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Initial development and validation of a patient-reported symptom survey for small-fiber polyneuropathy

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Abstract

Small-fiber polyneuropathy SFPN affects unmyelinated and thinly myelinated peripheral axons. Several questionnaires have been developed to assess polyneuropathy from diabeties or chemotherapy, but none for SFPN from other or unknown causes. A comprehensive survey could help clinicians diagnose and assess treatment responses, define prevalence natural history and cures, and identify research subjects. Thus, we developed the one-page Small-fiber Symptom Survey (SSS), using input from patients and 21 medical/scientific experts. Participants comprised consenting consecutive patients evaluated for SFPN at the Massachusetts General Hospital plus normal controls. Participants SFPN status was stratified based on the results of their objective diagnostic tests (distal-leg skin biopsy and autonomic-function testing). We measured internal consistency, test re-test reliability, convergent validity and performed a receiver operating curve analysis.

The 179 participants averaged 46.6±15.6 years old; they were 73.2% female and 92.2% Caucasian. Eighty-five had confirmed SFPN, mostly idiopathic. Principal component analysis revealed 5 symptom clusters. The questionnaire had good internal consistency (Cronbach alpha=0.893), excellent test re-test reliability (r=0.927, p<0.001) and good-to-fair convergent

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validity. Participants with confirmed SFPN had more severe symptoms than others (p=0.009). The SSS has satisfactory psychometric properties, indicating potential future utility for surveying patient-reported symptoms of SFPN regardless of its cause.

Perspective—This article reports the initial development and early psychometric validation of a new patient-reported outcome measure intended to capture the wide range of multi-system symptoms of small fiber polyneuropathy. Once further developed, it could potentially help clinicians diagnose and monitor patients, and help advance research.

Keywords

peripheral neuropathy; dysautonomia; sensory; neuropathic pain; skin biopsy

Introduction

Distal polyneuropathy is common, with the National Health and Nutrition Examination Survey (NHANES) reporting 14.8% prevalence among people over age 40 [10]. However, these figures do not fully capture patients with small-fiber polyneuropathy (SFPN), although it is the most common presentation of distal polyneuropathy. Multiple labs now report evidence of SFPN in about 40% of patients with fibromyalgia [11, 21, 26]. Since fibromyalgia affects 2-5% of the world's population [17, 28], SFPN may affect millions. SFPN involves preferential damage to the small diameter, unmyelinated C-fibers and/or thinly myelinated A-delta fibers that signal pain, tissue damage and inflammation, and regulate the body's tissues and organs [5]. If oxygen, nutrient, or energy supply is compromised, the distal ends of these long axons malfunction and degenerate, which causes diverse symptoms. Sensory symptoms can include spontaneous chronic widespread pain (CWP), stimulus-evoked hyperalgesia/allodynia, reduced nociceptive sensation, and neuropathic itch [20, 25]. The cardiovascular, gastrointestinal, microvascular and/or sweating symptoms can reflect either autonomic or somatic axonopathy since many internal organs and tissues have dual small-fiber innervation [1]. Neurogenic dysregulation of the microvessels alone causes a wide array of symptoms including postural orthostatic tachycardia syndrome [11] fatigue, and even cognitive dysfunction [22].

Current patient reported outcomes (PROs) focus on the polyneuropathies that predominantly affect the large myelinated motor and sensory fibers such as Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP), or neuropathies caused by one medical cause [3, 4, 6, 14, 15, 18, 23]. Examples include the Survey of Autonomic Symptoms for diabetic neuropathy [29], the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, the Chemotherapy Induced Peripheral Neuropathy Questionnaire [24] and the Treatment-Induced Neuropathy Assessment Scale [19]. No questionnaire has been designed to capture symptoms from patients with idiopathic SFPN, although they represent the 2nd largest group of SFPN patients (20%-50% in recent series [9, 13]) after those with diabetic SFPN. Thus, we developed and evaluated the Small-Fiber Symptom Survey (SSS), a one-page questionnaire concerning the full spectrum of SFPN symptoms and applicable to patients with undefined causes of their SFPN.

