European Journal of Paediatric Neurology 45 (2023) 36–46

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

journal homepage: www.journals.elsevier.com/european-journal-of-paediatric-neurology

Health-related quality of life of children with neurofibromatosis type 1: Analysis of proxy-rated PedsQL and CHQ questionnaires

Britt A.E. Dhaenens [a,b,*], André Rietman [b,c], Olga Husson [d,e], Rianne Oostenbrink [a,b,f]

[a] Department of General Paediatrics, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands
[b] The ENCORE Expertise Centre for Neurodevelopmental Disorders, Erasmus MC, Rotterdam, the Netherlands
[c] Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands
[d] Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, the Netherlands
[e] Department of Surgical Oncology, Erasmus MC, Rotterdam, the Netherlands
[f] Full Member of the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS), the Netherlands

ARTICLE INFO

Keywords:
Neurofibromatosis type 1
Quality of life
Health-related quality of life
Children
PedsQL
CHQ

ABSTRACT

This study aims to (1) investigate health-related quality of life (HRQoL) in children with Neurofibromatosis Type 1 (NF1) using the Pediatric Quality of Life inventory (PedsQL) and the Child Health Questionnaire (CHQ); and (2) compare the psychometric properties and content of these questionnaires in NF1 patients.

PedsQL and CHQ proxy-reports were administered to parents/caregivers of 160 patients with NF1 aged 5–12 years. HRQoL scores were compared with Dutch population norms using independent t-tests. Psychometric properties (feasibility and reliability) were assessed by floor/ceiling effects and Cronbach's alpha coefficient. A principal component analysis (PCA) with varimax rotation was performed to identify the data's internal structure. By content mapping, we identified unique constructs of each questionnaire.

Proxy-reported HRQoL was significantly lower on all PedsQL subscales for children aged 5–7 years, and on 4/6 subscales for children aged 8–12 years compared to norms. Significantly lower HRQoL was reported on 6/14 CHQ subscales (children 5–7 years) and 9/14 subscales (children 8–12 years). The PedsQL showed slightly better feasibility and reliability. The PCA identified two components, representing psychosocial and physical aspects of HRQoL, explaining 63% of total variance. Both questionnaires showed relevant loadings on both components. The CHQ subscales concerning parents and family were considered unique contributions.

Proxy-reported HRQoL of children with NF1 is significantly lower compared to norms on multiple domains. Both questionnaires adequately measure HRQoL in children with NF1. However, the PedsQL has slightly better psychometric properties, while the CHQ covers a unique dimension of HRQoL associated with disease impact on parents and family.

1. Introduction

Neurofibromatosis Type 1 (NF1) is a hereditary disorder with a reported birth frequency of 1 in 2.000 to 1 in 3.647 [1–4]. It is caused by a mutation in the *NF1* gene on chromosome 17q11.2 [5,6]. NF1 displays a wide range of disease manifestations in almost all organ systems [1,7,8]. Benign nerve sheath tumours, such as cutaneous and plexiform neurofibromas, are the most distinctive disease manifestations. Other manifestations include a variety of benign tumours and malignancies, skeletal abnormalities, cardiovascular disease, pain, and fatigue [8–11]. Cognitive impairment, emotional difficulties and behavioural problems occur frequently, with cognitive impairment being the most common neurological manifestation in paediatric patients [12].

Due to the abovementioned disease manifestations, NF1 can significantly impact Quality of Life (QoL). The World Health Organization (WHO) defines QoL as a multidimensional construct, comprising domains such as physical, social, emotional, and role functioning [13]. Health-related Quality of Life (HRQoL) reflects the impact of disease and treatment on QoL [14]. Studies have shown that children with NF1 and their parents report a significantly poorer HRQoL compared to population norms [15–17].

