SMALL FIBERS, LARGE IMPACT: QUALITY OF LIFE IN SMALL-FIBER NEUROPATHY

MAYIENNE BAKKERS, MD,[1] CATHARINA G. FABER, MD, PhD,[1] JANNEKE G.J. HOEIJMAKERS, MD,[1] GIUSEPPE LAURIA, MD, PhD,[2] and INGEMAR S.J. MERKIES, MD, PhD[3]

[1] Department of Neurology, Maastricht University Medical Centre, P.O. Box 5800, 6202 AZ, Maastricht, The Netherlands
[2] Neuromuscular Diseases Unit, IRCCS Foundation, National Neurological Institute "Carlo Besta," Milan, Italy
[3] Department of Neurology, Spaarne Hospital, Hoofddorp, The Netherlands

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ABSTRACT: *Introduction:* The impact of small-fiber neuropathy (SFN) on patients' quality of life (QOL) has not been studied extensively. Our aim was to determine the impact of SFN on QOL and examine possible determinants. *Methods:* We examined a total of 265 patients diagnosed with SFN. The SFN Symptoms Inventory Questionnaire (SFN-SIQ), the pain Visual Analog Scale (VAS), and the generic SF-36 Health Survey were assessed. Regression studies were undertaken to evaluate determinants of functioning. *Results:* SFN patients demonstrated a severe overall reduction in QOL. The biggest deficits were in Role Functioning–Physical, Body Pain, and Physical Component Summary (PCS) scores. VAS scores, changed sweating pattern, dry mouth, and age were the strongest predictors for PCS, explaining 32% of the QOL decrease. *Conclusions:* SFN leads to a reduction in overall QOL. The presence of pain and some autonomic symptoms explained only a small portion of the findings.

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Small-fiber neuropathy (SFN), a disorder of thinly myelinated A-δ and unmyelinated C fibers, is characterized by chronic and severe complaints, such as neuropathic pain and autonomic symptoms. SFN is associated with various disorders, such as metabolic (diabetes mellitus), infectious (human immunodeficiency virus), inflammatory (Sjögren's syndrome), and genetic (Fabry disease) diseases, but the cause is often idiopathic. The incidence and prevalence of SFN is unknown,[1,2] but it is probably not rare. In patients with diabetes mellitus, for example, a disease with increasing incidence and prevalence,[3] an estimated 16–20% have painful neuropathy.[4,5] This has been largely attributed to small-fiber involvement.[6]

Abbreviations: ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; HIV, human immunodeficiency virus; IENFD, intraepidermal nerve fiber density; MCS, Mental Component Summary; MUMC, Maastricht University Medical Center; PCS, Physical Component Summary; PGP-9.5, protein gene product 9.5; QOL, quality of life; QST, quantitative sensory testing; SF-36, Medical Outcomes Study 36-item Short-Form; SFN, small-fiber neuropathy; SFN-SIQ, Small-Fiber Neuropathy Symptoms Inventory Questionnaire; SLE, systemic lupus erythematosus; TSH, thyroid-stimulating hormone; TTT, temperature threshold testing; VAS, Visual Analog Scale

Key words: clinimetric evaluation; pain; polyneuropathy; quality of life; small-fiber neuropathy

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Correspondence to: M. Bakkers; e-mail: m.bakkers@mumc.nl

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The condition and its diagnosis has been gaining interest in the last 15 years, since the introduction of quantification of intraepidermal nerve fiber density (IENFD) in skin biopsies.[7] Although some have suggested that a reduced IENFD is a mandatory criterion for diagnosis of SFN,[8,9] various studies have proposed different definitions.[2,10–14] To date, the diagnosis of SFN relies on clinical features (neuropathic pain and autonomic symptoms not otherwise explained; loss of pinprick and temperature sensation without signs of large-fiber dysfunction) combined with abnormal quantification of IENFD and/or deficit in temperature threshold testing (TTT).[7,13,15–17] Skin biopsy findings are considered the strongest contributors to the diagnosis of SFN, because higher diagnostic accuracy has been demonstrated when compared with clinical features and quantitative sensory testing (QST) results.[18,19]

The impact of SFN on quality of life (QOL) and its possible explicatory determinants have not been examined systematically in patients with SFN. The primary aims of this study were to determine QOL in a cohort of patients with SFN using the Medical Outcomes Study 36-item Short Form Health Status (SF-36) and to compare the results with reported normative data for the healthy Dutch population.[20–23] Also, in this study we aimed to determine which SFN-related complaints would explain QOL findings through regression studies in this condition.

