Perceived Cognitive Functioning and Pain Interference Mediate Pain Predictive Effects on Health-Related Quality of Life in Pediatric Patients with Neurofibromatosis Type 1

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NF1 = Neurofibromatosis Type 1

HRQOL = health-related quality of life

PedsQL = Pediatric Quality of Life Inventory

PRO = Patient-Reported Outcome

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The PedsQL is available at http://www.pedsql.org.

Abstract

Objectives: The objective was to investigate the serial mediating effects of perceived cognitive functioning and pain interference in daily living in the relationship between perceived pain and overall generic health-related quality of life (HRQOL) in children, adolescents, and young adults with Neurofibromatosis Type 1 (NF1).

Methods: The Pain, Cognitive Functioning, and Pain Impact Scales from the PedsQL Neurofibromatosis Type 1 Module and the PedsQL 4.0 Generic Core Scales were completed in a multi-site national study by 323 patients ages 5-25 and 335 parents. A serial multiple mediator model analysis was conducted to test the hypothesized sequential mediating effects of perceived cognitive functioning and pain interference as intervening variables in the association between pain as a predictor and HRQOL.

Results: Pain predictive effects on overall generic HRQOL were serially mediated by perceived cognitive functioning and pain interference. In predictive analytics models utilizing hierarchical multiple regression analyses with age and gender demographic covariates, pain, perceived cognitive functioning and pain interference accounted for 66 percent of the variance in patient-reported generic HRQOL and 57 percent of the variance in parent proxy-reported generic HRQOL ($P < 0.001$), reflecting large effect sizes.

Conclusions: Perceived cognitive functioning and pain interference explain in part the mechanism of pain predictive effects on overall generic HRQOL in pediatric patients with NF1. Identifying NF1-specific pain, perceived cognitive functioning, and pain interference as salient predictors of overall generic HRQOL from the patient and parent perspective facilitates a family-centered orientation to the comprehensive care of children, adolescents, and young adults with NF1.

Introduction

Neurofibromatosis Type 1 (NF1) is a single-gene neurocutaneous disorder caused by a mutation in the gene encoding neurofibromin, and is the most common autosomal dominant disorder of the nervous system.[1-3] As a complex neurogenic chronic condition with wide variability in clinical manifestations,[1,4-6] NF1 can impact the central and peripheral nervous systems, with a predisposition toward the development of benign and malignant nervous system tumors.[7,8] Plexiform neurofibromas (peripheral nerve sheath tumors) are estimated to occur in approximately 25 to 50 percent of pediatric patients, with both asymptomatic and symptomatic plexiform neurofibromas manifested.[9,10] Further, NF1 has been demonstrated to have a significantly adverse impact on generic (general or nondisease-specific) health-related quality of life (HRQOL) in pediatric patients.[11]

Chronic and recurrent pain has been found to be a highly prevalent symptom in pediatric and adult patients with NF1, including peripheral neuropathic pain and headaches.[12-15] One of the major causes of neurogenic pain in NF1 are plexiform neurofibromas.[10,12,14] Prior research has shown that pain has a negative effect on overall generic HRQOL in pediatric chronic pain populations.[16-18] Additionally, the concept of " pain impact" or "pain interference" has emerged as a construct that measures pain-specific impact or interference with daily functioning.[16,19] The items in pain impact/interference scales include specific reference to the interference or impact caused by pain on daily activities.[19] Although these measures are typically multi-item scales, a recent study of pain interference in NF1 used a single item from an existing scale that was predictive of lower functioning.[20]

Cognitive functioning problems have also been identified as prevalent neurogenic manifestations in pediatric patients with NF1.[21] These neurocognitive deficits include difficulties

in executive functioning, memory problems, attention deficits, learning disabilities, and overall intellectual performance typically evidenced in the low average range, with moderate to severe impairment in one or more areas of cognitive functioning affected.[3,22,23] Estimated rates of cognitive dysfunction vary widely, with estimates ranging from 20 percent to as high as 80 percent of patients with NF1.[21,24]

Past research with other patient populations has demonstrated that chronic and recurrent pain has a deleterious effect on cognitive functioning.[25,26] Thus, while it would be expected that cognitive functioning problems in pediatric patients with NF1 would be exhibited as a consequence of their chronic health condition, it may be hypothesized that similar to other patient populations, pain would also have an additional deleterious direct effect on perceived cognitive functioning in these patients.

