64)	74 (7.81)	
Diabetes, 6-30 mo pre-index date	401 (42.08)	401 (42.08)	Blocked
Alcohol, drinks/wk			
0	740 (77.81)	739 (77.71)	0.956
1-3	86 (9.04)	89 (9.36)	
4-7	68 (7.15)	70 (7.36)	
8-14	40 (4.21)	40 (4.21)	
15+	17 (1.79)	13 (1.37)	
Chronic kidney disease	85 (8.92)	89 (9.34)	0.722
Rheumatoid arthritis or osteoarthritis	264 (27.70)	263 (27.60)	0.955
Cancer	135 (14.17)	129 (13.54)	0.673
Inpatient Charlson, 2-y			
0	664 (69.67)	674 (70.72)	0.216
1	101 (10.60)	104 (10.91)	
2	84 (8.81)	81 (8.50)	
3	46 (4.83)	41 (4.30)	
4+	58 (6.09)	53 (5.56)	
Outpatient Charlson, 1-y			
0	654 (68.63)	656 (68.84)	0.805
1	167 (17.52)	183 (19.20)	
2	76 (7.97)	57 (5.98)	
3	35 (3.67)	39 (4.09)	
4+	21 (2.20)	18 (1.89)	
Auxiliary Charlson, 1-y			
0	330 (34.63)	335 (35.15)	0.158
1	241 (25.29)	251 (26.34)	

Continued

diabetic neuropathy worsened at a faster rate than in patients with diabetes without neuropathy over 2 years of follow-up. Together, these studies suggest that diabetic neuropathy accelerates decline in quality of life over time, but neither study evaluated the effects of neuropathy on falls or pain. These studies also did not evaluate patient-oriented outcomes prior to a neuropathy diagnosis.

METHODS Population. Data for our analysis came from respondents to the Health and Retirement Study (HRS) biennial interview between 1998 and 2010, with linked claims data from Medicare Standard Analytic Files. We defined incident peripheral neuropathy as any ICD-9 diagnosis (354.5, 356.0, and 357.0-9; inpatient, outpatient, and carrier claims; 1998-2007) of peripheral neuropathy and no previous diagnosis during the preceding 30 months (to exclude prevalent cases). Individuals were included if they were at least 65 years of age 30 months prior to the incident peripheral neuropathy diagnosis, were continuously enrolled in Medicare parts A and B fee for service from 30 months preceding the index diagnosis through 6 months following the index diagnosis, completed an HRS interview within 3 years prior to the diagnosis date, and completed at least 1 of the first 3 HRS interviews after diagnosis date.

Demographics. Key demographic information identified from the HRS survey included age, sex, race/ethnicity, education, body mass index, alcohol intake, diabetes status, wealth, and other insurance status. A patient was considered to have diabetes if he or she reported a diagnosis by a physician in the HRS interview or met the Chronic Condition Warehouse definition of diabetes (at least 1 inpatient, skilled nursing, or home health claim, or 2 outpatient or carrier claims with diagnostic codes 249.x, 250.x, 357.2, 362.01, 362.02, or 366.31 during a 2-year time period beginning 30 months before peripheral neuropathy diagnosis).^{14,15} ICD-9 diagnosis codes identified patients with diabetic complications other than neuropathy (ICD-9 codes 249.4, 249.5, 249.7, 250.4, 250.5, 250.7, 362.01, or 362.02). Medicare claims also provided information on chronic kidney disease, rheumatoid arthritis/osteoarthritis, and cancer status. Charlson scores (inpatient, outpatient, and auxiliary [skilled nursing/carrier/home health]), which are comorbidity indexes, were generated using the claims database.