HRQoL can be measured with patient-reported outcome (PRO) measures. There are two types of HRQoL measures: generic and disease-

* Corresponding author. Department of General Paediatrics, Erasmus MC-Sophia Children's Hospital, Wytemaweg 80, 3015CN, Rotterdam, the Netherlands.
E-mail addresses: b.dhaenens@erasmusmc.nl (B.A.E. Dhaenens), a.rietman@erasmusmc.nl (A. Rietman), o.husson@nki.nl (O. Husson), r.oostenbrink@erasmusmc.nl (R. Oostenbrink).

https://doi.org/10.1016/j.ejpn.2023.05.010
Received 3 January 2023; Received in revised form 15 May 2023; Accepted 28 May 2023
Available online 30 May 2023

Abbreviations

CHQ	Child Health Questionnaire
HRQoL	Health-related Quality of Life
IRB	Institutional Review Board
NF1	Neurofibromatosis Type 1
OPG	Optic pathway glioma
PCA	Principal component analysis
PedsQL	Pediatric Quality of Life Inventory
QoL	Quality of Life

specific. Generic measures assess HRQoL in a general population and allow for a comparison between the HRQoL of patients and healthy population norms [18]. However, these measures often do not capture disease-specific problems and symptoms. In NF1, this is particularly relevant for skin manifestations and cognitive impairment. Only one disease-specific HRQoL questionnaire has been validated in children and adolescents with NF1 (The Neurofibromatosis Type 1 module of the PedsQL) [19], whereas multiple generic questionnaires are available.

The number of studies on HRQoL in children with NF1 have been relatively low. In addition, the use of different HRQoL measures in these studies prevents data comparison [15]. The aim of this study was twofold. First, to investigate HRQoL in Dutch children with NF1 using proxy-reports of two generic HRQoL-questionnaires: the Pediatric Quality of Life Inventory (PedsQL) [20] and the Child Health Questionnaire (CHQ) [21]. Second, to investigate whether one of these questionnaires would be more suitable to measure HRQoL in children with NF1, by studying the content and the psychometric properties of both questionnaires in this patient population.

2. Methods

This prospective cohort study was performed at the Sophia Children's Hospital in The Netherlands. PedsQL and CHQ proxy-reports are administered as part of regular care to parents/caregivers of children with NF1 that visit the outpatient clinic. This study contains data on patients aged 5–12 years old that visited the hospital from October 2016 through February 2020. Patients were eligible for the study when they met the National Institute of Health (NIH) diagnostic criteria for NF1 [22]. For each patient, one parent or caregiver was invited to complete the questionnaires through the digital "Kwaliteit van Leven in Kaart (KLIK)" (Dutch for Quality of Life in Clinical Practice) system one week prior to the visit to the outpatient clinic [23]. Informed consent for using routinely collected data was provided by the parents/caregivers of all participants (local Institutional Review Board (IRB) identifier MEC-2015-203).

2.1. PedsQL questionnaire

The PedsQL 4.0 Generic Core Scales measures HRQoL in children and adolescents with or without acute and chronic health conditions [24]. Consisting of 23 items, it has four subscales: 'Physical', 'Emotional', 'Social', and 'School functioning'. It provides three summary scales, consisting of a 'Physical Health Summary score', a 'Psychosocial Health Summary score' and a 'Total Scale score'. The proxy-reports for children aged 5–7 years old and 8–12 years old were used in this study. We used the PedsQL version that refers to the HRQoL of the past month. The parent/caregiver scores each item on a 5-point Likert scale. Each answer is then reversely scored and rescaled to a 0–100 scale. A higher score indicates better HRQoL. The PedsQL has shown adequate reliability and validity in various populations, including a healthy Dutch paediatric population [24,25].

2.2. CHQ questionnaire

The CHQ proxy-report with 50 items (CHQ-PF50) was used in this study [21]. This questionnaire assesses HRQoL in children and adolescents of 5–18 years old. It consists of 11 multi-item scales and four individual items that measure the health status over the last four weeks. Single items include 'Global health', 'Global behaviour', 'Change in health', and 'Family cohesion'. The CHQ also offers an overall Physical and Psychosocial health score based on the multi-item scales. The following scales are included in the physical domain: 'Physical functioning', 'Physical–social role limitations', 'General health perceptions', and 'Bodily pain'. The psychosocial domain consists of the 'Social–emotional/behavioural role limitations', 'Self-esteem', 'Mental health', 'General behaviour', 'Parental impact – emotion', 'Parental impact – time', and the 'Family activities' scales. The parent/caregiver scores each item on a 4 to 6-point Likert scale. Each answer is rescaled to a 0–100 scale. A higher score indicates better HRQoL. The psychometric properties were proven adequate in multiple studies and countries, including the Netherlands [21,26,27].