METHODS

Patients and Eligibility. The Maastricht University Medical Centre (MUMC) has experience in the diagnosis and management of patients with SFN. The MUMC serves as a tertiary referral center for patients with possible SFN, offering standardized evaluation. Between January 2009 and August 2011, all patients with a definite clinical diagnosis of SFN were approached for participation in this study.[15] Eligibility was based on the following criteria: age 18 years and older; definite clinical diagnosis of SFN based on: (1) the presence of at least 2 of the following complaints not otherwise explained: burning feet, redness of the skin, dry eyes or mouth, orthostatic dizziness, bowel disturbances (constipation,

diarrhea, irritability, gastroparesis, cramps), micturation disturbances, sweat changes (hyper/hypohidrosis), accommodation problems, impotence, diminished ejaculation or lubrication, flushes, and palpitations; (2) reduced IENFD when compared with age- and gender-matched normative values[24] and/or (3) abnormal temperature threshold testing (TTT) when compared with normative values[25,26]; (4) absence of large nerve fiber involvement on neurological examination (e.g., weakness, vibration threshold abnormalities as determined by Rydel–Seiffer graduated tuning fork[27]) and nerve conduction studies (examining at least median, fibular, tibial, and sural nerves, including late responses); and (5) possible presence of hyperpathia, diminished pain, and temperature sensation on examination.

IENFD and TTT examinations were performed as previously reported[28,29] and in accordance with the available guidelines.[7,30] Briefly, a 3-mm punch biopsy was taken 10 cm above the lateral malleolus, and the number of individual nerve fibers crossing the dermal–epidermal junction were counted in 3 randomly taken sections (50 μm) after immunostaining with polyclonal rabbit anti–protein gene product 9.5 antibody (PGP-9.5; Ultraclone; Wellow, Isle-of-Wight, UK). The linear density of IENF was calculated (IENF/mm of epidermal length, 1 of 2 observers, interobserver values 0.9). Findings were compared with normative data.[24] TTTs for warm, cool, and heat pain modalities were assessed (TSA-2001; Medoc, Ramat-Yishai, Israel) on the dorsum of both feet and thenar eminences. Results were considered abnormal if both method-of-limits and method-of-levels values were outside normative references.[25,29,31]

Medical Ethics Approval. The study was performed in accordance with ethics standards established by the 1964 Declaration of Helsinki and its later amendments. The investigation was approved by the medical ethics committee of the MUMC. The intentions of the study were explained to all patients, and informed consent was obtained from all patients before their inclusion in the study.

Additional Investigations. Additional investigations were performed to determine possible etiology of SFN. This included a complete history (including the use of alcohol, vitamins, or neurotoxic drugs), chest X-ray, and blood tests [blood cell counts, electrolytes, liver enzymes, creatinine, urea, lipids, fasting blood glucose, thyroid-stimulating hormone (TSH), free T4, vitamin B_6, serum immunofixation, autoantibodies for antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), SS-A/SS-B, and anti-sulfatide]; in selected patients, we also screened for Fabry disease (alfa-galactosidase, in women combined with sequencing of the *GLA* gene) and tested for infection with human immunodeficiency virus (HIV) and *Borrelia burgdorferi*.

