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Relationship between Whole-body Tumor Burden, Clinical Phenotype, and Quality of Life in Patients with Neurofibromatosis

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Abstract

Background: Patients with neurofibromatosis 1 (NF1), NF2, and schwannomatosis share a predisposition to develop multiple nerve sheath tumors. Previous studies have demonstrated that patients with NF1 and NF2 have reduced quality of life (QOL), but no studies have examined the relationship between whole body tumor burden and QOL in these patients.

Methods: We administered a QOL questionnaire (the SF-36) and a visual analog pain scale (VAS) to a previously described cohort of adult neurofibromatosis patients undergoing whole-body MRI. One sample t-tests were used to compare norm-based SF-36 scores to weighted population means. Spearman correlation coefficients and multiple linear regression analyses controlling for demographic and disease-specific clinical variable were used to relate whole-body tumor volume to QOL scales.

Results: 245 patients (142 NF1, 53 NF2, 50 schwannomatosis) completed the study. Subjects showed deficits in selected subscales of the SF-36 compared to adjusted general population means. In bivariate analysis, increased tumor volume was significantly associated with pain in schwannomatosis patients, as measured by the SF-36 bodily pain subscale (rho=-0.287, p=0.04) and VAS (rho=0.34, p=0.02). Regression models for NF2 patients showed a positive relationship between tumor burden and increased pain, as measured by the SF-36 (p=0.008).

Conclusions: Patients with NF1, NF2, and schwannomatosis suffer from reduced QOL, although only pain shows a clear relationship to patient's overall tumor burden. These findings suggest that internal tumor volume is not a primary contributor to QOL and emphasize the need for comprehensive treatment approaches that go beyond tumor-focused therapies such as surgery by including psychosocial interventions.

Keywords: neurofibromatosis 1, neurofibromatosis 2, schwannomatosis, quality of life, pain, nerve sheath tumor, whole body MRI, SF-36

INTRODUCTION

The neurofibromatoses, including neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis, are a group of related tumor suppressor syndromes that share a predisposition to develop multiple nerve sheath tumors. NF1 is the most common neurogenetic disorder with a birth incidence of approximately 1:3000; NF2 and schwannomatosis are less common, with an estimated birth incidence of 1:33000 for NF2 [Friedman., 1999]. Neurofibromas and schwannomas are the hallmark tumors of NF1, NF2, and schwannomatosis. Despite their benign histology, these tumors can cause significant morbidity, including disfigurement in NF1 patients, deafness and facial nerve weakness in NF2 patients, and chronic pain in schwannomatosis patients [Lu-Emerson and Plotkin., 2009a; Lu-Emerson and Plotkin., 2009b].

Previous investigations of patients with NF1 and NF2 have used both generic and disease-specific measures to demonstrate that neurofibromatosis patients have a reduced quality of life [Wolkenstein et al., 2001a; Page et al., 2006; Kodra et al., 2009; Neary et al., 2010b]. Studies using the Short Form-36 (SF-36) have correlated lower quality of life with increased disease severity in patients with NF1, and with communication, balance, and hearing difficulties in patients with NF2 [Wolkenstein et al., 2001a; Neary et al., 2010b]. However, no studies to date have investigated the possible relationship between internal nerve sheath tumors and quality of life in NF patients.

Our group has used whole-body MRI (WBMRI) to prospectively image adults with neurofibromatosis in order to determine their whole-body tumor burden [Plotkin et al., 2012]. Using WBMRI, along with the SF-36 and a visual analog pain scale (VAS), we assessed the association between tumor burden and quality of life in adults with NF1, NF2, or

schwannomatosis. Our primary goals were to compare quality of life between these related neurogenetic disorders and the general population and to identify any associations between tumor burden and quality of life.

