



Original article

The association between perceived discrimination in midlife and peripheral neuropathy in a population-based cohort of women: the Study of Women's Health Across the Nation



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ABSTRACT

Purpose: Peripheral neuropathy (PN) is a highly prevalent condition with serious sequelae. Many studies of the condition have been restricted to populations with diabetes, limiting evidence of potential contributing risk factors including salient psychosocial risk factors such as discrimination.

Methods: The longitudinal Study of Women's Health Across the Nation was used to assess the relationship between perceived discrimination and prevalent PN in 1718 ethnically diverse midlife women. We used multivariable logistic regression to determine the association between perceived discrimination (Detroit Area Study Everyday Discrimination Scale) and PN (symptom questionnaire and monofilament testing) and conducted an assessment of the mediating effects of body mass index (BMI).

Results: The prevalence of PN was 26.1% in the total sample and 40.9% among women with diabetes. Women who reported perceived discrimination had 29% higher odds of PN compared with women who did not report perceived discrimination (95% confidence interval, 1.01–1.66). Approximately 30% of the total effect of discrimination on PN was mediated indirectly by BMI.

Conclusions: More research is needed to determine the contributing factors to nondiabetic PN. Our findings reaffirm the impact of financial strain, BMI, and diabetes as significant correlates of PN and highlight discrimination as an important risk factor.

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Peripheral neuropathy (PN) is characterized by damage to various classes of peripheral nerves and is a common comorbidity associated with diabetes. The sensory, autonomic, and motor nerve damage that define the condition can cause a multitude of symptoms and signs including pain, numbness,

loss of sensation, muscle atrophy, loss of balance, incontinence, and blood pressure irregularities [1]. In the United States, approximately 20 million people are estimated to have PN [1]. According to the American Diabetes Association, about 25% of people aged older than 60 years have diabetes [2], and

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half of these older adults with diabetes are estimated to have PN [1,3].

Although PN is more prevalent in populations with diabetes, research suggests that the burden of PN is high even among populations without diabetes. One study of a nationally representative US sample estimated the prevalence of PN among individuals aged older than 40 years and without diabetes to be 13% [4]. Within the Study of Women's Health Across the Nation (SWAN) Michigan site, a subset of non-Hispanic White and African American participants from the larger SWAN cohort, the prevalence of PN among women with an average age of 57.6 years was 27.8% in the total sample and 26.2% among those without diabetes [5]. Although the pathophysiology of nerve damage is due, in part, to chronic hyperglycemia associated with diabetes, little is known about the pathogenesis of or risk factors for peripheral nerve dysfunction among individuals without diabetes. Emerging evidence suggests that mechanisms associated with obesity and the aging process may be detrimental to peripheral nerves [6–8].

Evidence is conflicting about the prevalence of PN in different racial/ethnic groups. Some studies have found minimal differences by racial/ethnic groups, with a lower prevalence among African Americans and Hispanics compared with Whites, whereas other studies have found no racial/ethnic difference in PN prevalence [9–11]. Diabetes is intricately related to the diagnosis and understanding of PN, and the distribution of diabetes is not uniform across racial/ethnic groups in the United States. The prevalence of diagnosed and undiagnosed diabetes among African Americans is estimated to be nearly twice that in Whites, and African Americans die of diabetes at a rate 1.3 times higher than Whites [12,13]. A higher prevalence of undiagnosed diabetes among African Americans [12,13] may also be contributing to the lower detected prevalence of diabetes-related sequelae such as PN.

Discrimination has been noted as a salient psychosocial factor linked to several chronic health conditions including hypertension, coronary artery disease, and insomnia among all racial/ethnic groups, with many studies reporting a higher prevalence of perceived discrimination among racial/ethnic minorities compared with Whites [14–20]. In addition, there has been conflicting evidence of moderation of the effect of discrimination among racial/ethnic minorities compared with Whites [16,17,19] particularly for conditions closely linked to diabetes such as metabolic syndrome [17,19]. Perceived discrimination, including internalized racism, is also associated with high-risk body size [21–23]. A commonly hypothesized model for the association between discrimination and chronic disease is that discrimination causes a chronic stress response that leads—through various biological mechanisms including allostatic load and inflammation—to chronic health conditions, such as diabetes [17,24,25]. This work suggests that studies evaluating chronic diseases such as diabetes and cardiovascular disease should account for the potential role of discrimination and obesity. However, the relationship between discrimination, obesity, and PN has not been investigated.