Assessment Scales. The Dutch V1 version of the SF-36 was used to assess aspects of QOL. This generic scale consists of 36 items assigned to the domains of Physical Functioning (10 items), Role Functioning–Physical (4), Role Functioning—Emotional (3), Social Functioning (2), Body Pain (2), Mental Health (5), Vitality (4), General Health Perception (5), and Change in Health, which is scored separately.[20,22] Each domain has a scoring range of 0–100, with a high score indicating better health or less body pain. The corresponding Physical (PCS) and Mental Component Summary (MCS) scores were also calculated.[23] All findings were compared with reported SF-36 mean (SD) domains and summary values among healthy Dutch individuals (n = 1742, including 976 men and 766 women).[20,21]

The 13-item Small-Fiber Neuropathy and Symptoms Inventory Questionnaire (SFN-SIQ), which assesses changes in sweating pattern, presence of diarrhea, constipation, urinary tract problems like hesitation and incontinence, dry eyes, dry mouth, dizziness when standing up, palpitations, hot flashes, sensitive leg skin, burning feet, sheet intolerance, and restless legs at night, was administered to each patient. Each item was scored on a 4-point Likert scale (0—never present; 1—sometimes, 2—often, and 3—always present). A very similar scale has demonstrated discriminatory validity in patients with and without SFN suffering from sarcoidosis.[28]

Pain intensity was examined using a pain Visual Analog Scale (VAS pain current: the current presence of pain intensity; VAS pain minimum: the minimum level of pain intensity during the day; VAS pain maximum: the maximum level of pain intensity during the day).[32]

Statistical Analysis. ***Comparison Studies.*** For the whole group and for the various subgroups, the mean SF-36 subscales and summary (PCS/MCS) values were compared between the subgroups and with the reported mean normal values for the Dutch population (Student t-test for independent groups).[20,21] Subgroups were based on test results: subgroup A, both IENFD and TTT abnormal; subgroup B, IENFD abnormal and TTT normal; subgroup C, IENFD normal and TTT abnormal; or etiological grouping: sarcoidosis subgroup (subgroup $Sarc^+$) versus other etiologies (subgroup $Sarc^-$); and finally "idiopathic" subgroup versus "non-idiopathic" subgroup. Subgroups of patients were examined to determine whether the patient group was homogeneous, and

Table 1. Basic characteristics of patients with small-fiber neuropathy

	Patients (n = 265)
Gender [n (%)]	
Women	137 (51.7)
Men	128 (48.3)
Age in years [mean (SD), range]	50.2 (12.6), 17–81
Duration of symptoms in years [mean (SD), range]	7.6 (9.9), 0–70
Etiology [n (%)]	
Idiopathic	102 (38.5)
Sarcoidosis/SLE/Sjögren	96/1/1 (37.0)
SCN9A mutation	17 (6.4)
Diabetic	12 (4.5)
B6 intoxication	6 (2.3)
Paraproteinemia	8 (3.0)
Lyme	3 (1.1)
Alcohol-induced	2 (0.8)
Fabry	1 (0.4)
Medication induced	2 (0.8)
Thyroid dysfunction	6 (2.3)
Celiac disease	2 (0.8)
Chronic lymphatic leukemia	1 (0.4)
VAS pain score (amount of current pain) [mean (SD), range]	47.8 (28.8), 0–100
VAS pain score (lowest pain intensity) [mean (SD), range]	26.6 (22.2), 0–100
VAS pain score (highest pain intensity) [mean (SD), range]	70.9 (26.6), 0–100

SLE, systemic lupus erythematosus; SCN9A mutation, mutation in sodium channel (NaV 1.7); VAS, visual analog scale.

whether the etiology of SFN biased the study outcome.