MATERIALS AND METHODS

Whole-body MRI. We performed WBMRI in adult patients with NF1, NF2, or schwannomatosis, as previously published [Plotkin et al., 2012]. Inclusion criteria for the study included age ≥ 18 years of age; diagnosis of NF1, NF2, or schwannomatosis by clinical criteria [Mulvihill et al., 1990; Baser et al., 2002; MacCollin et al., 2005], ability to undergo MRI, and ability to provide written informed consent. Patients were drawn from a convenience sample of patients seen at the Neurofibromatosis clinics at Massachusetts General Hospital and University of Hamburg, Eppendorf, Germany. WBMRI scans were performed as previously described [Cai et al., 2009]. In brief, coronal short time inversion-recovery sequences were obtained without contrast on a 1.5T MR imager with integrated body coil. Scans were reviewed by a board-certified radiologist and tumors were segmented using computerized 3D-volumetry method developed for WBMRI [Cai et al., 2009]. Whole-body tumor burden was determined by recording the number and volume of internal nerve sheath tumors for each patient. Internal nerve sheath tumors captured include neurofibromas (in patients with NF1) and schwannomas (in patients with NF2 or schwannomatosis) of the peripheral nervous system, but do not include the central nervous system tumors such as vestibular schwannoma, meningiomas, and ependymoma, due to lack of clear visualization of the brain and spinal canal using this imaging technique.

Patient reported measures. Each patient completed the SF-36, version 1 and a visual analog pain scale at the time of screening for entry to the study. The SF-36 is a short questionnaire that asks patients to report on various aspects of their life over the past month. Scores are reported for 8 subscales: physical functioning, physical role, bodily pain, general health, vitality, mental health, social functioning, and emotional role. Score are also reported for two summary scales (the physical component summary scale and mental component summary scale) that combine aspects of the subscales to reflect a more general picture of quality of life [Ware, Jr. et al., 2007]. Norm-based scores were calculated for each respondent using the QualityMetric Health Outcomes™ Scoring Software 2.0 [Saris-Baglama et al., 2007]. This software transforms raw scores for each scale into a norm-based score with a mean of 50 and standard deviation of 10, using data from a representative sample of the 1998 non-institutionalized general US population. Analysis of norm-based scores rather than raw scores was chosen to allow greater comparability of our results to other studies which have used subsequent versions of the SF-36. For all SF-36 scales, higher scores reflect increased quality of life (i.e. better health, less pain) and lower scores reflect decreased quality of life.

The visual analog pain scale was presented as a 10 cm line. Subjects were instructed to place a mark on the line to reflect their pain level that day. The leftmost point of the line reflected no pain (score = 0) and the rightmost point of the line reflected worst pain ever (score = 10). Marks were measured to the nearest tenth of a centimeter to obtain a numeric pain scale score.

Statistical analysis. We calculated descriptive statistics for clinical and demographic factors for the entire study population. We used a one-sample t-test to compare the SF-36 norm-based scores of each diagnosis group to general population means weighted by age and gender to

correspond to our study population.[Ware, Jr. et al., 2007] We then used Spearman correlation coefficients and multivariable linear regression to analyze the relationship between whole body tumor volume and quality of life scales. Multivariate models were created separately for each QOL scale, using the norm-based SF-36 score or VAS pain score as the dependent variable. Thus, a total of 11 multivariate models were run for each diagnosis group. The log transformation of tumor volume was the primary predictor of interest in each model. Because the log of 0 is undefined, patients with no identifiable internal tumor volume were instead assigned a value of 0 for this variable. The suitability of the linear regression lines were checked by residual and diagnostic plots to confirm residuals were normally distributed for the significant predictors.

Additional demographic and disease-related factors available from the primary data collection were also included in multivariate analysis as follows: age, gender, and mode of inheritance (sporadic vs. familial disease) were included for all patient groups. For patients with NF1 only, we included self-reported presence or absence of scoliosis, glioma, learning disability, attention deficit hyperactivity disorder (ADHD) or seizures as well as the number of cutaneous neurofibromas (categorically rated as 0, 1-9, 10-100, and >100). For patients with NF2 only, we included the presence of cutaneous schwannomas, and the presence of meningiomas or other non-vestibular intracranial tumors. For schwannomatosis patients, no relevant disease-related characteristics were identified.

All statistical calculations were performed with SAS software (version 9.2, SAS Institute Inc, NC, USA). The study was approved by the institutional review boards at Massachusetts General Hospital; University of Hamburg, Eppendorf, Germany; and the Department of Defense. Written informed consent was obtained from all participants.

RESULTS

Study patients Between January 2007 and November 2010, a total of 245 patients underwent WBMRI and completed the SF-36 and visual analog pain scale. The cohort included 142 NF1 patients, 53 NF2 patients, and 50 schwannomatosis patients. Baseline demographic characteristics of the cohort are shown in Table 1. Among NF1 patients, the prevalence of NF1-related disease characteristics are as follows: 39% learning disability, 30% scoliosis, 15% glioma, 14% ADD/ADHD, 5% seizures. In addition, 16% of NF1 patients had no cutaneous neurofibromas, 15% had 1-9 cutaneous neurofibromas, 32% had 10-99 cutaneous neurofibromas, and 37% had 100 or more cutaneous neurofibromas. Among NF2 patients, 40% had at least one cutaneous schwannoma and 62% had at least one non-vestibular intracranial tumor (meningioma or cranial nerve schwannoma).