2.3. Clinical characteristics

Information on demographics, mutation type (familial/de novo), date of NF1 diagnosis, and the presence of NF1-related manifestations was extracted from electronic health records. Extracted manifestations were plexiform neurofibroma, optic pathway glioma (OPG), low grade glioma, epilepsy, scoliosis, any osseous lesion (defined as sphenoid dysplasia and/or vertebrae dysplasia and/or long bone dysplasia and/or tibial bowing with or without pseudoarthrosis), Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), and attending special needs education.

2.4. Statistical analysis

Data were analysed using SPSS 28.0.1.0. Patients could visit the outpatient clinic multiple times during the study period. All completed questionnaires were included in the analysis of the psychometric properties. For all other analyses, only each patient's first completed PedsQL and CHQ were included. Descriptive analyses were calculated using the mean, standard deviation (SD) and range for continuous variables, and count and frequency for categorical variables.

PedsQL and CHQ scores were computed according to their respective manuals [21,28]. The following analyses were performed separately per age group (5–7 years and 8–12 years), mirroring the age groups of the PedsQL proxy-reports. Subscale scores were compared with a healthy Dutch reference population. A non-parametric test would have been appropriate, given the non-normal distribution of the data. However, we used independent t-tests and effect sizes as only the mean and SD of the population norms were available. Effect sizes were assessed using Cohen's d; $0.20 \leq d < 0.50$ was considered small, $0.50 \leq d < 0.80$ as medium, and a $d \geq 0.80$ was considered large [29]. Because only sex-specific PedsQL norms were available for children aged 8–12 years, we compared the HRQoL of this age group for boys and girls separately. A Bonferroni correction was applied to account for multiple comparisons, correcting for the number of multi-item subscales of each questionnaire (excluding summary scores).

We used the following healthy Dutch reference populations for our analysis. For the PedsQL, we used the studies of Schepers et al. and Hijkoop et al. [30,31]. In the first study, the authors used the PedsQL 4.0 questionnaire (acute version, 1-week recall) to assess HRQoL in 274 children from the general Dutch population, aged 5–7 years old (median age 6.5 years), of which 56% were boys. In the study by Hijkoop et al., the PedsQL 4.0 questionnaire (non-acute version, 1-month recall) was used to measure the HRQoL of 300 Dutch schoolchildren, aged 8–12 years old (median 11.0 years), of which 40% were boys. For the CHQ, we used the data from the study of Raat et al. [27]. In this study, the

CHQ-PF50 scores of 353 Dutch schoolchildren were reported. The age of the children ranged from 5 to 13 years of age (mean 8.8 years), and 48% were boys.

2.4.1. Psychometric properties analyses

Feasibility was assessed by calculating the mean, SD and range of the subscale and summary scores. Floor and/or ceiling effects were considered significant if ≥ 15% of the respondents appointed the lowest or highest absolute value. We calculated Cronbach's α to evaluate the reliability and internal consistency of the subscales. A Cronbach's α ≥ 0.70 was considered adequate [32].

To evaluate the known-groups validity (the ability to discriminate between subgroups of children with and without a certain manifestation), Mann-Whitney U tests were performed with Bonferroni corrections. This analysis was performed for mutation type and manifestations that occurred in 20 patients or more: plexiform neurofibroma, OPG, scoliosis, ADHD, and attending special needs education. We hypothesized that lower HRQoL would be reported for patients with a de novo mutation, based on literature [15]. We also expected lower reported HRQoL for patients with plexiform neurofibroma, ADHD, and patients attending special needs education. For the manifestations OPG and scoliosis, we expected no significant differences in HRQOL, since these conditions tend to be mild or asymptomatic in this age group.

Spearman's correlation coefficient was used to study the concurrent validity between the summary health scores of the PedsQL and the summary scores of the CHQ.

2.5. Content mapping

Content mapping was performed to identify overlapping and unique constructs in questionnaire subscales. The mapping was performed by a PhD-student (BD) and an experienced neuropsychologist (AR). Subscales of the PedsQL could overlap with multiple CHQ subscales, and vice versa. A subscale was considered unique if it contained topics that were not covered by any subscale of the other questionnaire. The results of the content mapping were verified by studying the Spearman's correlation coefficients between the subscales.