This article examined whether midlife perceived discrimination is associated prospectively with the prevalence of PN in the multiethnic SWAN. In addition, given the complex relationship between race, socioeconomic status, diabetes, and PN, we investigated whether the relationship between discrimination and PN varied by diabetes status. Finally, as perceived discrimination is associated with body mass index (BMI) and central obesity [21–23], we also assessed whether this association was mediated by BMI.

Methods

The SWAN is a multiethnic longitudinal study of midlife women from seven sites in the United States. Each of the clinical sites

selected White women and women of one designated racial/ethnic minority group to participate. African American women were recruited in Boston, MA, Chicago, IL, southeast MI, and Pittsburgh, PA; Chinese women in Oakland, CA; Hispanic women in Newark, NJ; and Japanese women in Los Angeles, CA. Women were eligible for the baseline assessment in 1996 if they were aged between 42 and 52 years, had an intact uterus and at least one ovary, had no reported current hormone use, had at least one menstrual period in the past 3 months, and self-identified as one of the site's designated racial/ethnic groups. There have been an additional 15 approximately annual visits following baseline. Visits include both self-reported questionnaires and clinic visits. Further detailed information about SWAN study procedures and methods have been published elsewhere [26]. Of the initial 3302 enrolled women, 2091 (63%) participated in study visit 15 (2016). The women who participated in visit 15 but were missing data for neuropathy status, diabetes status, BMI, or baseline perceived discrimination were excluded from the present analysis, leaving 1718 women (82%) in the analytic sample.

Perceived discrimination was assessed during the baseline visit using the Detroit Area Study Everyday Discrimination Scale [27,28]; responses on this scale have been shown to be consistent over time among women in the SWAN cohort [19]. This scale measures 10 experiences involving discrimination over the past 12 months such as being treated with less respect or courtesy than other people, receiving poorer service than others, and being ignored. Each question was assessed using a response scale of never, rarely, sometimes, and often. Responses were summed and averaged across the 10 questions to yield final scores between 1 (low perceived discrimination) and 4 (high perceived discrimination) [20]. The questions mentioned previously were not specific to reasons for discrimination; however, there was a follow-up question that asked participants to attribute their experience of discrimination to one major reason (race/ethnicity, sex, and so forth). Previous studies in SWAN show that African American and Chinese women report slightly higher levels of perceived discrimination than other racial/ethnic groups [20].

PN was assessed during visit 15 using both a symptom questionnaire and monofilament testing. The Michigan Neuropathy Screening Instrument (MNSI) symptom questionnaire acquired information about 15 neuropathy symptoms including burning pain, sensitivity, prickling, lack of hot/cold differentiation, severe dryness of the foot, numbness, open sores, and amputations [29]. Participants who identified having four or more of these 15 symptoms were categorized as having PN from the screening instrument. This questionnaire and cut-point have been previously validated with clinical diagnoses of PN [30].

The monofilament test was first administered using a 10-g filament placed on the big toe for less than 1 second for four repetitions. If the participant correctly identified all four repetitions, this procedure was repeated with a 1.4-g monofilament to measure more minute levels of insensitivity. Participants who responded correctly to two or fewer of four attempts on either the 10-g or the 1.4-g test were classified as having PN from the monofilament test. For this analysis, women who screened positive on either the questionnaire or the monofilament test were classified as having PN to capture a broad range of neuropathy symptoms and subtypes.