Patient reported outcomes The mean norm-based score for each diagnosis group on each SF-36 scale is shown in Table 2. Patients with NF1 had significantly lower scores on the physical functioning, physical role, general health, emotional role, and mental health subscales compared to weighted US population means ($p<0.05$ for all subscales). Compared with the general population, NF1 patients had significantly lower score on the mental component summary subscale ($p<0.005$), but not the physical component summary subscale.

Patients with NF2 had significantly lower scores on the physical function, physical role, general health and social functioning subscales compared to weighted US population means ($p<0.05$ for all). Overall, NF2 patients had significantly lower score on the physical component summary subscale ($p< 0.005$), but not the mental component summary subscale, compared with the general population.

Patients with schwannomatosis had significantly lower scores on the physical role ($p=0.04$) and bodily pain ($p=0.01$) subscales compared with weighted US population means. Overall, schwannomatosis patients had significantly lower score on the physical component summary subscale ($p<0.05$), but not the mental component summary subscale, compared with the general population.

Association between tumor burden and patient reported measures In bivariate analyses, the natural log of whole-body tumor volume was not related to any quality of life subscales for patients with NF1 or NF2. For patients with schwannomatosis, however, the log of whole-body tumor volume was significantly correlated to the SF-36 bodily pain subscale (rho= -0.29, $p=0.04$) and the visual analog pain scale (rho = 0.34, $p=0.02$). In multivariate analysis, however, the set of predictor variables used for schwannomatosis patients (i.e. tumor volume, age, gender, and mode of inheritance) was not significantly associated with any SF-36 scale or the VAS pain score (overall model significance $p>0.05$ in all cases). However, we note that the p-values for the multivariate models for the bodily pain SF-36 subscale and pain VAS were $p=0.08$ and 0.09, respectively, and within these models, log tumor volume had a relationship to pain ($p=0.01$).

While multivariate analysis of patients with NF1 did produce significant multivariate models (Table 3), log tumor volume was not significantly related to any SF-36 scale or the VAS in these models. Multivariate analysis of patients with NF2 revealed the only significant association of whole body tumor volume to QOL (Table 4). The full set of clinical and demographic variables significantly predicted the physical role ($p<0.01$, $R^2=.40$), bodily pain ($p<0.001$, $R^2=0.42$) and physical component summary scores ($p=0.01$, $R^2=0.28$) of the SF-36 in NF2 patients. Controlling for age, gender, mode of inheritance, presence of meningiomas, and presence of cutaneous schwannomas, increased tumor volume was significantly associated with

more bodily pain (β= -1.43, p=0.008) and with decreased physical summary scores (β= -1.60, p=0.007).

Association between other clinico-demographic factors and QOL While log tumor volume was not found to be associated with quality of life in the NF1 sample, age emerged as a strong predictor of quality life in this population across multiple subdomains. As shown in Table 3, the included clinical and demographic characteristics significantly predicted physical functioning, physical role, emotional role, social functioning, and mental health in patients with NF1, as well as their overall physical and mental summary scores ($p<0.05$, with $R^2= 0.13$ to 0.22). Within each of these models, increased age predicted decreased quality of life (β = -0.18 to -0.38, $p<0.01$ for all).

In addition, self-reported diagnosis of ADD/ADHD was a strong predictor of the psychological subdomains of the SF-36 in patients with NF1. ADD/ADHD diagnosis significantly predicted mental health, social functioning, and emotional role scores, as well as the overall mental summary score (β = -5.54 to -11.68, $p<0.001$ for all but social functioning, which had $p<0.05$). This would indicate that, controlling for confounding factors, adults with NF1 and ADHD have a mental health score that is on average, 10 points (one standard deviation) worse than NF1 patients without ADHD.

In patients with NF2, mode of inheritance (sporadic vs. familial disease) had a significant effect on multiple physical subscales of the SF-36. Controlling for other factors, patients with familial disease had on average greater physical role functioning, less bodily pain (represented as a higher score on this subscale), and increased physical summary scores. In addition, as in patients with NF1, increased age was a significant predictor of decreased physical role and

physical summary scores.