2.6. Principal component analysis

We performed a principal component analysis (PCA) to identify the internal structure of combined questionnaire data. The PCA was performed for subscales that were considered overlapping in content. Following the content mapping, the CHQ subscales 'General health perceptions', 'Parental emotional impact', 'Parental time impact', 'Family activities' and 'Family cohesion' were excluded. Spearman's correlation coefficients (*r*) for all subscales were computed. Subscales were excluded from the PCA if they showed negligible correlations to all other subscales (r < 0.300). Consequently, the CHQ subscale 'Change in health' was excluded. The final PCA included all four PedsQL subscales and eight CHQ subscales. The PCA was conducted using varimax rotation. The Kaiser–Meyer–Olkin test (KMO) verified the sampling adequacy for the analysis, with a KMO of 0.86. The scree plot showed an inflexion that would justify the selection of three components. Because the sample size was small and the third component had an eigenvalue below 1.0, we decided to retain two components. Component loadings of ≥ 0.4 were considered relevant [33].

3. Results

Questionnaires were completed for 160 patients, consisting of 196 PedsQL and 209 CHQ questionnaires (Fig. 1). With the exception of one patient, all patients completed both the PedsQL and the CHQ on at least one occasion. After including only the first completed PedsQL and CHQ questionnaires per patient, 160 PedsQL and 159 CHQ proxy-rated questionnaires remained.

Eighty-eight of the children with NF1 were male (55%) (Table 1). The mean age at NF1 diagnosis was 3.3 years old (SD 2.7), and a de novo mutation was most common (108 patients, 71%). Questionnaires were most often completed by the mother (80%). Data on the presence of

Table 1
Demographical and clinical characteristics of the study population (n = 160). SD = standard deviation, ASD = autism spectrum disorder, ADHD = Attention-Deficit/Hyperactivity Disorder.

	Mean (SD) or range	*n*	% of patients
Patient characteristics			
Gender (male)		88	55
Age at NF1 diagnosis (years)			
Mean (SD)	3.3 (2.7)		
Range	0–12.8		
De novo mutation		108	71
Age at first questionnaire (years)			
Mean (SD)	8.4 (2.2)		
Manifestations (available for n = 152)			
Plexiform neurofibroma		37	23
Optic pathway glioma		20	13
Low grade brain glioma		11	7
Epilepsy		3	2
Scoliosis		28	18
Any osseous lesion		11	7
Attending special needs education		34	21
ASD		12	8
ADHD		43	27
Parent characteristics			
Mother		128	80
Father		29	18
Legal guardian		3	2

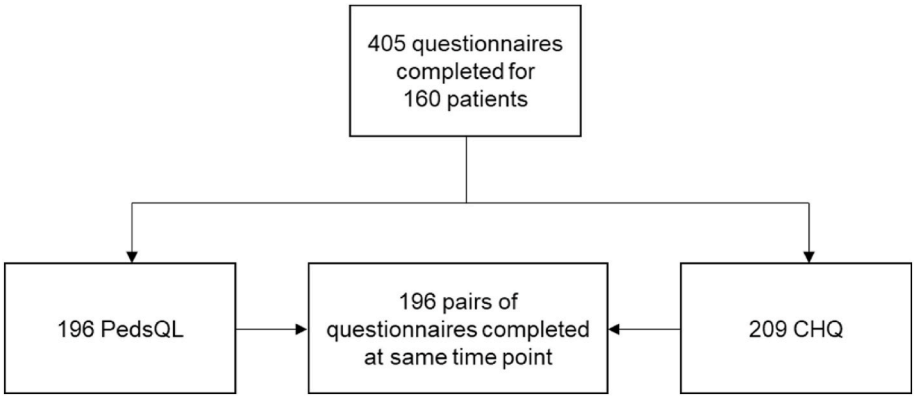


Fig. 1. Flowchart depicting the number of completed questionnaires in this study.

manifestations was available for 152 patients. The most common manifestations were ADHD (43 patients (27%)) and plexiform neurofibroma (37 patients (23%)).