Diabetes status was ascertained using a combined measure that included self-reported use of a diabetes medication including insulin, self-reported doctor-diagnosed diabetes, or a fasting glucose 126 mg/dL or greater at any follow-up visit. Race/ethnicity was self-identified at baseline as African American, Chinese, Hispanic, Japanese, or White. To ensure temporality between perceived discrimination and BMI and because BMI has been hypothesized to change through the menopausal transition independently of

discrimination [31–33], BMI was ascertained concurrently (visit 15) with PN when most women in the sample were postmenopausal. BMI was calculated as weight in kilograms divided by measured height in meters squared. Smoking status was based on self-report at visit 15 of smoking regularly since the last study visit. Financial strain at baseline was assessed by self-report of how hard it is for the respondent to pay for basics.

Frequencies, means, and 95% confidence intervals (CI) were calculated to define the characteristics of the eligible study population. χ^2 and *t* tests were used to test for significant differences in characteristics between women with and without diabetes and with and without PN. Logistic regression adjusted for race/ethnicity, financial strain, smoking status, and diabetes was performed to investigate the relationship between perceived discrimination reported at baseline and PN at visit 15. In addition, an interaction between race/ethnicity and perceived discrimination was tested. BMI was added to the models to assess whether BMI could potentially mediate the relationship between perceived discrimination and PN. A formal mediation analysis to determine whether BMI mediated the effect of discrimination on PN was conducted using the STATA package Paramed (StataCorp LP, College Station, TX), which decomposes the total effect of discrimination on PN into direct (effect of discrimination alone), indirect (effect of discrimination via BMI) and interactive (discrimination and BMI interaction) effects using the methods outlined by Vanderweele, 2013 [34–36]. Because diabetes is a strong risk factor for PN, we also tested for interactions between discrimination and diabetes status in all models.

Results

The median baseline age of participants was 46.2 years, and the median age at visit 15 was 65.4 years. Approximately one-third of the sample (33.9%) reported financial strain at baseline (Table 1). The average discrimination score was 1.7 (SD = 0.5) with a range of 1.0–3.6, and 8.91% of the sample reported no instances of discrimination at baseline. The prevalence of diabetes was 3.6% at baseline and 18.6% by visit 15. At visit 15, 68.6% of the sample was overweight or obese, and the average BMI was 29.2 kg/m² (SD = 7.1).

By visit 15, 26.1% of women had PN. The prevalence of PN was higher among women with diabetes (40.9%) compared with women without diabetes (22.8%). Of those with PN, 62.8% were classified as having the condition based on the MNSI questionnaire, 51.7% based on the monofilament test, and 14.5% based on both measures (Table 2).

In unadjusted analyses, financial strain and higher perceived discrimination at baseline as well as higher BMI, smoking, and diabetes at visit 15 were positively associated with PN at visit 15 (Table 3). Each unit increase in the level of perceived discrimination was associated with 43% higher odds of PN (odds ratio [OR] = 1.43, 95% CI, 1.14–1.79). Japanese women had 72% lower odds of PN compared with White women (OR = 0.28, 95% CI, 0.16–0.48), but there were no significant differences in the odds between African American, Chinese, or Hispanic women and White women.

After adjustment for race/ethnicity, financial strain, current smoking, and diabetes, perceived discrimination remained positively associated with PN (Model 1). Each unit increase in perceived discrimination was associated with 29% higher odds of PN (OR = 1.29, 95% CI, 1.01–1.66). Next, we further adjusted for BMI (Model 2). Doing so attenuated the estimate for perceived discrimination, and it was no longer significantly associated with PN (OR = 1.21, 95% CI, 0.94–1.56). In the fully adjusted model, Japanese women had 67% lower odds of PN compared with White women (OR = 0.33, 95% CI, 0.19–0.58), and financial strain, smoking status, diabetes, and BMI were positively associated with PN. There was no significant interaction between discrimination and racial/ethnic group or diabetes.