DISCUSSION

In this study, we used whole-body MRI, the SF-36, and a visual analog pain scale to examine the effect of internal tumor burden on quality of life in three closely related tumor-suppressor syndromes. Our findings agree with previous reports in which patients with all forms of neurofibromatosis suffer deficits in their quality of life [Wolkenstein et al., 2001a; Page et al., 2006; Neary et al., 2010b]. However, compared to previous work which revealed deficits in all domains of the SF-36, deficits in our study population appear to be restricted to specific domains. All patient groups showed a significant decrease in physical role, indicating that neurofibromatosis patients experience limitations in carrying out work and other activities due to their physical health.

Patients with NF2 had deficits primarily in the physical domain, as shown by their significant decrease in multiple physical subdomains of the SF-36 as well as the physical component summary score compared to the general population. In multivariate models, patients with NF2 showed the only significant relationship between internal tumor volume and quality of life. Controlling for potential demographic and clinical confounders, increased tumor volume was significantly associated with decreases in scores for the bodily pain and physical summary scales of the SF-36. For this reason, early identification of NF2 patients with high tumor burden may be helpful, since these patients may benefit from proactive interventions aimed at improving physical function and from close monitoring of pain.

Schwannomatosis patients also had decreased scores on multiple physical subscales of the SF-36. Bivariate analyses showed a significant relationship between increased tumor volume

and higher levels of pain, as measured by both the bodily pain subscale of the SF-36 and the VAS. While the mechanism is unknown, larger tumors may cause more pain by impinging on nerves or by secreting greater amounts of nociceptive factors. Pain is one of the most common presentations of schwannomatosis,[Merker et al., 2012] and this finding emphasizes the importance of proactive and aggressive treatment of pain in these patients.

While multivariate models predicting pain scores were not significant overall, we believe this reflects an imperfect understanding of disease characteristics related to schwannomatosis (leading to suboptimal *a priori* selection of predictor variable), as well as a low sample size. In post-hoc analysis excluding gender and mode of inheritance – which were not significant in any model for any disease group – the multivariate models that examine the relationship of tumor burden to pain were statistically significant in schwannomatosis patients in this post-hoc analysis (data not shown). More investigation is needed to expand on the possible role between internal tumor burden and pain in a relatively large cohort of schwannomatosis patients. Use of the International Schwannomatosis Database, sponsored by the Children's Tumor Foundation, may provide a way for investigators to recruit sufficient sample sizes for this type of investigation.

In contrast to patients with NF2 and schwannomatosis, patients with NF1 had significant deficits in the mental domains of the SF-36. The increased emotional burden of patients with NF1 compared to those with NF2 and schwannomatosis may result from the higher frequency of visible stigmata of their disease, which has been associated with higher levels of psychological stress [Granstrom et al., 2012]. The high frequency of cognitive deficits and behavioral difficulties in patients with NF1 may result in less functional coping strategies for emotional stressors [Kayl and Moore, III., 2000; Hyman et al., 2005]. As such, comprehensive psychosocial interventions may be particularly helpful for this patient population.

Patients with NF1 also have high rates of attention deficit disorder, which has previously been associated with psychological problems [Mautner et al., 2012]. Indeed, our multivariate models showed a strong association between diagnosis of ADD/ADHD and decreased scores in emotional role, social functioning, and mental health on the SF-36. While attention difficulties have been associated with impaired cognitive functioning in children with NF1 [Pride et al., 2012], little is known about the persistence of ADD symptoms into adulthood and their effect on cognitive and psychological functioning. Proactive identification and management of attention problems in adults with NF1 is warranted to improve cognitive functioning as well as to improve quality of life.

Finally, age was a consistent predictor of decreased quality of life for mental and physical SF-36 subscales in patients with NF1. The general population also shows consistent declines in physical subscales with increasing age; however, this is not the case for mental subscales [Ware, Jr. et al., 2007]. This unexpected decline in mental aspects of quality of life with increasing age in patients with NF1 warrants future research to examine the cause of and potential interventions to ameliorate this effect.