Previously, we investigated the direct effects of pain as a predictor variable of overall generic HRQOL in children, adolescents, and young adults with NF1.[27] A distinctive feature of the study was the inclusion of NF1-specific multi-item measurement scales developed specifically for NF1 through extensive cognitive interviews with children, adolescents, and young adults with NF1 and their parents,[28] rather than utilizing generic measures of these constructs. These NF1-specific multi-item measurement scales were subsequently nationally tested during the PedsQL Neurofibromatosis Type 1 Module field test study, demonstrating excellent reliability and validity.[29]

Nonetheless, unique to the current study, we are not aware of prior research which has investigated the hypothesized mechanism that may explain in part the predictive effects of pain on overall generic HRQOL in pediatric patients with NF1 utilizing an a priori conceptual model that includes NF1-specific perceived cognitive functioning and pain interference in daily living

as hypothesized sequential mediating variables. By understanding the mechanism in which pain affects overall generic HRQOL, treatment strategies may be developed to ameliorate in part the negative impact of NF1-specific pain on overall HRQOL by targeting the hypothesized intervening variables that may be potentially modifiable.

To address this significant empirical gap in the pediatric NF1 research literature, we utilized the database from the PedsQL Neurofibromatosis Type 1 Module field test study to test the hypothesized mediators of pain predictive effects on overall total generic HRQOL in pediatric patients with NF1. We investigate a serial multiple mediator conceptual model in which the serial (sequential) mediating effects of perceived cognitive functioning and pain interference in daily living are hypothesized as intervening variables in the relationship between pain and overall generic HRQOL. We conducted a serial multiple mediator analysis to test the following hypothesized conceptual model: pain → perceived cognitive functioning → pain interference in daily living → overall generic HRQOL in which the predictive effects of pain on generic HRQOL are mediated sequentially by perceived cognitive functioning and pain interference in daily living.

Methods

Participants and Settings

Pediatric patients with physician-diagnosed NF1 using the National Institutes of Health diagnostic criteria were recruited across the United States. Participants were recruited through the Children's Tumor Foundation (CTF) Neurofibromatosis (NF) registry, NF clinics at Indiana, Michigan, California, and Washington, D.C., and NF organizations including the Texas NF foundation, NF mid-west and NF network forums. A total of 343 families (323 pediatric patients ages 5-25 and 335 parents) participated.[29] Families completed the PedsQL measurement

instruments either using paper mode of administration (n = 204, 59.5%) at home or Internet electronic model of administration at home (n =139, 40.5%). The average age of the 169 males (49.3%) and 174 females (50.7%) was 12.38 years (SD = 5.89). With respect to race/ethnicity, the sample contained 256 (74.6%) White non-Hispanic, 23 (6.7%) Hispanic, 14 (4.1%) Black non-Hispanic, 3 (0.9 %) Asian/Pacific Islander, 1 Native American (0.3%), 30 (8.7%) Other, and 16 (4.7%) missing. Data collection for the field test took place between September 2015 and December 2016.[29] Parental informed consent and patient assent/consent (when age appropriate) were obtained. The research protocol was approved by the Institutional Review Board at Indiana University, Indianapolis (protocol # 1403632840).

Measures

PedsQL Neurofibromatosis Type 1 Module

The PedsQL Neurofibromatosis Type 1 Module items and scales were developed through qualitative and quantitative methods with pediatric patients with NF1 and their parents.[28,29] The PedsQL NF1 Module items were developed using detailed qualitative methods as recommended by the FDA[30] and the patient-reported outcomes (PRO) measurement literature,[31] including individual cognitive interviews with patients and parents.[28,32] Based on the readability, clarity, and understandability of the items as perceived by the patients and parents, changes were made until no further changes were recommended by patients and parents, including the youngest patients.[28]

To measure the NF1-specific constructs for the present study, we utilized the following scales from the PedsQL Neurofibromatosis Type 1 Module: Pain Scale (6 items, e.g., “I have pain so much that I need medicine”), Cognitive Functioning Scale (15 items, e.g., “It is hard for

me to think quickly"), and Pain Impact Scale (16 items, e.g., "I have so much pain that I have to stop what I am doing").