Comparison group. Potential controls were assigned random index dates in the time period in which the incident neuropathy sample was identified, and the same restrictions regarding Medicare enrollment and HRS survey participation were applied. Potential pairs were matched one-to-one on diabetes status and HRS survey year. Then, a propensity score method was used to generate controls based on the demographic and health measures derived from the HRS survey and Medicare claims as detailed above. This technique matches neuropathy cases and controls on key potential confounding variables (see table 1 for specific variables included). The propensity model also included all 2-way interactions of diabetes status with each of the variables in the model. Propensity score matching was completed using a greedy match with a 0.01 caliper, one control per neuropathy case, and selection without replacement.

Patient-oriented outcomes. Patient-oriented outcomes were derived from responses to HRS interview questions (see table 2 for specific wording). A priori, we chose to focus our longitudinal

Table 1 Continued

Measure	Cases (n = 953), n (%) unless otherwise indicated ^a	Controls (n = 953), n (%) unless otherwise indicated ^a	p Value
2	150 (15.74)	162 (17.00)	
3	115 (12.07)	98 (10.28)	
4+	117 (12.28)	107 (11.23)	

^aPatients with neuropathy and controls were also balanced on days from Health and Retirement Study interview -1 to index date, wealth, and presence of other insurance in addition to Medicare.

analysis on falls, self-rated health, and pain to limit the number of comparisons. Other HRS questions were only analyzed at the first HRS interview after the neuropathy diagnosis. Nondichotomous variables were transformed into dichotomous variables by combining adjacent categories based on clinical judgment. For example, for the self-rated health question "Would you say your health is excellent, very good, good, fair, or poor?" we combined those who responded excellent, very good, and good compared with those who responded fair or poor. Four questions pertaining to sleep and 3 questions pertaining to exercise were analyzed. Trouble with activities of daily living (ADL) was defined as some difficulty in 1 of 6 domains (bathing, dressing, eating, bedding, walking, and toileting). Trouble with instrumental ADL (IADL) was defined as some difficulty in 1 of 3 domains (telephone, money, medications). Trouble with mobility was defined as difficulty with 2 or more of the 5 questions focused on walking and climbing stairs. Depression was defined as endorsing 4 or more of the 8 Center for Epidemiologic Studies Depression Scale questions, which is a validated screening instrument.¹⁶

Statistical analysis. Matched comparisons between neuropathy cases and controls were conducted using McNemar tests for categorical variables and paired *t* tests for continuous variables. A generalized estimating equations (GEE) approach was used to analyze differences in falls, pain, and self-rated health (longitudinal binary outcomes) between neuropathy cases and controls. We performed overall as well as stratified analyses by diabetic status. Time since index date (entered as a continuous variable), group (i.e., neuropathy case vs control), and time by group interaction were entered as independent variables. The GEE approach allowed us to investigate the associations between neuropathy status and longitudinal outcomes, while accounting for the correlation among repeated measures in the outcomes. Ignoring the correlation can lead to biased estimates of the standard errors, thereby affecting the inference regarding associations between neuropathy status and outcomes. The interaction term of time by group was used to assess whether the patient-oriented outcome trajectories for neuropathy cases differed from controls over time. For each patient-oriented outcome, we determined the odds ratios (ORs) comparing neuropathy cases to controls at the index date, as well as ORs of change per year for neuropathy cases and for controls. All analyses were performed with SAS 9.3 (Cary, NC).

Standard protocol approvals, registrations, and patient consents. The University of Michigan institutional review board approved this study. All patients participating in the HRS provide oral or implied consent by participating in the interview.

RESULTS A total of 1,039 subjects met our definition of incident peripheral neuropathy. Of this

population, 52 died before the HRS interview wave immediately following diagnosis, 19 did not complete an HRS interview within the first 6 years following diagnosis, and 15 had no match within our designated caliper after 3 rounds. Our final cohort consisted of 953 neuropathy cases and 953 controls.