Univariate and Multivariate Regression Studies. Linear regression analyses were performed to determine which variables (age, gender, duration of symptoms prior to start of the study, SFN symptoms measured with SFN-SIQ, VAS scores, explanatory variables) would have the greatest impact on patients' own PCS and MCS measures (dependent variables). The PCS was chosen, because it captures limitations in care, physical, social and role activities, amount of pain, and level of energy as a comprehensive overall score. The MCS measures the frequency of psychological distress and limitations in usual social and role activities due to emotional problems.[23] Prior to the regression studies, the distribution patterns of the dependent PCS and MCS variables were examined and, if necessary, transformed to obtain a normal distribution pattern. Univariate regressions were performed subsequently, striving for the best fit between the dependent and each explanatory variable, separately. This was accomplished through systematic evaluation of constructed graphs with linear regression studies, including a restricted cubic spline function on the independent variable where possible.[33] In addition, multivariate linear regressions were performed using a forward-adding stepwise strategy (significant level for adding set at 0.10) of explanatory variables on both the PCS and MCS scores, separately. The strength of association between the dependent variable and explanatory variables was presented as R^2, which is the fraction of variance explained by the independent variables from the regression model. The impact of age, gender, duration of symptoms, SFN-SIQ questions, and VAS scores was examined (in the multivariate setting) on each SF-36 domain separately (for the whole group of patients) to determine the strongest correlating domain of interest. All analyses were performed using Stata (version 12.0) for Windows XP. $P < 0.05$ was considered significant.

RESULTS

Patients. A total of 315 patients were screened. Of these, 9 had large-fiber involvement at examination or on nerve conduction studies, 7 had incomplete data (refused skin biopsy or TTT, or poor compliance to TTT), and 34 had normal IENFD and TTT values. These 50 patients were excluded from the study. Eventually, 265 patients were diagnosed with SFN and entered in the study.

The demographic and clinical features of these patients are presented in Tables 1 and 2. Approximately one-third (35.1%) of the patients had both abnormal IENFD and TTT values (subgroup A, n = 93). Most patients (57.7%) had normal IENFD and abnormal TTT (subgroup C, n = 153). No differences were seen between the subgroups regarding age, duration of symptoms, and number and severity of SFN complaints. The probable etiologies are also listed in Table 1. In most patients, SFN was associated with a systemic illness (particularly sarcoidosis) or remained idiopathic after thorough etiological screening.

SF-36 Findings. All SF-36 domains and summary scores were significantly ($P < 0.0001$) lower for the

Table 2. SFN-SIQ findings (265 patients).*

	Never	Sometimes	Often	Always
Changed sweating pattern	53.2	62.3	16.6	6.4
Diarrhea	62.3	24.2	12.1	1.5
Constipation	62.6	21.5	13.2	2.6
Micturation problems	55.9	24.2	14.3	5.7
Dry eyes	60.8	18.5	15.5	5.3
Dry mouth	50.9	22.3	20.4	6.4
Dizziness on standing	54.0	32.8	11.3	1.9
Palpitations	60.0	32.8	6.4	0.8
Hot flashes	57.0	23.4	17.4	2.3
Sensitive skin	48.3	14.3	15.5	21.9
Burning feet	41.1	11.7	20.8	26.4
Sheet intolerance	50.2	19.6	17.4	12.8
Restless legs	43.4	18.9	22.3	15.5