Sensitivity analysis indicated no significant interactive effect between discrimination and BMI in association with PN (likelihood ratio χ^2 = 0.29, two-sided *P* = .59); therefore controlled (noninteractive) direct and indirect effects are presented in the mediation analysis (Table 4). The total effect of discrimination on PN is estimated to be 28.3% (95% CI, 17.1%–36.5%) mediated by BMI (indirect effect); the direct effect of discrimination is nonsignificant and is slightly higher (OR = 1.21, 95% CI, 0.94–1.56) than the indirect effect of discrimination via BMI (OR = 1.07, 95% CI, 1.03–1.12).

Discussion

This is the largest known study of PN in women without and with diabetes. Among women aged 60–73 years, the prevalence of neuropathy was 22.8% in women without diabetes and 40.9% in women with diabetes. Perceived discrimination in midlife was a predictor of having PN 20 years later, and this association was mediated significantly by BMI. We also found that financial strain, higher BMI, current smoking, and diabetes were all associated with an increased odds of PN, confirming prior observations [6–8,37–40].

This is the first analysis of the association of discrimination and PN, and we found that each increasing level of perceived discrimination in midlife was associated with 43% higher odds of PN.

Table 1
Characteristics of all participants, participants with diabetes, and participants with peripheral neuropathy, Study of Women's Health Across the Nation, 1996–2016

Variable	Total (n = 1718)	Diabetes (n = 320)	<i>P</i> ^a	Peripheral neuropathy (n = 449)	<i>P</i> ^b
Visit 15 age in years, mean (SD)	65.6 (2.7)	65.6 (2.7)	.88	65.6 (2.7)	.73
Race/ethnicity, n (%)			<.01		<.01
African American	454 (26.4)	134 (41.9)		141 (31.4)	
Chinese	174 (10.1)	26 (8.1)		40 (8.9)	
Hispanic	97 (5.7)	35 (10.9)		31 (6.9)	
Japanese	171 (10.0)	18 (5.6)		16 (3.6)	
White	822 (47.9)	107 (33.4)		221 (49.2)	
Financial strain, n (%)			<.01		<.01
Very or somewhat hard	570 (33.9)	144 (45.1)		185 (42.0)	
Not hard	1111 (66.1)	175 (54.9)		256 (58.0)	
Smoking, n (%)			<.01		<.01
Current	111 (6.5)	49 (12.3)		43 (9.7)	
Former or never	1590 (93.5)	277 (87.7)		401 (90.3)	
BMI in kg/m ² , mean (SD)	29.2 (7.1)	33.1 (7.4)	<.01	31.4 (7.6)	<.01
Perceived discrimination, mean (SD)	1.7 (0.5)	1.8 (0.5)	<.01	1.8 (0.5)	<.01

^a Two-sided *P* value comparing women with and without diabetes; χ^2 test for categorical variables; *t* test for continuous variables.

^b Two-sided *P* value comparing women with and without peripheral neuropathy; χ^2 test for categorical variables; *t* test for continuous variables.

Table 2

Prevalence of peripheral neuropathy by diabetes status, Study of Women's Health Across the Nation, 1996–2016

Peripheral neuropathy measures	Total (n = 1718)	With diabetes (n = 320)	Without diabetes (n = 1398)	P ^a
	n (%)	n (%)	n (%)	
Peripheral neuropathy	449 (26.1)	131 (40.9)	318 (22.8)	<.01
MNSI, ≥4 symptoms	282 (16.4)	106 (33.1)	176 (12.6)	<.01
Monofilament insensitivity, <3 correct responses	232 (13.7)	58 (18.8)	174 (12.5)	<.01
Both MNSI and monofilament	65 (3.8)	33 (10.7)	32 (2.3)	<.01

^a Two-sided χ^2 test comparing women with and without diabetes.