Population demographic and clinical variables are presented in table 1. No statistically significant differences were noted between neuropathy cases and controls. Cases were followed for a mean (SD) 4.7 (2.6) years before and 5.0 (3.1) years after the index date. Controls were followed for 4.7 (2.6) years before and 5.5 (3.2) years after the index date. Table 2 displays the differences in patient-oriented outcomes between neuropathy cases and controls at the first HRS interview after diagnosis.

Evaluating the trajectories of the main patient-oriented outcomes in the entire cohort revealed that neuropathy cases were more likely to fall (OR = 1.41, 95% confidence interval [CI] 1.25–1.58) and to be troubled often by pain (OR = 1.69, 95% CI 1.46–1.94) and less likely to rate their health as good or better (OR = 0.60, 95% CI 0.52–0.70) at the index date (table 3). These results were almost identical when looking at the subset of patients with diabetes or the subset without diabetes. However, in the entire cohort, only falls revealed a statistically significant time by group effect ($p = 0.002$) (table 3, figure 1). Neuropathy cases had a 1.11 (95% CI 1.09–1.12) times greater odds of falling each year compared to 1.07 (95% CI 1.05–1.09) times greater odds for controls. The proportion of fallers at the fourth HRS interview before the index date (6.9 years before the index date) was 23% of cases and 29% of controls (figure 1). By the fourth HRS interview after the index date (7.1 years after the index date), the proportion had changed to 56% of cases (33% increase) and 41% of controls (12% increase). While the proportion of cases often troubled by pain increased from 37% to 47% and the proportion of controls remained relatively stable (29%–30%), the time by group interaction effect did not reach statistical significance ($p = 0.08$). Self-rated health declined slowly in both neuropathy cases and controls over time with no significant difference between the groups. When evaluating for the earliest changes between neuropathy cases and controls, differences were detected in falls at an average of 3.0 years prior to diagnosis (case vs control; 32% vs 25%, $p = 0.008$), 5.0 years prior to diagnosis for pain (36% vs 27%, $p = 0.002$), and 5.0 years prior to diagnosis for self-rated health (61% vs 74%, $p < 0.0001$).

When comparing patients with diabetes and those without diabetes, the patient-oriented outcome trajectories were different (figure 2). Specifically, patients with diabetic neuropathy deteriorated more

Table 2 Patient-oriented outcomes at the first Health and Retirement Study interview after diagnosis

HRS question	No.	Case, %	Control, %	p Value
Falls				
Have you fallen down in the last 2 years?	923	46	36	<0.0001
Percentage of respondents that have injured themselves in a fall enough to need medical treatment	923	17	14	0.0558
Percentage of respondents that have fallen at least 3 times in the past 2 years	923	17	9	<0.0001
Have you fractured your hip ever/since previous wave?	926	2	2	0.4927
Self-rated health				
Would you say your health is excellent, very good, good (vs fair or poor)?	927	49	65	<0.0001
Pain				
Are you often troubled with pain?	926	47	32	<0.0001
How bad is the pain most of the time? (moderate or severe vs none/mild)	921	36	25	<0.0001
Does the pain make it difficult for you to do your usual activities such as household chores or work?	921	33	20	<0.0001
Sleep				
How often do you have trouble falling asleep? (most of the time or sometimes vs rarely or never)	617	47	40	0.0077
How often do you often have trouble with waking up during the night? (most of the time or sometimes vs rarely or never)	617	68	65	0.2484
How often do you have trouble with waking up too early and not being able to fall asleep again? (most times or sometimes vs rarely or never)	617	44	45	0.8155
How often do you feel really rested when you wake up in the morning? (most times vs rarely or sometimes)	731	54	66	<0.0001
Exercise				
How often do you take part in sports or activities that are vigorous? (more than once per week vs once/week or less)	525	14	17	0.1227
How often do you take part in sports or activities that are moderately energetic? (more than once per week vs once/week or less)	524	38	44	0.0825
How often do you take part in sports or activities that are mildly energetic? (more than once per week vs once/week or less)	526	43	48	0.0909
ADL, IADL				
Difficulty with ADL?	930	38	27	<0.0001
Difficulty with IADL?	930	21	15	0.0012
Difficulty with mobility?	928	55	41	<0.0001
Depression				
Depression	749	23	15	<0.0001
Other				
Since we last talked to you, have you had persistent swelling in your feet or ankles?	495	38	27	0.0007
Since we last talked to you, have you had persistent dizziness or lightheadedness?	494	21	13	0.0007
Since we last talked to you, have you had severe fatigue or exhaustion?	491	30	20	0.0002
Since we last talked to you, have you had back pain or problems?	495	43	37	0.0447
Have you ever had or has a doctor ever told you that you have arthritis or rheumatism?	927	76	70	0.0042