Methods

Subjects and Data Acquisition

Participants provided informed consent to a protocol approved by the hospital's institutional review board. Most were patients being evaluated for symptoms suggesting SFPN despite no evident medical cause (e.g., diabetes, chemotherapy exposure), thus they had been referred for potentially confirmatory objective testing for SFPN at Massachusetts General Hospital (MGH) in 2014-2015. A small sample of screened healthy volunteers was added to expand to the full range of symptom presence and severity. Eligibility required age ≥18 years, English fluency, and distal-leg, PGP9.5-immunolabeled skin biopsy or diagnostic Autonomic Function Testing (AFT) conducted within 18 months of recruitment for this study. These tests had been performed in JC-accredited clinical diagnostic laboratories using standard clinical diagnostic methods, equipment and interpretations [2, 8, 16]. Patients were stratified into "confirmed SFPN" or "possible SFPN" based on whether the medical report interpreting their skin biopsy and/or AFT diagnosed them with SFPN or not.

Al eligible patients were sent invitation letters followed by a phone call. Respondents were screened for eligibility, consented, and demographic and medical information including comorbid medical conditions was captured using an approved telephone script. Study aims and instructions were provided. Data were captured using the Research Electronic Data Capture system (REDCap), a secure web-based application for securely capturing medical data [12]. Participants who completed the study were compensated $15.

Questionnaire Development

The initial 23-item first version was based on the most common symptoms reported by patients during medical care, and by review of the literature pertaining to symptoms of SFPN. The questionnaire was then used during patients evaluations for 16 months, during which we added new items that patients reported, and improved comprehensibility. This revised 32-item version was then circulated to 21 experts for input. They consisted of 11 neurologists (including 4 pediatric neurologists and three peripheral-nerve specialists), an internist/pediatrician, a cardiology expert on dysautonomia, 4 gastrointestinal specialists including one pediatrician, 1 urologist, and three experts in design of pain-related PROs. They added one item, rephrased several items, and modified the scale. The third version (33 items) underwent cognitive debriefing interviews with patients to improve comprehensibility.

The fourth version of the survey that was studied here containing 33 items and is one page long. The instructions are "Rate how much you have been affected by each symptom below in the last week". Participants were asked to rate the first 32 items on a 0-4 scale (0 not at all, 1 a little bit, 2 somewhat, 3 quite a bit, 4 very much), a scale recommended by the NIH Patient Reported Outcomes Measurement Information System (PROMIS) project (http://www.nihpromis.org). The 33rd item is a 0-10 numerical pain rating scale (NPS) asking respondents to rate "Intensity of your chronic widespread pain (on both sides of your body) at its worst during the last week". A free-text section was available to capture additional symptoms or suggestions for improvement.

Preliminary validation

A link was emailed to each consented subject directing them to the REDCap survey, which included questions on demographics and the SSS. Subjects could mail back paper documents if preferred. To assess convergent validity, subjects also completed the Composite Autonomic Symptom Score (COMPASS-31) [25], the Short-form McGill Pain Questionnaire (SF-MPQ -2) [7] and the Medical Outcomes Study Short-Form Health Survey (SF-36) [27]. Two weeks after completing the first REDCap survey, participants completed the SSS a second time to assess test re-test reliability.

Statistical analyses

Analyses were conducted with SPSS for Windows version 19 (Chicago, IL, USA) and SAS version 9.3 (SAS Institute, Cary NC). Descriptive statistics described prevalence. Symptom scores were reported as means ± standard deviations. Internal validity was assessed by Cronbach's alpha. Test re-test reliability and convergent validity were assessed by zero order Pearson product-moment correlations. Exploratory factor analysis (EFA) with principal components extraction was conducted on the responses of all 179 participants with varimax rotation, with factor weights sorted and suppressed if less than |4|. This produces an orthogonal (i.e., uncorrelated) factor solution. This process was repeated until the full underlying factor structure emerged. Differences in dependent variables were compared between groups using independent t-test. P-values ≤ 0.05 were considered statistically significant. Receiver operating characteristic (ROC) analysis was conducted with SFPN diagnosis as the state variable and the SSS total score as the test variable, using age and gender as covariates. Due to the exploratory nature of the study, no corrections for multiple comparisons were used.