The format, instructions, Likert response scale, and scoring method for the PedsQL Neurofibromatosis Type 1 Module scales are identical to the PedsQL 4.0 Generic Core Scales,[33] with higher scores indicating better HRQOL and hence lower symptoms and problems. The scales are comprised of parallel patient self-report and parent proxy-report formats. Patient self-report and parent proxy-report forms are specific for ages 5-7 (young child), 8-12 (child), 13-17 (adolescent), and 18-25 (young adult) and assess patient's and parent's perceptions of the patient's NF1-specific symptoms and problems. The items for each of the forms are essentially identical, differing in developmentally appropriate language, or first or third person tense. The instructions ask how much of a problem each item has been during the past 7 days using the PedsQL 5-point Likert-type response scale (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). To further increase the ease of use for the young child self-report (ages 5-7), the response scale is reworded and simplified to a 3-point scale (0 = not at all a problem; 2 = sometimes a problem; 4 = a lot of a problem). This simplification to a 3-point scale for the young child self-report is consistent with the PedsQL 4.0 Generic Core Scales as well as with all of the PedsQL disease-specific modules.[34]

Items are reverse-scored and linearly transformed to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that lower scores demonstrate more NF1 symptoms and problems and hence lower NF1-specific HRQOL. Scale Scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the Scale Score is not computed.[35] This accounts for the small differences in

sample sizes for some scales reported in the analyses. Although there are other strategies for imputing missing values, this computation is consistent with the previous PedsQL peer-reviewed publications as well as other well-established HRQOL measures.[34]

PedsQL 4.0 Generic Core Scales

The 23-item PedsQL 4.0 Generic Core Scales encompass: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items).[33,36] To create the Total Scale Score, the mean is computed as the sum of the items divided by the number of items answered in the Physical, Emotional, Social, and School Functioning Scales. The Total Scale Score measures overall generic HRQOL.[33] Higher scores indicate better HRQOL.

PedsQL Family Information Form

Participants completed the PedsQL Family Information Form which contains demographic information including the child's age, gender, and race/ethnicity.[33]

Statistical Analysis

Pearson product-moment correlation analyses were conducted to test the bivariate associations between the Pain, Cognitive Functioning, and Pain Impact Scales with the Generic Core Scales Total Scale Score. Bivariate correlation effect sizes are designated as small (0.10), medium (0.30), and large (0.50) in magnitude.[37] Predictive analytics models utilizing hierarchical multiple regression analyses were conducted to statistically predict the Generic Core Scales Total Scale Score by the Pain, Cognitive Functioning, and Pain Impact Scales after controlling for age and gender.[38] Age and gender, but not race/ethnicity, have been previously demonstrated to be statistically significant in univariate analyses with the Generic Core Scales Total Scale Score dependent variable for this database,[27] and hence are entered as demographic covariates in the multivariate analyses. Hierarchical multiple regression analyses tested the

change in the variance accounted for by perceived pain in Step 2, and cognitive functioning and pain interference in Step 3 (R^2 changes) after controlling for age and gender (coded male=1, female=2) in Step 1. R^2 values are reported for each step and the full model. Total R^2 is the percentage of variability in the outcome variable (HRQOL) explained by the full model (demographic covariates, predictor, mediators). R^2 effect sizes are designated as small (0.02), medium (0.13), and large (0.26) in magnitude.[37] These statistical analyses were conducted using IBM SPSS (Armonk, New York).

Mediator variables are hypothesized as the intervening mechanism to account in part for the relationship between a predictor variable and an outcome variable.[39,40] The predictor variable is hypothesized to have a direct effect on the outcome variable, as well as a potentially indirect effect through the mediator variables, which may clarify the mechanism linking the predictor variable to the outcome.

A serial multiple mediator model [41] was tested with perceived cognitive functioning and pain interference in daily living as hypothesized sequential mediators in the relationship between pain as a predictor variable and overall generic HRQOL as the outcome variable. Specifically, we tested the following serial multiple mediator model: pain → perceived cognitive functioning → pain interference in daily living → overall generic HRQOL. Indirect effects were tested utilizing 10,000 bias-corrected bootstrapped resamples with replacement yielding 95% confidence intervals. Significant indirect effects are demonstrated when the 95% confidence intervals do not include zero.[41] These analyses were conducted using the PROCESS macro for SPSS (processmacro.org) as described in Hayes.[42]

Results

Bivariate Intercorrelations between Pain, Cognitive Functioning, and Pain Impact/Interference Scales with Generic Core Scales Total Scale Score

Table 1 contains the means, standard deviations and bivariate correlations of the Pain, Cognitive Functioning, and Pain Impact (Interference) Scales with the Generic Core Total Scale Score for patient self-report and parent proxy-report. The Pain, Cognitive Functioning, and Pain Impact (Interference) Scales were significantly correlated with the Generic Core Scales Total Scale Score (all *P*s < 0.001), demonstrating large effect sizes.