Abbreviations: ADL = activities of daily living; HRS = Health and Retirement Study; IADL = instrumental activities of daily living.

slowly on self-rated health compared to diabetic controls ($p < 0.05$), whereas no statistically significant difference was observed when comparing the self-rated health trajectory of patients with nondiabetic

neuropathy to nondiabetic controls ($p = 0.1$). In contrast, patients with diabetic and nondiabetic neuropathy fell more frequently over time than controls ($p = 0.02$ and $p = 0.05$, respectively). No statistically

Table 3 Differences in longitudinal patient-oriented outcome trajectories between neuropathy cases and controls

HRS question	Overall cohort, OR (95% CI)	Diabetes, OR (95% CI)	No diabetes, OR (95% CI)
Have you fallen down in the last 2 years?			
Case vs control at index date ^a	1.41 (1.25-1.58)	1.37 (1.13-1.65)	1.44 (1.24-1.67)
Change per year for control ^b	1.07 (1.05-1.09)	1.07 (1.05-1.10)	1.07 (1.05-1.09)
Change per year for case ^c	1.11 (1.09-1.12)	1.12 (1.09-1.15)	1.10 (1.08-1.12)
p Value for time × group effect	0.002	0.02	0.05
Would you say your health is good, very good, or excellent (vs fair or poor)?			
Case vs control at index date ^a	0.60 (0.52-0.70)	0.60 (0.48-0.74)	0.60 (0.49-0.73)
Change per year for control ^b	0.96 (0.94-0.97)	0.95 (0.93-0.97)	0.96 (0.94-0.98)
Change per year for case ^c	0.96 (0.95-0.97)	0.99 (0.96-1.01)	0.94 (0.92-0.96)
p Value for time × group effect	0.9	0.04	0.1
Are you often troubled with pain?			
Case vs control at index date ^a	1.69 (1.46-1.94)	1.51 (1.21-1.87)	1.84 (1.52-2.21)
Change per year for control ^b	1.03 (1.01-1.04)	1.02 (0.99-1.04)	1.03 (1.01-1.05)
Change per year for case ^c	1.05 (1.03-1.06)	1.04 (1.02-1.06)	1.05 (1.03-1.07)
p Value for time × group effect	0.08	0.2	0.3

Abbreviations: CI = confidence interval; HRS = Health and Retirement Study; OR = odds ratio.

^aDerived from the group variable (i.e., neuropathy case compared to control at the index date).

^bDerived from the time variable.

^cDerived from the combination of the time and time by group variables.

significant difference was seen when comparing pain over time between diabetic and nondiabetic patients with neuropathy and controls ($p = 0.2$ and $p = 0.3$).

DISCUSSION Utilizing a nationally representative population, we aimed to evaluate longitudinal trajectories of self-rated health, pain, and falls in those with diabetic and nondiabetic peripheral neuropathy before and after diagnosis over a 14-year follow-up period. Compared to previous longitudinal studies, we were able to investigate our study population for a longer time period, track trajectories prior to a peripheral neuropathy diagnosis, evaluate multiple patient-oriented outcomes within the same study, and compare patients with and without diabetes. We found that older adults with neuropathy have more falls and pain and lower self-rated health compared to carefully matched controls without neuropathy. These differences were present 3–5 years prior to a neuropathy diagnosis and persist for several years after diagnosis. However, of these 3 patient-oriented outcomes, the only outcome that worsened more rapidly over time in patients with neuropathy was falls. Surprisingly, patients with diabetic neuropathy had a slower deterioration in self-rated health than diabetic controls.