Results

Cohort characteristics

From 470 eligible potential subjects contacted, 179 (162 patients and 17 healthy volunteers) completed the first REDCap survey (38% response rate). Their mean age was 46.6 ± 15.6 years (range 18-88 years), 73.2% (131/179) identified as female, and 92.2% as Caucasian. Table 1 tallies their most common comorbid medical diagnoses and their most common classes of medications used. Overall, 85 subjects were diagnosed with "confirmed SFPN" by one or both diagnostic tests. Specifically, 67 diagnostic skin biopsies (epidermal nerve fiber density ≤ 5^{th} centile of predicted) and 29 had diagnostic AFTs. The demographic characteristics of participants is presented in Table 2.

Table 3 reveals that participants' 5 most prevalent symptoms (rated as present in any severity) were "Tiredness (fatigue)", present in 98.1%, "Reduced endurance or strength for activities" in 96.3%, "Difficulty thinking, concentrating, or remembering" in 90.1%, "Tingling or "pins and needles" in 88.9%, and "Deep pains or aches" in 87.0%. Subjects' worst pain in the last week averaged 5.3 ± 3.4, with 84.4% reporting having chronic widespread pain (non-zero score) and 67.6% reporting pain scores ≥ 4.

Principal components analysis

Extraction of the 33 items produced a 7-component solution that explained 61.2% of the variance. The 7 items that correlated with more than one component were: “Intensity of chronic widespread pain”, “Tingling or “pins and needles”, “Need to move legs often for comfort”, Abdominal pain”, “Feeling dizzy or faint when standing up”, “Deep pains or aches”, and “Skin that has less sensation (numbness)”. The second iteration restricted to the remaining 26 items yielded a 6-component solution that explained 58.7% of the variance. After “Difficulty thinking, concentrating or remembering” was excluded, a third analysis of 25 items yielded 6 components that explained 58.8% of the variance. After “Deep vibration or fluttering” and “Blisters, sores or ulcers on feet and hands” were excluded, a forth analysis yielded a 5 component 23-item version that explained 58.7% of the variance. After “Blisters or sores inside mouth” was excluded, a fifth iteration yielded 5 components (each item falling in a single component), that explained 57.8% of the variance (Table 4). Since some of the items detected are medically important, we decided to re-evaluate the overlapping items to see which made medical sense to delete, and which should be revised to improve their clinical and statistical utility in a subsequent study.

Preliminary validation of the SSS

Cronbach’s alpha analysis on all 179 subjects revealed good internal consistency for the entire survey (0.893) and for each of the 5 components (0.785, 0.799, 0.759, 0.708 and 0.715 respectively; Table 5). One hundred sixty-four subjects (147 patients and 17 healthy controls) completed the surveys twice. Stability over time was excellent for the entire questionnaire (Pearson $r=0.927$, $p<0.001$) and for each component (0.884, 0.867, 0.887, 0.883, 0.837, respectively; $P<0.001$ for all tests). There was good convergent validity between total scores of the SSS and the McGill ($r=0.795$, $p<0.001$), the COMPASS-31 ($r=0.769$, $p<0.001$) and fair convergence with the SF-36 ($r=-0.644$, $p<0.001$). Diagnostic potential of SSS for SFPN was evaluated by ROC analysis. The SSS had poor accuracy in predicting SFPN, with area under the curve of 0.599.

Symptom profile in patients with objectively confirmed SFPN

The results from the 85 “gold-standard” patients with objective confirmation of SFPN are presented in Figure 1. Their 5 most severe symptoms were “Tiredness (fatigue)”, “Reduced endurance or strength for activities”, “Deep pains or aches”, “Tingling or “Pins and needles”, and “Difficulty thinking, concentrating, or remembering”. Table 5 summarizes the analysis of the questionnaire’s discriminative ability. This showed higher overall symptom severity among the patients with confirmed SFPN (32.4 ± 14.8) than in the others (26.1 ± 17.2; $p=0.009$). Those with confirmed SFPN also had higher scores in 4/5 components. The range of symptoms reported by the 17 healthy volunteers was far lower, with total scores ranging from 0 – 15 and a mean of 5.06 ± 5.3

Discussion

The SSS version 4 questionnaire had good psychometric properties including excellent test re-test reliability, good internal consistency and convergent validity. Participants with

confirmed SFPN had higher scores than non-SFPN healthy controls, providing evidence of potential diagnostic utility.