There are multiple reasons why our findings for the SF-36 may differ from previous results. Our particular sample may have less severe disease manifestations than those studied previously, which may explain why previous researchers have measured a greater deficit in quality of life.[Wolkenstein et al., 2001b; Neary et al., 2010a] However, if so, it is not clear why there would be differences among patient populations among these large tertiary NF centers. Additionally, our study sample size may not have been large enough within each diagnosis group to reveal all significant differences in the neurofibromatosis patients as compared to the general population. Finally, SF-36 norm-based scores for both US and German patients were calculated

from norming data collected from the United States population in 1998. While this allowed for consistent scoring across the entire study population, the application of US norms to German patients could skew our results. Additionally, shifts in population results since 1998 may have resulted in finding smaller than actual differences between NF and the general population. However, recent analysis comparing scores from a 2009 US sample to the 1998 based-norms found that while the 2009 norms were somewhat higher, this difference was not of a sufficient magnitude to be clinically meaningful.[Ware., 2011]

The limitations of our study include the use of a sample of convenience at two large referral centers. For this reason, our study population does not represent all patients with neurofibromatosis or schwannomatosis. Whole body tumor volumes were derived from coronal STIR images, and did not include intracranial or spinal tumors such as vestibular schwannomas, meningiomas, or ependymomas, which may also affect quality of life. However, presence of gliomas was included in multivariate models for NF1 patients and presence of meningiomas was included in models for NF2 patients to help account for any effects of these tumors on our analysis. In addition, our analysis was not able to address tumor location, which likely plays an important role in which subscales of quality of life are most affected at the individual level. Tumors of equal size located in the abdomen or pelvis as opposed to an extremity may cause extremely different impairments in pain, physical functioning, and ability to carry out activities of daily living.

Our analysis included multiple statistical comparisons. For this reason, some of the significant associations found between quality of life and our independent variables may be due to chance. In addition, because the SF-36 scales are intercorrelated, it is possible that significant associations are not independent, but rather reflect a single overarching association (e.g.,

between ADD/ADHD and psychological aspects of quality of life in patients with NF1). Future studies with more focused areas of inquiry are necessary to clarify these methodological issues and to confirm our results.

To do this, future studies of quality of life in NF patients should investigate specific areas of deficit with more tailored questionnaires, such as using validated scales for depression and anxiety to investigate mental health in NF1 and more comprehensive pain questionnaires for further investigations into the role of pain in NF2 and schwannomatosis. Investigations into the effects of ADD/ADHD and learning disability on quality of life should similarly use a standardized method of diagnosis.

In conclusion, in this large cross-sectional international study, we found that patients with NF1, NF2, and schwannomatosis suffer decreases in their quality of life compared to the general population. Different quality of life domains are affected to different degrees, and only pain shows a clear relationship to patients' tumor burden. Thus, proactive monitoring and aggressive treatment of pain related to internal tumors with pharmacologic, surgical, and complementary and alternative medicine interventions in patients with NF2 and schwannomatosis is needed. Additionally, these findings emphasize the need for a comprehensive approach to treatment that goes beyond tumor-focused therapies and includes psychosocial interventions to more effectively improve all domains of quality of life in these patients.

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Conflicts of Interest: None.

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Table 1. Demographic and clinical features of 245 study subjects

	NF Diagnosis		
	NF1	**NF2**	**Schwannomatosis**
Subjects	142	53	50
United States – n (%)	107 (75%)	43 (81%)	45 (90%)
Germany – n (%)	35 (25%)	10 (19%)	5 (10%)
Sex (% male)	46%	42%	52%
Mean (Median) age - years	38.7 (39) [range, 18 – 70]	39.7 (37) [range, 19 – 76]	47.6 (44) [range, 25 – 86]
Mean Age at Diagnosis - years	14.5	29.6	40.9
Inheritance			
Familial	30%	23%	14%
Sporadic	70%	77%	86%
Subjects with Internal Tumors			
Number of subjects (%)	85 (60%)	24 (45%)	35 (70%)
Tumor number – median (range)	4 (1-66)	2 (1-63)	4 (1-27)
Tumor volume – median (range)	105.4 ml (2.7-9106.1)	68.1 ml (1.2-3500.3)	32.0 ml (7.0-1371.5)

Table 2. Comparison of mean SF-36 scores between each diagnosis group and age- and gender-weighted U.S. population means