3.1. HRQoL scores and comparison with reference values

Table 2 shows the mean subscale scores of the PedsQL. Parents/caregivers of the 5-7 year-old children with NF1 reported a significantly lower HRQoL on all subscales, the summary scores, and the Total Score compared to the reference population. The effect sizes ranged from 0.30 (small) to 0.68 (medium). For the 8-12 year-old boys, proxy-reported HRQoL was significantly lower on 'Social functioning', the Physical Health Summary score, the Psychosocial Health Summary score and the Total score. Effect sizes ranged from 0.47 (small) to 0.60 (medium). For girls of the same age-group, significantly lower HRQoL was reported on 'Social functioning', 'School functioning', the Psychosocial Health Summary score and the Total score, with effects sizes ranging from 0.52 to 0.69 (medium).

On the CHQ, a significantly lower HRQoL was reported on six out of fourteen subscales in the 5–7 age group, and for nine out of fourteen subscales in the 8–12 age group (Table 3). Effect sizes ranged from 0.33 (small) to 1.04 (large) in the 5–7 age group, and from 0.33 (small) to 1.02 (large) in the older children. The Physical summary score was significantly lower compared to the reference population for both age groups, but for the Psychosocial summary score this was only seen in the patients aged 8–12.

3.2. Psychometric properties

No significant floor effects were observed in either questionnaire (Table 4). For the PedsQL, significant ceiling effects were seen on two subscales of the 5–7 age group, and on four in the 8–12 age group. All Cronbach's alpha coefficients were adequate, ranging from 0.76 to 0.89. For the CHQ, a significant ceiling effect was seen in 10 out of 14 subscales in the younger age group, and in eight out of 14 subscales in the older patients. Cronbach's α ranged from 0.48 to 0.96. Internal consistency was adequate for 10 out of 11 multi-item subscales in the 5–7 age group, and for nine out of 11 multi-item subscales in the older patients.

For known-groups validity, both the PedsQL and CHQ were able to detect significant differences in HRQoL between patients with and without ADHD, and in children who attended special needs education vs. children who did not (Appendix A, Appendix B). Additionally, the CHQ revealed a significantly lower HRQoL on at least one subscale for patients with a de novo mutation and patients with OPG.

Concerning concurrent validity, a moderate to high positive correlation was found between the summary health scores of the questionnaires (Physical $r = 0.64$, $p < 0.001$; Psychosocial $r = 0.74$, $p < 0.001$).

3.3. Content mapping

The 'Physical functioning' subscale of the PedsQL was considered overlapping in content with the 'Physical functioning', 'Physical role functioning', and 'Bodily pain' subscales of the CHQ. The items in the 'Emotional functioning' subscale of the PedsQL were deemed overlapping with the 'General behavior' and 'Mental health' subscales of the CHQ. The 'Social' domain was similar in content to the subscales 'Emotional/behavioural role limitations', 'General behavior' and 'Self-esteem' of the CHQ. Finally, the 'School' domain was considered similar in content to the 'Emotional/behavioural role limitations', 'Physical role limitations' and 'General behavior' subscales of the CHQ. The CHQ subscales 'General health perceptions', 'Parental emotional impact', 'Parental time impact', 'Family activities' and 'Family cohesion' were considered unique contributions, containing topics that were not covered in the four subscales of the PedsQL. The results from the content mapping were mostly confirmed by studying the correlations between subscales (Appendix D). Subscales that overlapped in content, correlated stronger with one-another than with other subscales. Although not similar in content, all PedsQL subscales showed moderate correlation to one or more of the unique subscales of the CHQ, indicating that physical, emotional, social, and school HRQoL influences the impact of the condition on parents and family.

3.4. Principal component analysis

The PCA revealed a two-component model, explaining 62.6% of the total variance (Table 5). The subscales that clustered on the first PCA

Table 2
Comparison of the PedsQL subscale, summary and total scores with healthy Dutch reference populations per age group, and per sex for the 8–12 age group. Bonferroni-adjusted significance level of $\alpha = 0.05/4 = 0.013$. Reference populations:[1] = [31],[2] = [30].