Discrimination has been found to be a strong indicator for risk of many serious health conditions, including diabetes, obesity, and hypertension [14,16,18–23,27,28,41–60]. Discrimination, along with other types of stressors, increases allostatic load, or the overstimulated or abnormal neurologic, immunologic, and inflammatory physiological responses induced by chronic stressors [18,19,44–54,61]. Discrimination and other chronic stressors are associated with heightened responsiveness of the cardiovascular system including increased blood pressure reactivity [55,56], red blood cell oxidative stress [57], and increased inflammation [52]. Cardiometabolic risk factors including diabetes are associated with PN among individuals with and without diabetes [40], and more recently, diabetic PN was associated with endothelial dysfunction [62]. Thus, chronic stressors such as discrimination may be associated with PN through the dysregulation of cardiovascular and metabolic function and proinflammatory responses that lead to damage of the peripheral nerves [16,17]. Furthermore, previous work has found an association between discrimination and chronic pain [58,59], potentially through psychological distress [58]. Because the symptoms of PN, particularly in the early stages, are characterized by chronic pain, it could be that discrimination is at play through the same neurologic pathways as chronic pain among both diabetic and nondiabetic PN cases.

Although perceived discrimination was a strong predictor for PN in the unadjusted model, this association was attenuated to non-significance when adjusted for BMI: BMI was the most highly significant predictor of PN in the present analysis. Formal mediation results suggest that the association between discrimination and PN is approximately 28.3% (95% CI, 17.1%–36.5%) mediated by BMI. In SWAN and elsewhere, discrimination has been shown to be an independent predictor of BMI [60,63], and discrimination has been found to be a predictor of inflammation with significant moderation by BMI [52]. Furthermore, increased BMI has been shown to contribute to decreased nerve conduction among individuals

without diabetes who do not yet have any symptoms of PN [38]. Even when no neuropathy symptoms were reported by those participants, they had significantly lower thermal and pain thresholds. This lends support to the mediation results and suggests that the underlying mechanism for discrimination's effect on the risk of PN may be related to the physiological effects of obesity and inflammation.

Other factors such as low socioeconomic status and smoking were found to be associated with prevalent PN. Women with lower socioeconomic status have been shown to have higher allostatic load stress markers, which according to the proposed biological mechanism above, could account for some of the increased odds of developing PN for women reporting financial strain [17,37]. People of lower socioeconomic status also have poorer nutrition, exercise less, have potentially more exposure to environmental toxins, and have less access to health care than women of higher socioeconomic status [37,64–67]. Even women who seek care for PN symptoms may be less likely to be properly tested and diagnosed based on their socioeconomic status [68]. All these factors may lead to poorer management and greater exacerbations of diseases such as PN among women of lower socioeconomic status. Furthermore, a recent metaanalysis found that smoking was significantly associated with an increased odds of diabetic PN [39]. Our results are consistent with these findings. Smoking is hypothesized to contribute to neuropathies by constricting the blood vessels that supply nerves with blood and nutrients [69].

The observed prevalence of PN in our present analysis is higher than reported in previous studies among women with and without diabetes [4,70]. In this analysis of the full SWAN cohort, the prevalence of PN is similar to that observed 8 years earlier at the Michigan SWAN site [5]. Notably, this current analysis found a high prevalence (22.8%) of PN in women without diabetes, suggesting that increased clinical focus on the problem of PN in the general population of women is needed, especially given evidence that PN

Table 3

Unadjusted and adjusted logistic regression models predicting peripheral neuropathy by perceived discrimination and body mass index, Study of Women's Health Across the Nation (n = 1665), 1996–2016

Variable	Unadjusted			Model 1 ^a			Model 2 ^b		
	OR	95% CI	P ^c	OR	95% CI	P ^c	OR	95% CI	P ^c
Perceived discrimination	1.43	1.14, 1.79	<.01	1.29	1.01, 1.66	.04	1.21	0.94, 1.56	.14
BMI	1.06	1.04, 1.07	<.01	—	—	—	1.04	1.03, 1.06	<.01
Diabetes ^d	2.35	1.82, 3.04	<.01	2.05	1.57, 2.69	<.01	1.78	1.35, 2.34	<.01
Race/ethnicity									
African American	1.23	0.95, 1.58	.11	0.91	0.69, 1.20	.55	0.80	0.60, 1.06	.11
Chinese	0.81	0.55, 1.19	.29	0.75	0.50, 1.12	.16	0.95	0.63, 1.44	.82
Hispanic	1.28	0.81, 2.01	.29	1.01	0.61, 1.67	.97	0.99	0.54, 1.50	.68
Japanese	0.28	0.16, 0.48	<.01	0.26	0.15, 0.46	<.01	0.33	0.19, 0.58	<.01
White	REF			REF			REF		
Financial strain ^d	1.66	1.28, 2.01	<.01	1.45	1.14, 1.84	<.01	1.46	1.14, 1.86	<.01
Current smoker ^d	1.88	1.26, 2.79	<.01	1.45	0.95, 2.2	.09	1.64	1.07, 2.52	.02