The Principal Component Analysis yielded a 5-component solution that mostly divided into medically appropriate categories, containing symptoms likely to share underlying mechanisms. Component 1 was mainly gastrointestinal symptoms and Component 2 mainly somatosensory symptoms. Component 2 had the largest severity differences between the two groups, suggesting that sensory symptoms might be a potentially useful discriminator for screening. Component 3 was a cluster of miscellaneous symptoms with no evident link at present. Component 4 comprised largely vascular symptoms and Component 5 contained only 3 questions about urological symptoms. It had the lowest severity score overall and it differed only modestly between groups, perhaps because urological symptoms are common and often multifactorial. However, some of the items that “fell out” were medically important to retain, so they were flagged for further revision to improve their psychometric performance. This illustrates a limitation of principal component analyses, and the need to balance them with real-world considerations.

This study’s strengths included rigorous development over 3 years using input from hundreds of patients and a broad spectrum of experts in relevant medical specialties and in questionnaire design (see Acknowledgements). Another strength is the large sample of 85 patients with objective confirmation of SFPN. These gold-standard subjects provide some assurance of the specificity of symptoms, although having SFPN does not preclude having other unrelated causes of symptoms, e.g., urological complaints from prostate hypertrophy.

One limitation is that the SSS cannot distinguish between primary versus secondary symptoms, for instance caused by medications, co-morbidities, or inactivity. For instance, 24% of the entire cohort used opioids (which cause constipation), and 15% were also diagnosed as suffering from depression. These are among the factors that might explain why cognitive concerns, not traditional symptoms of polyneuropathy, were prevalent, although there is increasing evidence that SFPN causes trans-synaptic network effects on brain neurons [22]. However, whether primary or secondary, all SFPN-associated symptoms are important to capture. Another limitation is that the SSS was administered up to 18 months after participants had their objective tests, whereas ideally, they should have been administered concomitantly.

Another consideration is that both of the recommended objective diagnostic tests for SFPN were used to identify the gold-standard patients, skin biopsy and AFT. Using both permitted us to capture patients with the full spectrum of somatic and autonomic symptoms, but each test can capture different patients. The cohort had too few patients with confirmation by only one of these tests but not the other, to perform subgroup analyses in this initial study. As additional data are collected, clusters of questions might be identified that predict skin biopsy or AFT results sufficiently well to serve as non-invasive surrogates for these expensive tests, or to identify which patients should or should not undergo these tests.

The ROC analysis of the SSS for identifying SFPN had an AUC of 0.599 using autonomic function testing and skin biopsy to define SFPN. It is likely adding other potential risk

factors and easily measured clinical characteristics (e.g., heart rate) along with a more advanced version of the SSS would lead to a higher AUC that could identify at-risk patients who should have more in-depth clinical testing. Further, such a model could also be used to improve population-based research to identify novel risk factors for SFPN that could further enhance prediction. More research is needed to expand the predictive capacity of the model.

To conclude, we report preliminary evidence of good psychometric properties and clinical relevance of the SSS. Responses from of the 85 gold standard patients with confirmed SFPN suggest that patients with SFPN have more symptoms than classically reported, including fatigue, chronic headache, deep aches, and reduced endurance. Future tasks include clarifying which questionnaire items should be removed and which should be rewritten to improve their psychometric performance, defining scoring algorithms for clinical and research use, and validating performance in subgroups with common causes of SFPN such as diabetes or chemotherapy exposure. Correlation with outcomes of skin biopsy and AFT can be explored to assess the potential utility of the SSS as an inexpensive patient-administered screening tool for SFPN.

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Highlights

- Current neuropathy-related PRO's do not capture the full range of SFPN symptoms
- We report the development and initial validation of a new survey for SFPN symptoms
- This survey is suitable for patients with ill-defined causes of SFPN
- It can support diagnosis and monitoring symptoms, for clinically and research wise