PedsQL scale	NF1 patients 5–7 (n = 85)		Reference population 5–7 (n = 274)[1]		Effect sizes (Cohen's d)	p-value
	Mean	SD	Mean	SD		
Emotional functioning	72.4	18.4	77.9	16.7	0.30	**0.007**
Social functioning	72.6	21.8	86.4	16.7	0.63	< **0.001**
School functioning	76.7	18.1	85.8	15.4	0.51	< **0.001**
Physical Health Summary score	76.7	21.0	91.1	12.6	0.68	< **0.001**
Psychosocial Health Summary score	73.9	16.5	83.4	13.7	0.57	< **0.001**
Total score	74.9	16.9	86.1	11.6	0.66	< **0.001**
PedsQL scale	**Male NF1 patients 8–12 (n = 40)**		**Male reference population 8–12 (n = 121)[2]**		**Effect sizes (Cohen's d)**	**p-value**
	Mean	**SD**	**Mean**	**SD**		
Emotional functioning	68.2	16.0	72.9	14.0	0.30	0.066
Social functioning	72.7	21.4	85.5	13.4	0.60	< **0.001**
School functioning	74.1	18.1	77.5	15.2	0.19	0.243
Physical Health Summary score	79.0	21.6	90.5	11.0	0.53	**0.001**
Psychosocial Health Summary score	71.7	14.8	78.6	10.8	0.47	**0.005**
Total score	74.2	15.0	82.8	9.3	0.57	< **0.001**
PedsQL scale	**Female NF1 patients 8–12 (n = 35)**		**Female reference population 8–12 (n = 179)[2]**		**Effect sizes (Cohen's d)**	**p-value**
	Mean	**SD**	**Mean**	**SD**		
Emotional functioning	67.3	21.0	72.9	16.2	0.27	0.123
Social functioning	69.1	22.9	85.0	14.8	0.69	< **0.001**
School functioning	71.7	18.1	84.1	13.3	0.68	< **0.001**
Physical Health Summary score	84.2	19.0	88.3	11.3	0.22	0.209
Psychosocial Health Summary score	69.4	18.0	80.7	11.6	0.63	< **0.001**
Total score	74.5	16.9	83.4	10.4	0.52	**0.004**

Table 3
Comparison of the CHQ subscale and summary scores with a healthy Dutch reference population per age group. Bonferroni-adjusted significance level of α = 0.05/12 = 0.0042. Reference population[1] = [27].

CHQ-PF50 scale	Reference population 5–13 (n = 353)[1]		NF1 patients 5–7 (n = 78)				NF1 patients 8–12 (n = 81)			
	Mean	SD	Mean	SD	Effect sizes (Cohen's d)	p-value	Mean	SD	Effect sizes (Cohen's d)	p-value
General health perceptions	82.9	13.4	60.4	21.8	1.04	< **0.001**	66.1	16.5	1.02	< **0.001**
Physical functioning	99.1	4.3	87.5	16.4	0.71	< **0.001**	92.2	10.7	0.65	< **0.001**
Role functioning-emotional/behavioural	97.9	7.2	93.0	16.9	0.29	0.013	90.5	18.9	0.39	< **0.001**
Role functioning-physical	95.8	15.6	92.9	13.6	0.21	0.067	93.8	14.1	0.14	0.210
Bodily pain	85.7	17.2	73.3	21.5	0.57	< **0.001**	78.3	20.9	0.36	**0.002**
General behaviour	78.5	13.1	74.5	17.6	0.23	0.047	72.8	18.1	0.31	0.006
Mental health	81.4	12.1	80.7	14.7	0.05	0.678	76.1	15.8	0.34	**0.003**
Self-esteem	79.2	11.0	80.5	15.1	0.09	0.448	77.5	13.9	0.12	0.266
Parental emotional impact	86.3	15.2	74.8	21.1	0.55	< **0.001**	73.8	19.8	0.63	< **0.001**
Parental time impact	94.0	13.0	87.0	24.6	0.28	0.015	86.7	22.5	0.32	0.005
Family activities	91.5	11.9	83.7	23.5	0.33	**0.004**	84.3	21.5	0.33	**0.004**
Family cohesion	72.2	19.4	73.4	20.9	0.06	0.624	73.4	22.5	0.05	0.642
Physical summary score	56.4	5.7	47.5	9.4	0.94	< **0.001**	50.8	6.9	0.81	< **0.001**
Psychosocial summary score	53.2	6.4	52.2	9.6	0.10	0.385	49.7	9.8	0.36	**0.002**

Table 4
The range, percentage of floor and ceiling effect and Cronbach's alpha (internal consistency reliability) for the PedsQL and CHQ.