^a Model 1 adjusted for diabetes, race/ethnicity, financial strain, and current smoking.^b Model 2 additionally adjusted for BMI.^c All P values are two sided.^d Referent groups: no diabetes, “not very hard” to pay for basics, never smoked regularly.

Table 4

Controlled direct and indirect effects (odds ratio scale) of perceived discrimination on peripheral neuropathy via body mass index (BMI), Study of Women's Health Across the Nation, 1996–2016

Effects of perceived discrimination	OR* (95% CI)	P-value†	% Mediated	95% CI
Total Effect‡	1.30 (1.01, 1.68)	.04	—	—
Direct Effect‡	1.21 (0.94, 1.56)	.14	28.34	17.1, 36.5
Indirect Effect via BMI‡	1.07 (1.03, 1.12)	<.01	—	—

* ORs (95% CIs) for peripheral neuropathy are per 1-unit increase in perceived discrimination.

† All P values are two sided.

‡ Mediation models adjusted for race/ethnicity, financial strain, current smoking, and diabetes.

is a significant determinant of multiple dimensions of disability [5,71]. Furthermore, the increased prevalence of PN may be because of the method of measurement of PN. Many previous studies have used only monofilament testing to characterize PN, which in the present analysis would lead to a reduction in the number of PN cases by approximately 50% [4,72]. Early work describing the use of two instruments (in this case, the MNSI and monofilament testing) proved to provide a more sensitive and reliable measure of neuropathies among individuals with diabetes than one instrument alone as each may be capturing differing severities of PN [30].

There are several limitations to this study. First, PN was not measured at baseline or at other early study visits; therefore, we could not separate existing PN from neuropathy that developed over the course of the study period. This may have introduced issues of temporality into our study; however, increasing age contributes to neuropathy development, and measures were chosen to establish temporality between perceived discrimination (baseline) and BMI (the mediator, measured concurrently with PN). Perceived discrimination was assessed at baseline, but these experiences can accumulate over time and can be a regular and pervasive experience throughout the life course. Perceived discrimination has been shown to be stable over time in the SWAN cohort [19]. Because 68 women (10.6%) reported that they experienced discrimination mainly because of their physical appearance, we ran a sensitivity analysis with these women removed to reduce the possibility of reverse causation—that is that for some, higher BMI (physical appearance) could be leading to discrimination. The estimates of the association of perceived discrimination with PN did not change significantly in this sensitivity analysis (unadjusted OR = 1.39, 95% CI, 1.10–1.75; adjusted model OR = 1.18, 95% CI, 0.90–1.53). Despite these limitations, this analysis has many strengths overall. Using two standardized measures of PN gives more robust estimates of disease [19,39]. This large, community-based cohort design allowed us to investigate PN among women with and without diabetes, as well as women of diverse racial/ethnic backgrounds.

Conclusions

Nearly all previous PN research has focused primarily on populations with diabetes; however, our analysis found that almost one-fourth of women without diabetes have PN. More research is needed to determine the contributing factors to nondiabetic PN. Clinicians should consider this high prevalence when diagnosing and treating both patients with and without diabetes for neuropathy. This study also found that midlife perceived discrimination was a significant predictor of PN, and that this association was significantly mediated by BMI. Our findings reaffirm the impact of financial strain, BMI, and diabetes as significant correlates of PN measured by symptom questionnaire and monofilament testing

and show the impact of discrimination as an important risk factor for PN in women with and without diabetes.

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