**Data expressed as percentage of responders.*

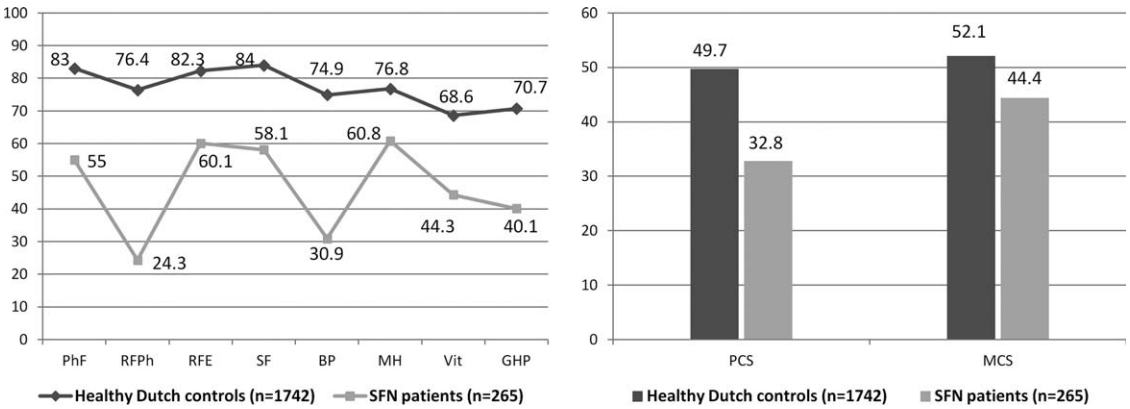

FIGURE 1. All domains and component summary of SF-36 findings were significantly lower in patients with small-fiber neuropathy (SFN) when compared with corresponding values in healthy Dutch controls ($^{*}P < 0.0001$ for all comparisons).[20,21] PhF, Physical Functioning; RFPh, Role Functioning–Physical; RFE, Role Functioning–Emotional; SF, Social Functioning; BP, Body Pain; MH, Mental Health; Vit, Vitality; GHP, General Health Perception; PCS, Physical Component Summary score; MCS, Mental Component Summary score.

whole group of patients when compared with reported normative values for the healthy Dutch population (Fig. 1). The domains Physical Functioning, Role Functioning–Physical, and Body Pain, and PCS demonstrated the lowest values in the SFN group (Fig. 1). When the results of the various subgroups of patients (A, B, and C; subgroup $Sarc^{+}$ and subgroup $Sarc^{-}$; idiopathic vs. non-idiopathic subgroup) were compared with reported Dutch normative data, the scores remained significantly lower in the subgroups.

No differences between subgroups A (both IENFD and TTT abnormal), B (only IENFD abnormal), and C (only TTT abnormal) were seen for the SF-36 domains and summary scores (Table 3, and Table A in Supplementary Material). No differences in summary (PCS and MCS) scores were seen between the $Sarc^{+}$ and $Sarc^{-}$ subgroups. However, at the domain level, subgroup $Sarc^{-}$ demonstrated a lower mean score in the domains of Physical Functioning, Social Functioning, Body Pain (indicating more pain), and Mental Health when compared with subgroup $Sarc^{+}$ (Table B in Supplementary Material - available online). The remaining domains and summary scores did not differ between these 2 subgroups. For all domains

Table 3. SF-36 health-related quality of life in patients with small-fiber neuropathy.

SF-36 domain	Subgroup A vs. B vs. C					
	PCS			MCS		
Group	Mean	SD	Range	Mean	SD	Range
A (n = 93)	32.3	8.7	12.2–50.3	43.2	11.3	22.6–72.5
B (n = 19)	32.1	11.8	13.8–60.3	43.6	9.8	23–57.4
C (n = 153)	33.2	9.2	13.8–55.9	45.3	10.7	20–75.8
	Patients with SFN related to sarcoidosis ($Sarc^{+}$) vs. SFN patients with non-sarcoidosis etiology ($Sarc^{-}$)					
	PCS			MCS		
Group	Mean	SD	Range	Mean	SD	Range
$Sarc^{+}$ (n = 96)	34.1	9.5	13.2–60.3	45.3	10.5	20–72.5
$Sarc^{-}$ (n = 169)	31.9	9	12.2–53.3	43.6	10.8	20.8–64.6
	Patients with idiopathic SFN (idSFN) vs. non-idiopathic SFN patients (nidSFN)					
	PCS			MCS		
Group	Mean	SD	Range	Mean	SD	Range
idSFN (n = 102)	32.3	8.4	13.8–49.5	43.2	11.4	20.8–62.1
nidSFN (n = 163)	33	9.6	12.2–60.3	45.1	10.5	20–75.8

PCS, Physical Component Summary score; MCS, Mental Component Summary score. $Sarc^{+}$, small-fiber neuropathy (SFN) associated with sarcoidosis; $Sarc^{-}$, idiopathic SFN or associated with other etiology than sarcoidosis; idSFN, idiopathic SFN, nidSFN, non-idiopathic SFN. Subgroup A: abnormal intra-epidermal nerve fiber density (IENFD) and temperature threshold testing (TTT); subgroup B: abnormal IENFD and normal TTT; subgroup C: normal IENFD and abnormal TTT.

except 2 (Body Pain and General Health Perception) and for both summary (PCS and MCS) scores, no differences were seen between the idiopathic SFN subgroup and the non-idiopathic SFN subgroup (Table C in Supplementary Material). The mean score for Body Pain was significantly lower in the idiopathic SFN subgroup. The mean score for General Health Perception was significantly lower in the non-idiopathic SFN subgroup (Table C in Supplementary Material).