	NF1 population aged 5–7 years					NF1 population aged 8–12 years				
	n	range	% Min[a]	% Max[a]	Cronbach's α	n	range	% Min[a]	% Max[a]	Cronbach's α
PedsQL	111					85				
Physical functioning		15.6–100	0	13.5	0.89		28.1–100	0	**31.8**	0.89
Emotional functioning		25.0–100	0	10.8	0.76		35.0–100	0	12.9	0.80
Social functioning		10.0–100	0	**20.7**	0.84		0–100	1.2	**15.3**	0.85
School functioning		30.0–100	0	**19.8**	0.76		25.0–100	0	**20.0**	0.76
Physical summary health score		15.6–100	0	13.5	0.89		28.1–100	0	**31.8**	0.89
Psychosocial summary health score		28.3–100	0	6.3	0.80		23.3–100	0	7.1	0.81
Total score		32.6–100	0	4.5	0.86		33.7–100	0	7.1	0.83
CHQ	109					100				
Global health		30.0–100	0	**22.0**			30.0–100	0	**25.3**	
General health perceptions		5.0–100	0	3.7	0.71		17.5–100	0	2.3	0.48
Physical functioning		38.9–100	0	**42.2**	0.82		44.4–100	0	**49.4**	0.71
Role functioning - emotional/behavioural		0–100	0.9	**79.8**	0.93		0–100	1.1	**70.1**	0.92
Role functioning - physical		33.3–100	0	**77.1**	0.84		33.3–100	0	**80.5**	0.96
Bodily pain		20.0–100	0	**27.5**	0.89		20.0–100	0	**43.7**	0.94
General behaviour		5.0–100	0	5.5	0.82		8.3–100	0	8.0	0.83
Mental health		35.0–100	0	11.9	0.77		40.0–100	0	12.6	0.74
Self-esteem		41.7–100	0	12.8	0.84		37.5–100	0	12.6	0.80
Change in health		0–100	0.9	**17.4**			25.0–100	0	8.0	
Parental emotional impact		16.7–100	0	**18.3**	0.66		16.7–100	0	14.9	0.59
Parental time impact		0–100	1.8	**69.7**	0.90		0–100	1.1	**59.8**	0.83
Family activities		41.7–100	0	**38.5**	0.91		0–100	1.1	**43.7**	0.93
Family cohesion		0–100	0.9	**22.9**			0–100	1.1	**24.1**	
Physical summary score		22.4–61.9			0.94		27.8–62.2			0.75
Psychosocial summary score		15.7–65.6			0.90		18.2–64.6			0.92

Bold values = significant floor or ceiling effect, defined as ≥15% respondents having either the lowest or highest scale score.
[a] Min = percentage of respondents with minimum scale score, Max = percentage of respondents with maximum scale score.

component appear to represent the psychosocial aspect of HRQoL. The second component of the PCA seems to represent the physical aspect of HRQoL. Both questionnaires showed relevant loadings on both components. These data correspond with the content mapping results, and suggest that both the PedsQL and the CHQ adequately measure the two principal components that constitute HRQoL.

4. Discussion

Using PedsQL and CHQ parent-proxy reports, we studied the HRQoL in 160 Dutch patients with NF1 aged 5–12 years. Parents/caregivers of children with NF1 reported a significantly lower HRQoL on both the PedsQL and CHQ on a variety of domains, including physical, emotional, and social functioning. The psychometric properties of both questionnaires were adequate, but the PedsQL has slightly better feasibility and reliability. Following content mapping, the subscales for 'General health perceptions', 'Parental emotional impact', 'Parental time impact', 'Family cohesion', and 'Family activities' were considered unique contributions of the CHQ. The PCA revealed a two-component model, which suggested to represent the psychosocial and physical aspects of HRQoL. Both questionnaires showed relevant loadings on these components.