Correlational analyses and independent samples *t*-tests were conducted to explore whether there were any significant age correlations or gender differences in the PedsQL NF1 Module scales for patient self-report and parent proxy-report. For patient self-report, increasing age was significantly correlated with lower (worse) Pain Scale scores (r = -0.37, $P < 0.001$), Cognitive Functioning Scale scores (r = -0.13, $P < 0.05$), and Pain Impact (Interference) Scale scores (r = -0.26, $P < 0.001$). For parent proxy-report, increasing age was significantly correlated with lower (worse) Pain Scale scores (r = -0.33, $P < 0.001$) and Pain Impact (Interference) Scale scores (r = -0.28, $P < 0.001$), but not Cognitive Functioning Scale scores (r = -0.09, $P > 0.05$).

For patient self-report, females reported lower (worse) scores than males on the Pain Scale (59.76 vs. 73.11, $t[321] = -4.71$, $P < 0.001$) and the Pain Impact (Interference) Scale (69.84 vs. 77.47, $t[320] = -2.68$, $P < 0.01$), but not the Cognitive Functioning Scale (55.57 vs. 60.14, $t[319] = -1.49$, $P > 0.05$). For parent proxy-report, females were reported as manifesting lower (worse) scores than males on the Pain Scale (62.22 vs. 71.43, $t[331] = -3.26$, $P < 0.001$) and the Pain Impact (Interference) Scale (71.49 vs. 80.14, $t[330] = -3.14$, $P < 0.01$), but not the Cognitive Functioning Scale (52.55 vs. 49.86, $t[330] = 0.89$, $P > 0.05$).

Hierarchical Multiple Regression Analysis Predicting Generic HRQOL

A hierarchical multiple regression analysis was conducted prior to the serial multiple mediator model analysis to determine the percentage of the variance accounted for in the Generic Core Scales Total Scale Score by the pain predictor variable and the perceived cognitive functioning and pain interference mediator variables after controlling for age and gender. As shown in Table 2, pain accounted for 38 percent of the variability in patient self-reported generic HRQOL and 34 percent of the variability in parent proxy-reported generic HRQOL in Step 2, after accounting for age and gender in Step 1. The perceived cognitive functioning and pain interference mediator variables together accounted for an additional 25 percent of the variability in patient self-reported generic HRQOL and 21 percent of the variability in parent proxy-reported generic HRQOL in Step 3, after accounting for the demographic covariates and pain predictor variable in Steps 1 and 2, respectively.

Serial Multiple Mediator Model Predicting Generic HRQOL

Controlling for age and gender, the serial multiple mediator model demonstrated that the total indirect effect of the pain predictor variable on generic HRQOL as estimated by the sum of the indirect effects for perceived cognitive functioning and pain interference was .4303 for patient self-report and .3835 for parent proxy-report, and different from zero as determined by the bias-corrected bootstrap 95% confidence intervals that were above zero for patient self-report (.3440, .5214) and parent proxy-report (.2617, .5034). Within the multiple mediator model, the serial indirect effects for pain → perceived cognitive functioning → pain interference in daily living → overall generic HRQOL was .0262 for patient self-report and .0088 for parent proxy-report, and the bias-corrected bootstrap 95% confidence intervals did not contain zero for patient self-report (.0130, .0455) and parent proxy-report (.0022, .0205). The full serial multiple

mediator model accounted for 66 percent of the variability for patient self-report generic HRQOL and 57 percent of the variability for parent proxy-report generic HRQOL ($P < 0.001$), demonstrating large effect sizes (see Table 2).

Discussion

The findings demonstrate that perceived cognitive functioning and pain-specific interference in daily living serially mediate the association between pain and overall generic HRQOL in pediatric and young adult patients with NF1. The mediators as a group (perceived cognitive functioning and pain interference in daily living) contributed an additional 25 percent of the variance in patient self-reported generic HRQOL and an additional 21 percent of the variance in parent proxy-reported HRQOL for their children beyond the direct effects of pain. These are unique findings not previously reported in the published empirical literature for pediatric and young adult patients with NF1. The full serial multiple mediator model accounted for 66 and 57 percent of the variance in overall generic HRQOL from the perspective of patients with NF1 and their parents, respectively, reflecting large effect sizes.