The observation that neuropathy patients have more falls and pain and lower self-rated health than

those without neuropathy is in agreement with several past studies.^{6–13,17} Our study builds on these prior findings and provides stronger epidemiologic support for neuropathy as a prime mediator of these outcomes given our ability to track outcome trajectories several years before and after a diagnosis of neuropathy. For all 3 of these patient-oriented outcomes, differences are seen 3–5 years prior to diagnosis. This finding may be partly explained by a delay in diagnosis in this highly prevalent condition, and also highlights the fact that neuropathy often develops slowly over time. Patients typically report neuropathic symptoms to their physician years after their insidious onset. In fact, in a community neurologist setting, patients with a new diagnosis of distal symmetric polyneuropathy had symptoms for a mean of 39 months at their first visit.¹⁸ How long neuropathic symptoms occur prior to seeing a general practitioner is unknown. The implication for future neuropathy clinical trials is that interventions are more likely to be successful if implemented before patients are typically diagnosed with neuropathy. Earlier diagnosis will require studies to evaluate current barriers to a neuropathy diagnosis early in the disease course. Intervening after patients are typically diagnosed may be too late if significant nerve injury has already occurred.

We also demonstrated that falls were the only patient-oriented outcome that increased more rapidly

Figure 1 Comparison of the patient-oriented outcome trajectories between patients with neuropathy and propensity-matched controls

Patient-oriented outcome trajectories for the entire cohort: (A) falls within the last 2 years, (B) self-rated health, (C) frequent pain. HRS = Health and Retirement Study.

in cases than controls. While pain and self-rated health were worse in neuropathy cases compared to controls, these outcomes did not worsen more rapidly over time in cases vs controls. The importance of this result to future clinical trials is that falls should be considered as a main outcome measure, especially in

an elderly population. When patient-oriented outcomes are assessed at all, most previous trials have focused on pain and/or quality of life. Falls are often ignored as an important patient-oriented outcome, but the quick separation between neuropathy cases and controls over time indicates that falls may be a sensitive and objective neuropathy outcome measure. The magnitude of falls in the neuropathy population, rising from 23% to 56% over the course of this study, also emphasizes the need for clinicians to address falls with their patients. In agreement with this assessment, the American Academy of Neurology recently released quality measures for patients with distal symmetric polyneuropathy with 1 of the 6 measures pertaining to falls.¹⁹ Falls should not only be an important outcome measure of future clinical trials, but also a focus of the clinical care of patients with neuropathy.

Interestingly, self-rated health declined at the same rate in those with neuropathy compared to controls. However, patients with diabetic neuropathy deteriorated more slowly than diabetic controls. One potential explanation for this finding is a possible floor effect. Only 46% of patients with diabetic neuropathy rated their health as good or better 6+ years prior to their neuropathy diagnosis. By comparison, 76% of patients with nondiabetic neuropathy had positive self-rated health. In support of this explanation, previous studies have demonstrated a floor effect when utilizing quality of life measures in stroke patients.^{20,21} Further evidence to support a floor effect is that when we analyzed self-rated health as the proportion that declined by one or more levels compared to their last HRS interview, no difference was observed over time between patients with diabetic neuropathy and diabetic controls. Regardless of the reason, the lack of significant change in self-rated health in patients with diabetic neuropathy either before or after diagnosis makes this a less than ideal patient-oriented outcome for clinical trials.