Univariate Regression Studies on PCS and MCS. The distribution patterns for the PCS and MCS were fairly normal. Age and duration of symptoms did not have a significant impact on PCS and MCS scores. Gender had a very minor impact on PCS (explaining 2%) (Table 4). All SFN-SIQ inquiries demonstrated a very weak association with PCS, with each question explaining <10% of PCS, except for Q6 (dry mouth; 13% explained by this question) (Table 4). The pain VAS scores showed a slightly better explanation for PCS values (VAS pain current: $R^2 = 0.23$; VAS pain minimum: $R^2 = 0.21$; VAS pain maximum: $R^2 = 0.21$; $P \leq 0.007$). The VAS scores and some SFN-SIQ items (Q1, Q3, Q6, Q9, and Q10) were very weakly related to MCS, each explaining <5% of the MCS findings (Table 4). The remaining items did not have any significant impact on MCS.

Multivariate Regression Analyses on PCS and MCS. Through a stepwise-adding approach, a total of 32% ($R^2 = 0.32$) of PCS scores were explained by SFN-SIQ inquiry 06 (dry mouth), inquiry 01 (changes in sweating pattern), all VAS scores, and age (Table 4). The strongest predictor was SIQ 06 (dry mouth), showing a significant inverse correlation with PCS findings. Only 7% of MCS could be explained by gender, VAS 03, and SFN-SIQ Q9, Q10, and Q12. The remaining items did not contribute to model on MCS (Table 4).

Multivariate Regression Analyses on SF-36 Domains. A multivariate regression stepwise adding analyses approach was performed on each individual SF-36 domain separately to determine which domain would have the strongest association with the explanatory variables (age, gender, duration of symptoms, SFN-SIQ, and VAS scores). The domain Body Pain showed a very strong association: a total of 43% [$R^2 = 0.43$, $F(3.214) = 55.95$, $P < 0.0001$] was explained by VAS 03 (the maximum level of pain intensity during the day; β −7.71, $P < 0.001$), as did VAS 02 (the minimum level of pain intensity during the day; β −3.55, $P < 0.001$) and Q7 of the SFN-SIQ (dizziness when standing up; β −2.41, $P = 0.017$). The second best domain of interest being explained was Physical Functioning [$R^2 = 0.31$, $F(4, 208) = 25.24$, $P < 0.0001$], explained by Q1 (sweating pattern; β 2.32, $P = 0.022$) and Q6 (dry mouth; β −3.98, $P < 0.001$)] of the SFN-SIQ plus VAS 02 (β −6.41, $P < 0.001$) and gender (β 2.25, $P = 0.026$).

DISCUSSION

We have examined the impact of SFN on QOL. Using the SF-36 generic tool, there was a generally severe reduction in all domains and component summary scores compared with reported normative healthy Dutch control values (Fig. 1). In particular, the domains Role Functioning–Physical, Body Pain, and PCS had lower scores, indicating a worse physical condition.[20,23] The disability caused by polyneuropathy has been shown to correlate with a decrease in QOL.[34] The body pain scores were also significantly lower, thus demonstrating severe SFN-related neuropathic pain, which conforms with earlier reports.[7,13,15,35] It is known that painful polyneuropathy leads to a more severe reduction in QOL when compared with painless neuropathy.[36–39] Also, patients with a disease complicated by the presence of peripheral polyneuropathy may show a reduced QOL that cannot be explained merely by the disease alone.[40,41] In fact, the idiopathic SFN subgroup hardly showed differences from the non-idiopathic subgroup of patients, implying that the underlying illness that may lead to SFN did not have much impact on reduction of QOL (Table 3 and Tables A–C in the Supplementary Material - available online).