As comprehensively reviewed by Moriarty and colleagues, there are a number of theories postulated to delineate the pathophysiological mechanisms involved in the negative effect of chronic and recurrent pain on cognitive functioning.[25] These hypotheses include the competing of nociceptive stimuli for attentional resources, central nervous system neuroplastic changes resulting from persistent pain that undermine cognitive functioning, and neurochemical adverse effects that are a function of chronic and recurrent pain that interference with cognitive functioning. These theories as extensively reviewed by Moriarty et al. have varying levels of empirical support, with no one theory predominate in human or animal models.[25] It is essential to

note that even though patients with NF1 demonstrate brain structural abnormalities and differences in neural activation patterns within brain regions (in comparison to typically developing controls) that may be associated with cognitive impairment,[43-45] we hypothesized in developing our serial multiple mediator conceptual model that the experience of chronic and recurrent pain would additively further comprise perceived cognitive functioning in these patients. Thus, we hypothesized that individuals with NF1 are at even greater risk for cognitive impairment as a result of their pain experiences. Future research utilizing functional magnetic resonance imaging (fMRI)[44] and other pain research strategies,[26,46,47] will be needed to disentangle the complexities of pre-existing cognitive impairment and the potentially additional direct effects of pain on cognitive functioning in pediatric patients and young adults with NF1.

In the present study, the serial multiple mediator conceptual model further illustrates the complex relationship between perceived pain and overall generic HRQOL and may explain in part the mechanism linking pain to generic HRQOL. This conceptual model identifies potentially modifiable targets for treatment interventions to improve impaired generic HRQOL in pediatric patients with NF1. Specifically, chronic pain management strategies, including cognitive behavioral therapy techniques,[48] may help lessen the negative direct effects of pain on perceived cognitive functioning in pediatric patients with NF1, which in turn may reduce the negative effect of pain and perceived cognitive functioning on pain-specific interference in daily functioning, and subsequently in combination lessen the negative impact on overall generic HRQOL. Further, pharmaceutical interventions may facilitate coping with the attentional deficits in pediatric patients with NF1.[49] These emerging interventions for pediatric patients with NF1 may serve as important components of a comprehensive care approach in improving overall

HRQOL in these patients. Further intervention research will be necessary to determine the potential efficacy of these intervention strategies in pediatric patients with NF1.

The overall generic HRQOL in the present sample as measured by the PedsQL 4.0 Generic Core Scales is substantially impaired as evidenced by patient self-report and parent proxy-report, with the Total Scale Score of 65.47 for patient self-report being close to 20 points lower than published PedsQL data for healthy pediatric populations (83.84), while the parent proxy-report score of 63.47 is also substantially lower than healthy comparison data (82.70).[50] Though these scores are not matched for age and gender with the published healthy comparison data, they nevertheless provide a relative benchmark of impaired overall functioning.

The present study strengths include the inclusive age range of ages 5-25 years, the large sample size for this rare disease, the nationwide recruitment, and the testing of a unique predictive analytics model with NF1-specific pain, perceived cognitive functioning, and pain interference in daily living constructs as predictor and mediator variables. The inclusion of both patient self-report and parent proxy-report further increases the strength of the data although shared method variance may limit the generalizability of the findings since it may have inflated the associations among constructs. Additional limitations include the absence of information in the database regarding the characteristics of any families who declined participation, the sample was predominantly White non-Hispanic which may limit the generalizability of the findings to other race/ethnicity groups, and the existing database did not contain information on whether the children were in school at the time the measures were completed. Although parents were instructed that it was important for parents and children to complete the forms separately, given that the forms were completed at home, we were not able to monitor whether these instructions were followed. Additionally, no specific instructions were given to parents regarding form

administration if their child had a learning disability. Although participants completed the PedsQL using either paper or Internet electronic modes of administration, previous PedsQL research has demonstrated the measurement equivalence of these two modes of administration.[51]