We found that patients with neuropathy are more likely to have difficulties with sleep and depression, but engagement in exercise is not significantly affected. Previous studies have shown that patients with painful diabetic neuropathy have a higher prevalence of impaired sleep and that the greater the severity of pain, the worse the sleep outcome scores.^{22–24} In agreement with these studies, our results demonstrate that patients with neuropathy are less likely to be well-rested than controls and that the reason for sleep disturbance is likely secondary to problems with falling asleep rather than maintaining sleep. Given that the 2 most likely contributors to sleep disturbance in this population are pain and restless legs syndrome, trouble with sleep initiation would be expected. Similarly, other groups have reported that neuropathy

Figure 2 Patient-oriented outcome trajectories in patients with diabetic and nondiabetic neuropathy and their corresponding controls

Patient-oriented outcome trajectories for patients with diabetic neuropathy (A-C) and nondiabetic neuropathy (D-F): (A, D) falls within the last 2 years, (B, E) self-rated health, (C, F) frequent pain. DM = diabetes mellitus; HRS = Health and Retirement Study.

severity is associated with depression severity in both cross sectional and longitudinal studies.^{25,26} We also demonstrate that neuropathy cases are more likely to have depression compared to a propensity-matched control group with a large magnitude of effect (23% vs 15%). On the other hand, there were no differences

in varying levels of exercise performed comparing neuropathy cases to controls. Our finding is similar to a previous study using the National Health and Nutrition Examination Survey (NHANES) population, which failed to reveal an association between peripheral neuropathy and reduced moderate to

vigorous physical activity as measured by an accelerometer.²⁷

Not only is neuropathy associated with sleep disturbance and depression, but we also found that neuropathy cases were more likely to have difficulties with ADLs, IADLs, and mobility than controls. One previous study revealed an independent association between diabetic neuropathy and the development of mobility limitations, but not new ADL disability.²⁸ A separate group reported an association between women with diabetes and both mobility and ADL limitations that was in part mediated by neuropathy.²⁹ Our results confirm that neuropathy is associated with mobility limitations and provides further support for an association with ADL disability. Furthermore, we report an association with IADL disability, which has not been previously investigated.

Limitations of our study include utilizing ICD-9 codes to identify incident neuropathy cases, which may lead to misclassification bias. Furthermore, patient-oriented outcomes were based on HRS questions and not formally validated questionnaires. While our propensity score-matched controls were well-matched on key demographic and clinical variables, unmeasured residual confounding remains possible. The matching technique made evaluation of obesity-related complications difficult as body mass index and other comorbidities were included in our method. Our propensity score method was maximized to increased length of follow-up; however, this method did not allow us to determine differences in mortality between cases and controls. Although neuropathy status is significantly associated with more falls over time, other important risk factors must be present, as demonstrated by the large proportion of fallers in the control group. Our data are unable to determine how often falls led to the discovery of neuropathy. While falls occurred more rapidly over time in neuropathy cases compared to controls, our study did not have adequate power to determine if fall-related injuries also increased over time. We were unable to determine whether subjects required ambulatory assistance. The generalizability of these results to populations younger than 65 years is unclear.

In older people, peripheral neuropathy significantly impacts patient-oriented outcomes such as falls, pain, and self-rated health. These changes can be observed several years prior to a neuropathy diagnosis and continue for several years after. Falls, an outcome measure that has typically not been used in past clinical trials, was the only patient-oriented outcome that worsened faster over time in neuropathy cases compared to controls. Future studies are needed to explore barriers to earlier diagnosis of neuropathy, and falls should be considered as a main

patient-oriented outcome in future intervention trials.

AUTHOR CONTRIBUTIONS

Brian Callaghan was involved in the study design, interpretation of the statistical analysis, and wrote the manuscript. Kevin Kerber, Mousumi Banerjee, Ann Rodgers, Ryan McCammon, Jim Burke, Ken Langa, and Eva Feldman were integrally involved in the study design, interpretation of the data, and critical revisions of the manuscript.

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