In a recent study involving various forms of peripheral neuropathies, similar SF-36 Body Pain findings were seen in patients classified as having pain. However, the PCS values in our patients were notably lower when compared with the reported scores.[42]

The SF-36 values in our SFN population were also substantially lower than in other chronic diseases, such as myocardial infarction and angina pectoris with hypertension, as has been reported in the USA population by those who established the SF-36.[22] Even the mental condition in our SFN patients was significantly reduced. This is in contrast to literature findings, which suggests an unaltered mental state in chronic conditions, including various forms of peripheral neuropathy.[42–45] This is usually explained by adaptation or development of coping mechanisms over the years. Apparently, patients with SFN have ongoing, sometimes excruciating pain and experience continuous difficulty dealing with the consequences of their illness.

With respect to the objectives of this study, there are some methodological issues that should be addressed. First, because only 32% of PCS values were explained by SFN-related complaints, including pain, future studies should focus on

Table 4. Univariate and multivariate regression studies on SF-36 Physical and Mental Component Summary Scores in patients with small-fiber neuropathy.

	Physical Component Summary score					
	Univariate regressions			Multivariate regressions* [R^2 = 0.32; F(6, 200) = 17; $P < 0.0001$]		
SF-36	R^2	F	β	β	P-value	R^2
Age	0.0001	(1, 232) = 0.02	0.14, P = 0.89		0.04	0.004
				2.07		
Gender	0.02	(1, 232) = 5.01	2.24, P = 0.026			0.004
Symptoms duration	0.003	(1, 218) = 0.38	–0.62, P = 0.537			0.003
VAS pain current	0.23	(1, 228) = 69.06	–8.31, $P < 0.001$		0.147	0.04
				–1.46		
VAS pain minimum	0.20	(1, 224) = 56.20	–7.50, $P < 0.001$		0.036	0.04
				–2.12		
VAS pain maximum	0.21	(1, 222) = 59.37	–7.71, P < 0.001		0.008	0.04
				–2.68		
Changed sweating	0.02	(1, 232) = 6.10	–2.47, P = 0.014		0.004	0.02
				2.90		
Diarrhea	0.02	(1, 232) = 5.71	–2.39, P = 0.018			0.001
Constipation	0.03	(1, 232) = 9.43	–3.07, P = 0.002			0.03
Micturation problem	0.06	(1, 232) = 15.78	–3.97, $P < 0.001$			0.006
Dry eyes	0.05	(1, 232) = 13.41	0.05, $P < 0.001$			0.002
Dry mouth	0.13	(1, 232) = 36.08	–6.01, $P < 0.001$		0.001	0.01
				–3.53		
Dizziness standing	0.07	(1, 232) = 17.53	–4.19, $P < 0.001$			0.0002
Palpitations	0.08	(1, 232) = 20.75	–4.56, $P < 0.001$			0.0002
Hot flashes	0.05	(1, 232) = 12.28	–3.5, P = 0.001			0.03
Sensitive skin	0.06	(1, 232) = 16.74	–4.09, $P < 0.001$			0.03
Burning feet	0.05	(1, 232) = 13.90	–3.73, $P < 0.001$			0.009
Sheet intolerance	0.07	(1, 232) = 19.73	–4.44, $P < 0.001$			0.005
Restless legs	0.06	(1, 232) = 15.34	–3.92, $P < 0.001$			0.01