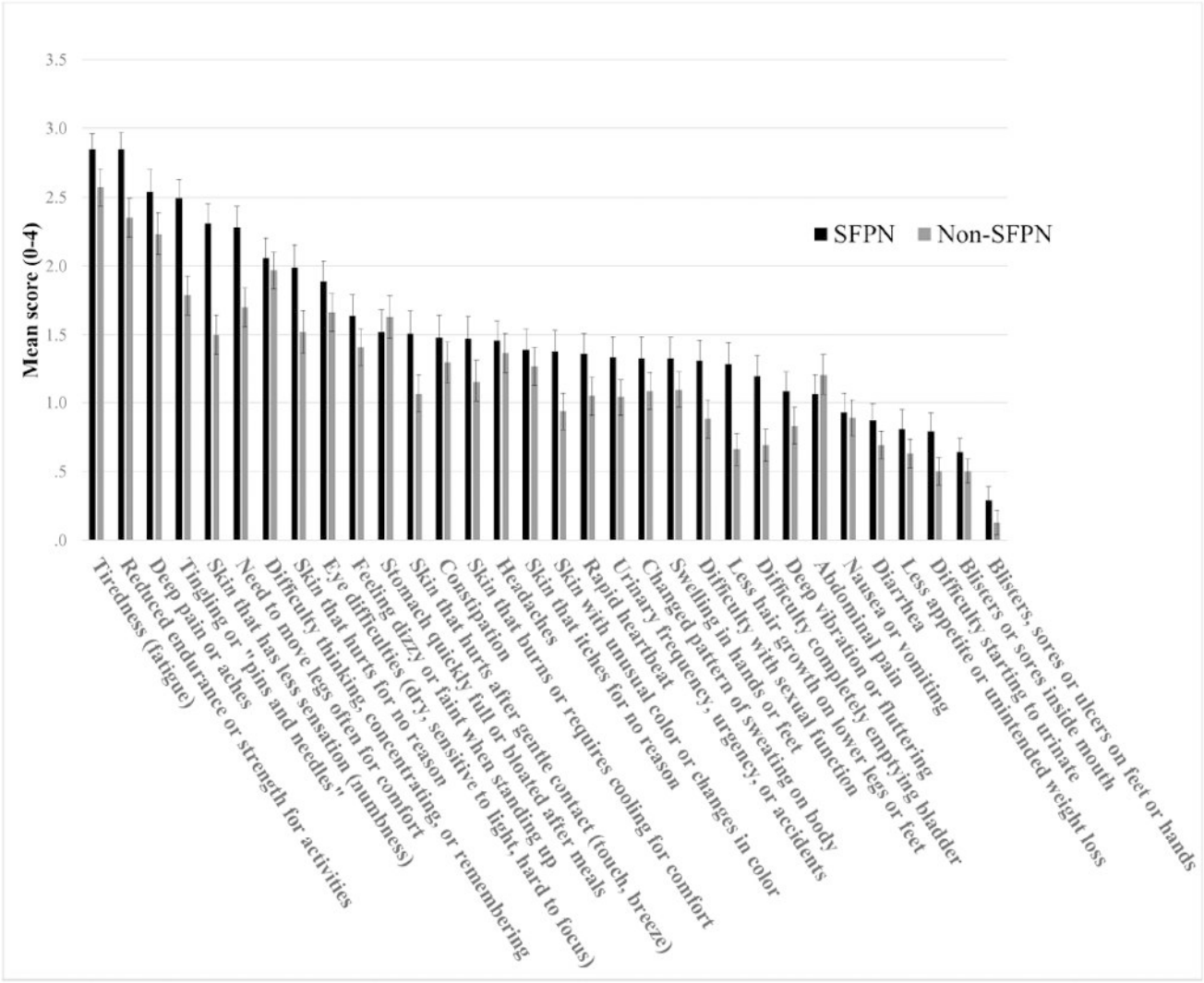

Figure 1.

Severity of symptoms in patients with objectively confirmed SFPN (n = 85) and in Non-SFPN (n=94).

Table 1

Top 10 diagnoses and classes of medication (n=179)

Diagnoses	% (n)	Medication classes	% (n)
Fibromyalgia	29.1 (52)	Antidepressants	42.5 (76)
Hypertension	20.1 (36)	Cardiovascular-related	39.7 (71)
Hypothyroidism	16.2 (29)	Gastrointestinal-related	38.5 (69)
Depression	15.1 (27)	Antiepileptic	33.0 (59)
Gastroesophageal reflux disease	12.3 (22)	Corticosteroids	29.6 (53)
Asthma	11.7 (21)	NSAID/Anti-inflammatory	29.1 (52)
Migraine	8.4 (15)	Benzodiazepine	27.4 (49)
Anxiety	7.8 (14)	Opioids	24.0 (43)
Allergic Rhinitis	7.3 (13)	Antibiotic, antiviral and anti-fungal	21.8 (39)
Headache	7.3 (13)	Asthma and allergies	20.7 (37)