The existing database also lacked data on specific clinical subgroups of patients such as those with plexiform neurofibromas.[10] Further, we do not have in the field test database information on the number of patients who were diagnosed with brain tumors.[52] However, it is important to note that there are neurocognitive deficits manifested by pediatric patients with NF1 that are not secondary to brain tumors, but which may result from minor brain malformations, white matter structural abnormalities and deficient neural response inhibition.[43,44,53,54] Thus, even in patients with NF1 who have not developed brain tumors, neurocognitive deficits may be manifested. We also do not have in our field test database information on the number of patients who received a comorbid diagnosis of attention-deficit-hyperactivity disorder (ADHD). However, executive functioning deficits have been found to be manifested in pediatric patient with NF1 regardless of whether they have received a comorbid diagnosis of ADHD,[55] suggesting that executive functioning deficits exist even in patients who are not diagnosed with ADHD. Lastly, it should be noted that the PedsQL Neurofibromatosis Module Cognitive Functioning Scale is a patient self-report and parent proxy-reported measure of perceived cognitive functioning. Recent research with adults with neuropathic pain found that pain was predictive of cognitive functioning as measured by neurocognitive subtests of standardized intelligence tests, particularly impacting memory and attention.[26] Nevertheless, whether generic measures of neurocognitive functioning such as those contained in standardized intelligence tests would generate similar findings as the current study in pediatric patients with NF1 is an area for future research.

In conclusion, the findings with these NF1-specific scales indicate that a serial (sequential) multiple mediator intervening mechanism explains in part how perceived pain may predict overall generic HRQOL in pediatric patients with NF1. This serial multiple mediator conceptual model and its findings may facilitate the development of future targeted interventions to improve the health and well-being of these pediatric and young adult patients. Further, the systematic utilization of NF1-specific measurement scales in clinical research and clinical practice may be imperative in identifying those patients who are in the greatest need of symptom-specific interventions to enhance their overall HRQOL.

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Table 1. PedsQL Neurofibromatosis Scales and Generic Core Scales Total Scale Score Bivariate Intercorrelations in Pediatric Patients with Neurofibromatosis Type 1

Neurofibromatosis Scales and Generic Core Scales Total Scale Score	Items	α	Mean	SD	*r**[1]	*r**[2]	*r**[3]	*r**[4]
Symptoms								
Pain	6	0.87	66.12	26.48	0.15[a]	0.49*	0.55*	0.64*
Skin Itch Bother	6	0.84	76.71	21.75	0.28*	0.31*	0.33*	0.55*
Skin Sensations	3	0.82	83.64	22.61	0.17*	0.31*	0.38*	0.50*
Mediators								
Speech Difficulties	4	0.93	64.89	30.22	—	0.33*	0.21*	0.42*
Health Communication	6	0.92	58.59	32.65	—	—	0.68*	0.59*
Worry	10	0.93	65.33	29.70	—	—	—	0.61*
Generic Core Total Scale Score	23	0.93	65.65	20.84	—	—	—	—

Note: *All *P*s < 0.001, except [a] *P* < 0.01.
SD = standard deviation. α = Cronbach's alpha internal consistency reliability.
r = Pearson product-moment correlation coefficient. Dash line = not applicable.
[1]Bivariate correlations with Speech Difficulties.
[2]Bivariate correlations with Health Communication.
[3]Bivariate correlations with Worry.
[4]Bivariate correlations with the Generic Core Scales Total Scale Score.
Effect sizes for Pearson *r* designated as small (0.10), medium (0.30), and large (0.50) in magnitude.
Lower scores demonstrate worse symptoms and problems.

Table 2. Hierarchical Multiple Regression Analyses with the Mediators Variables Predicting Generic Core Scales Total Scale Score Controlling for the Symptoms Predictors, Age, and Gender in Step 1 (data not shown)

Mediator Variables	Regression Values
Pain Predictor Model Step 2	
Speech Difficulties (β)	0.24*
Health Communication (β)	0.16[a]
Worry (β)	0.25*
R^2 change	0.19*
R^2 Full Model	0.61*
Skin Itch Bother Predictor Model Step 2	
Speech Difficulties (β)	0.21*
Health Communication (β)	0.20*
Worry (β)	0.29*
R^2 change	0.23*
R^2 Full Model	0.59*
Skin Sensations Predictor Model Step 2	
Speech Difficulties (β)	0.24*
Health Communication (β)	0.22*
Worry (β)	0.31*
R^2 change	0.30*

R^2 Full Model	0.56*

Note: *All *P*s < 0.001, except [a] *P* < 0.01.
β = Standardized regression coefficients (beta weights).
R^2 =Percentage of variability in the criterion variable (HRQOL) explained by the step.
R^2 effect sizes designated as small (0.02), medium (0.13), and large (0.26) in magnitude.