	Mental Component Summary score					
	Univariate regressions			Multivariate regressions* [R^2 = 0.07; F(5, 201) = 4.26, P = 0.001]		
SF-36	R^2	F	R^2	F	R^2	F
Age	0.004	(1, 232) = 0.02	0.004	(1, 232) = 0.02	0.004	(1, 232) = 0.02
Gender	0.004	(1, 232) = 0.05	0.004	(1, 232) = 0.05	0.004	(1, 232) = 0.05
Symptoms duration	0.003	(1, 218) = 0.27	0.003	(1, 218) = 0.27	0.003	(1, 218) = 0.27
VAS pain current	0.04	(1, 228) = 11.17	0.04	(1, 228) = 11.17	0.04	(1, 228) = 11.17
VAS pain minimum	0.04	(1, 224) = 10.53	0.04	(1, 224) = 10.53	0.04	(1, 224) = 10.53
VAS pain maximum	0.04	(1.222) = 9.54	0.04	(1.222) = 9.54	0.04	(1.222) = 9.54
Changed sweating	0.02	(1, 232) = 5.74	0.02	(1, 232) = 5.74	0.02	(1, 232) = 5.74
Diarrhea	0.001	(1, 232) = 0.68	0.001	(1, 232) = 0.68	0.001	(1, 232) = 0.68
Constipation	0.03	(1, 232) = 9.40	0.03	(1, 232) = 9.40	0.03	(1, 232) = 9.40
Micturation problem	0.006	(1, 232) = 2.31	0.006	(1, 232) = 2.31	0.006	(1, 232) = 2.31
Dry eyes	0.002	(1, 232) = 0.47	0.002	(1, 232) = 0.47	0.002	(1, 232) = 0.47
Dry mouth	0.01	(1, 232) = 3.99	0.01	(1, 232) = 3.99	0.01	(1, 232) = 3.99
Dizziness standing	0.0002	(1, 232) = 1.04	0.0002	(1, 232) = 1.04	0.0002	(1, 232) = 1.04
Palpitations	0.0002	(1, 232) = 0.96	0.0002	(1, 232) = 0.96	0.0002	(1, 232) = 0.96
Hot flashes	0.03	(1, 232) = 7.44	0.03	(1, 232) = 7.44	0.03	(1, 232) = 7.44
Sensitive skin	0.03	(1, 232) = 8.34	0.03	(1, 232) = 8.34	0.03	(1, 232) = 8.34
Burning feet	0.009	(1, 232) = 2.99	0.009	(1, 232) = 2.99	0.009	(1, 232) = 2.99
Sheet intolerance	0.005	(1, 232) = 2.06	0.005	(1, 232) = 2.06	0.005	(1, 232) = 2.06
Restless legs	0.01	(1, 232) = 3.85	0.01	(1, 232) = 3.85	0.01	(1, 232) = 3.85

VAS, Visual Analog Scale; VAS pain current, the current presence of pain intensity; VAS pain minimum, the minimum level of pain intensity during the day; VAS pain maximum, the maximum level of pain intensity during the day.

**Only those items that remained in the multivariate model are reported.*

other factors that may contribute to lower QOL in these patients. Factors like anxiety, depression, disturbed sleep, and fatigue have been demonstrated to contribute to decreased QOL in peripheral neuropathies.[42,46,47] Second, because the MUMC is also a referral center for patients with sarcoidosis,

our study population was biased toward this illness. The SF-36 component summary findings in the sarcoidosis group versus the other etiological SFN patients did not differ; however, some differences were seen at the domain level (Table B in Supplementary Material - available online). Despite this etiological bias, the findings in the sarcoidosis subgroup demonstrated approximately the same differences with the healthy Dutch community as seen in Figure 1. Similar findings were seen for the idiopathic versus non-idiopathic subgroup of patients. Therefore, we consider the findings from the total SFN group representative of SFN in general. Understanding the disabling complaints leading to a reduced QOL is essential in optimizing the guidance and hopefully the therapeutic approach in this condition. Third, we used a generic QOL metric, because our aim was to compare the findings with reported normative healthy community scores. The SF-36 is not a disease-specific tool, and perhaps a more specific questionnaire, such as the Vickrey 97-QoL scale, would have shown better targeting with stronger associations with the SFN complaints in our study population.[48] The percentage of the physical summary score explained is, however, is slightly lower than that the reported explanation ($\backsim$40%) in other peripheral neuropathies with more physical impairments.[49,50] Because QOL may complement traditional outcome measures, a limited correlation is not unexpected.[50]

In conclusion, SFN has an overall severe impact on QOL, both physically and mentally. Some SFN symptoms, including pain, had an inverse correlation with QOL scores, explaining about one-third of physical QOL findings. Future studies are warranted to determine which additional factors may influence QOL in SFN.

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