Table 2

Demographic characteristics of participants stratified by SFPN status

Characteristic		Confirmed SFPN	Non-SFPN (n=94) n (%)	
		85 patients with confirmed SFPN n (%)	77 patients with possible SFPN	17 healthy controls
Age	(mean± SD)	50.18±15.4	45.22±14.6	34.00±15.2
Gender				
	Female	64 (75.3%)	62 (80.5%)	5 (29.4%)
	Male	21 (24.7%)	15 (19.5%)	12 (70.6%)
Race/Ethnicity				
	Hispanic	2 (2.4%)	1 (1.3%)	0
	White	80 (94.1%)	71 (92.2%)	14 (82.4%)
	Asian	1 (1.2%)	3 (3.9%)	1 (5.9%)
	Other (black and mixed race)	2 (2.4%)	2 (2.6%)	2 (11.8%)
Employment status				
	Employed	34 (40.0%)	38 (49.4%)	12 (70.6)
	Disabled	30 (35.3%)	17 (22.1%)	0
	Retired	17 (20%)	8 (10.4%)	0
	Other (including students)	4 (4.7%)	14 (18.2%)	5 (29.4%)
Educational status				
	High school or lower	33 (38.9%)	26 (33.8%)	9 (52.9%)
	Bachelor	21 (24.7%)	24 (31.2%)	6 (35.3%)
	Graduate or higher	31 (36.5%)	27 (35.1%)	2 (11.8%)
Marital status				
	Single	21 (24.7%)	26 (33.8%)	9 (52.9%)
	In relationship	56 (65.9%)	49 (63.6%)	7 (41.1%)
	Divorced or widowed	8 (9.4%)	2 (2.6%)	1 (5.9%)

Table 3

Ranked prevalence of specific symptoms in all 179 participants

Item	Not at all	A little bit	Somewhat	Quite a bit	Very much
Tiredness (fatigue)	1.9% (3)	10.5% (17)	17.9% (29)	37.0% (60)	32.7% (53)
Reduced endurance or strength for activities	3.7% (6)	11.1% (18)	16.7% (27)	37.7% (61)	30.9% (50)
Difficulty thinking, concentrating, or remembering	9.9% (16)	24.1% (39)	23.5% (38)	24.7% (40)	17.9% (29)
Tingling or “pins and needles”	11.1% (18)	16.0% (26)	24.7% (40)	25.9% (42)	22.2% (36)
Deep pains or aches	13.0% (21)	7.4% (12)	19.1% (31)	27.2% (44)	33.3% (54)
Need to move legs often for comfort	14.8% (24)	19.1% (31)	22.2% (36)	24.1% (39)	19.8% (32)
Eye difficulties (dry, sensitive to light, hard to focus)	17.3% (28)	21.0% (34)	26.5% (43)	21.0 (34)	14.2% (23)
Skin that has less sensation (numbness)	17.3% (28)	17.9% (29)	23.5% (38)	23.5% (38)	17.9% (29)
Feeling dizzy or faint when standing up	23.5% (38)	27.8% (45)	22.2% (36)	13.0% (21)	13.6% (22)
Skin that hurts for no reason	27.2% (44)	13.6% (22)	21.0% (34)	16.0% (26)	22.2% (36)
Headaches	29.6% (48)	25.9% (42)	16.7% (27)	19.1% (31)	8.6% (14)
Stomach quickly full or bloated after meals	32.1% (52)	16.0% (26)	16.0% (26)	18.5% (30)	17.3% (28)
Skin that itches for no reason	34.0% (55)	25.3% (41)	16.7% (27)	11.7% (19)	12.3% (20)
Swelling in hands or feet	37.0% (60)	24.7% (40)	17.9% (29)	9.9% (16)	10.5% (17)
Constipation	38.3% (62)	15.4% (25)	15.4% (25)	17.3% (28)	13.6% (22)
Rapid heartbeat	41.4% (67)	24.1% (39)	8.0 (13)	16.0% (26)	10.5% (17)
Abdominal pain	41.4% (67)	24.1% (39)	13.6% (22)	9.3% (15)	11.7% (19)
Urinary frequency, urgency, or accidents	41.4% (67)	15.4% (25)	22.2% (36)	14.2% (23)	6.8% (11)
Skin that hurts after gentle contact (touch, breeze)	42.6% (69)	12.3% (20)	17.9% (29)	15.4% (25)	11.7% (19)
Skin that burns or requires cooling for comfort	42.6% (69)	13.6% (22)	16.0% (26)	12.3% (20)	15.4% (25)
Changed pattern of sweating on body	43.2% (70)	15.4% (25)	16.0% (26)	17.3% (28)	8.0% (13)
Skin with unusual color or changes in color	44.4% (72)	16.0% (26)	19.8% (32)	8.0% (13)	11.7% (19)
Difficulty with sexual function	47.5% (77)	17.3% (28)	14.2% (23)	9.9% (16)	11.1% (18)
Diarrhea	50.0% (81)	27.2% (44)	13.6% (22)	5.6% (9)	3.7% (6)
Deep vibration or fluttering	50.6% (82)	18.5% (30)	13.0% (21)	10.5% (17)	7.4% (12)
Nausea or vomiting	51.9% (84)	21.0% (34)	9.3% (15)	8.6% (14)	9.3% (15)
Difficulty completely emptying bladder	52.5% (85)	16.7% (27)	13.6% (22)	10.5% (17)	6.8% (11)
Less hair growth on lower legs or feet	53.1% (86)	14.2% (23)	13.6% (22)	12.3% (20)	6.8% (11)