	NF1 (n=141)			NF2 (n=53)			Schwannomatosis (n=50)		
SF-36 Subscales	Study Mean	Weighted U.S. Pop Mean	p-value	Study Mean	Weighted U.S. Pop Mean	p-value	Study Mean	Weighted U.S. Pop Mean	p-value
Physical functioning	49.2	51.7	**0.006**	46.1	51.4	**0.002**	49.2	50.2	0.48
Physical role	48.0	51.5	**<0.001**	44.5	51.1	**<0.001**	46.6	50.2	**0.04**
Bodily pain	50.9	50.7	0.86	50.3	50.5	0.89	46.1	49.9	**0.01**
General health	48.6	50.4	**0.05**	42.8	50.4	**<0.001**	47.5	50.1	0.07
PCS	50.4	51.6	0.16	45.6	51.3	**<0.001**	47.2	50.1	**0.04**
Vitality	50.3	49.7	0.50	47.8	49.7	0.21	49.1	50.3	0.40
Social functioning	48.7	50.2	0.09	45.0	50.1	**0.002**	48.1	50.1	0.17
Emotional role	46.2	50.6	**<0.001**	47.4	50.4	0.09	47.9	50.2	0.16
Mental health	46.5	49.4	**0.004**	48.0	49.5	0.31	49.2	50.1	0.56
MCS	46.8	49.5	**0.009**	47.7	49.3	0.31	49.0	50.2	0.42

Differences that are significant by t-test at <0.05 are presented in bold. PCS = Physical Component Summary Score, MCS= Mental Component Summary Score

Table 3. Multiple linear regression results of selected SF-36 subscales in patients with NF1 (n=142)

	Physical Subscales			Mental Subscales			
Variables	Physical Function	Physical Role	Physical Summary	Emotional Role	Social Function	Mental Health	Mental Summary
Log Tumor Volume	-0.3	-0.51	-0.41	0.06	-0.29	-0.16	0.06
Demographic Covariates							
Age (in years)	**-0.20****	**-0.30*****	**-0.18****	**-0.38*****	**-0.21****	**-0.24****	**-0.29*****
Female	0.54	2.44	0.34	2.16	0.20	1.42	1.71
Familial disease	-2.53	0.50	-1.50	-0.57	-1.46	-0.46	-0.26
Clinical Covariates							
ADD/ADHD	1.20	-3.58	1.66	**-10.26*****	**-5.54***	**-9.97*****	**-11.68*****
Seizures	-6.99	**-9.18***	-7.15	**-11.34***	**-11.15****	-6.32	-8.30
Learning Disability	**-4.81***	-2.80	**-3.89***	-1.90	-2.30	-2.02	-1.02
Cutaneous Neurofibromas	0.96	0.64	1.01	0.81	0.31	-0.34	0.07
Scoliosis	0.43	1.30	0.61	-1.53	1.50	1.49	0.16
Glioma	-2.33	0.23	-2.34	0.86	-2.35	-3.33	-1.22

Note: Only subscales for which overall models were significant ($p<0.05$) are presented. Positive beta values indicate higher quality of life. For continuous variables (log tumor volume and age), beta values reflect the increase or decrease in norm-based SF-36 score for each unit increase of the predictor variable if the effect of all other variables were held constant. For categorical variables, beta values reflect the difference in mean norm-based SF-36 score when the variable is present (compared to when the variable is absent) if the effect of all other variables were held constant. *$p<0.05$, **$p<0.01$, ***$p<0.001$

Table 4. Multiple linear regression results of selected SF-36 subscales in patients with NF2 (n=53)

	Physical Subscales		
Variables	Physical Role	Bodily Pain	Physical Summary
Log Tumor Volume	-1.05	**-1.43****	**-1.60****
Demographic Covariates			
Age (in years)	**-0.31****	-0.11	**-0.23***
Female	3.72	-0.24	2.88
Familial disease	**9.13***	**14.53*****	**7.92***
Clinical Covariates			
Intracranial tumor (non-VS)	3.72	**6.57***	3.38
Cutaneous schwannoma	0.37	3.08	-2.51

Note: Only subscales for which overall models were statistically significant ($p<0.05$) are presented. Positive beta values indicate higher quality of life. For continuous variables (log tumor volume and age), beta values reflect the increase or decrease in norm-based SF-36 score for each unit increase of the predictor variable if the effect of all other variables were held constant. For categorical variables, beta values reflect the difference in mean norm-based SF-36 score when the variable is present (compared to when the variable is absent) if the effect of all other variables were held constant. *$p<0.05$, **$p<0.01$, ***$p<0.001$