Item	Not at all	A little bit	Somewhat	Quite a bit	Very much
Less appetite or unintended weight loss	58.0% (94)	21.6% (35)	9.3% (15)	5.6% (9)	5.6% (9)
Blisters or sores inside mouth	60.5% (98)	22.8% (37)	12.3% (20)	3.1% (5)	1.2% (2)
Difficulty starting to urinate	66.0% (107)	13.0% (21)	9.3% (15)	8.0% (13)	3.7% (6)
Blister, sores or ulcers on feet or hands	84.6% (137)	10.5% (17)	3.1% (5)	1.2% (2)	0.6% (1)

Table 4

The 5 component solution of the Principal Component Analysis

Rotated Component Matrix					
	Component				
	1	2	3	4	5
Nausea or vomiting	.815				
Stomach quickly full or bloated after meals	.744				
Less appetite or unintended weight loss	.686				
Headaches	.564				
Constipation	.476				
Skin that hurts for no reason		.762			
Skin that hurts after gentle contact (touch, breeze)		.754			
Skin that burns or requires cooling for comfort		.744			
Difficulty with sexual function		.577			
Reduced endurance or strength for activities			.784		
Tiredness (fatigue)			.759		
Eye difficulties (dry, sensitive to light, hard to focus)			.521		
Diarrhea			.471		
Rapid heartbeat			.450		
Skin with unusual color or changes in color				.722	
Less hair growth on lower legs or feet				.679	
Changed pattern of sweating on body				.619	
Swelling in hands or feet				.587	
Skin that itches for no reason				.467	
Difficulty completely emptying bladder					.851
Difficulty starting to urinate					.786
Urinary frequency, urgency, or accidents					.587

Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 5 iterations.

Table 5

Means in cohort (±SD), Cronbach's alpha values of the 5 components

Component	Number of items	Cronbach's alpha	Cohort Mean (±SD)	SFPN Mean (±SD)	Non-SFPN Mean (±SD)	p-value
The entire survey	22	0.893	29.06 (16.35)	32.38 (14.76)	26.05 (17.20)	**0.009**
Component 1	5	0.785	6.02 (4.99)	6.24 (4.97)	5.82 (5.01)	0.578
Component 2	4	0.799	5.41 (4.64)	6.27 (4.63)	4.64 (4.54)	**0.018**
Component 3	5	0.759	9.04 (4.48)	9.82 (3.99)	8.33 (4.80)	**0.026**
Component 4	5	0.708	5.83 (4.59)	6.72 (4.50)	5.03 (4.54)	**0.014**
Component 5	3	0.715	2.75 (2.96)	3.33 (3.08)	2.23 (2.75)	**0.013**