Proxy-reported HRQoL was significantly lower on multiple domains compared to the general Dutch paediatric population, which is in accordance with previously published literature [15]. For the PedsQL, the Summary Health scores and Total scores were significantly lower compared to norms, except for the Physical Summary score in girls aged 8–12 years old. While no data on PedsQL scores in NF1 patients aged 5–12 years have been published, parents of children with NF1 aged 12–18 years old in the USA reported relatively similar PedsQL scores [34]. In our study, a significantly lower HRQoL was reported on multiple

Table 5
Results of the principal component analysis.

Subscale	Psychosocial aspects	Physical aspects
CHQ		
Physical functioning		0.79
Role functioning - emotional/ behavioural	0.69	
Role functioning - physical		0.65
Bodily pain		0.70
General behaviour	0.86	
Mental health	0.81	
Self-esteem	0.69	
PedsQL		
Physical functioning		0.80
Emotional functioning	0.77	
Social functioning	0.77	
School functioning	0.61	
Eigenvalues	5.6	1.3
% of variance	50.6%	12.0%

subscales of the CHQ: on 6 out of 14 subscales in the 5–7 age group, and for 9 out of 14 subscales in the 8–12 age group. Similar findings were seen in a previous study in a Dutch NF1 paediatric patient population aged 10–18 years [16]. These results reveal the profound impact of NF1 on HRQoL of patients with NF1 and their parents/caregivers. Based on effect sizes, general health perceptions, physical functioning, and social functioning seem to be especially affected.

There were differences in HRQoL between male and female patients aged 5–7 years. When comparing the HRQoL scores of patients with a healthy reference population, only parents/caregivers of boys report a significantly lower HRQoL on 'Physical functioning', while only parents/caregivers of girls report lower HRQoL on the 'School functioning' domain of the PedsQL. Exploratory Mann-Whitney U tests revealed no significant differences in HRQoL between boys and girls in our study population (results not shown in manuscript). The association of sex and HRQoL in NF1 remains unclear, with previous studies showing mixed results [16,35,36].

This study showed that significantly lower HRQoL scores were reported by parents/caregivers of patients that attended special needs education and patients that suffered from ADHD. Some of the worst HRQoL scores are reported for these patients, which corresponds with evidence from the literature, indicating that learning, emotional, and behavioural issues could be predictors of Quality of Life in NF1 [15]. There have been few studies on how these issues impact the daily life of patients and their HRQoL [37]. Further research should be conducted into the functional implications of the presence and severity of learning and behavioural impairments, in order to improve HRQoL in this patient group.

Generally, the psychometric properties of the PedsQL and the CHQ were considered adequate. However, the PedsQL shows adequate internal consistency on all subscales, while the CHQ had two subscales with poor internal consistency coefficients. Internal consistency of all summary scores were sufficient to high. Ceiling effects were considerably more prevalent in the CHQ than in the PedsQL. These could partly be explained by the study sample, which also included less severely affected patients. Nonetheless, it could imply that items in generic HRQoL-questionnaires may not always be relevant to children with NF1, although disease-specific HRQoL questionnaires also display ceiling effects [19]. Ceiling effects could prove problematic when trying to distinguish among groups of patients with high HRQoL and may complicate detecting changes on affected subscales.

The content mapping of the questionnaires revealed five domains that were considered unique to the CHQ: the domains that assess general health perceptions, the emotional and time impact on parents, and the impact on family activities and family cohesion. In addition to the impact of NF1 on HRQoL of the patient, the CHQ therefore also assesses the impact of the disease on the parents themselves and on the family as a whole, which is not covered by the PedsQL. Parents reported a significantly lower HRQoL on four out of five of these unique subscales for both age groups in our study, with only the subscale 'Family cohesion' showing no significant difference compared with the reference population. Information on these subscales could be especially relevant for NF1-centres that offer family-centred care. This more extensive assessment of HRQoL of the CHQ does lead to an increased time of completion, however. While the proxy-report of the PedsQL takes around 4 min to complete [38], the CHQ-PF50 form requires approximately 10–15 min [21]. Increased effort for patients to complete these measurements could lead to lower compliance and response rates, which should be taken into considerations when choosing outcome measures.

Harmonization of outcome measures in clinical care and clinical trials facilitates data-sharing and comparison of data across institutions and countries, which is especially important in rare conditions like NF1. The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration tries to reach a consensus on the most appropriate outcome measures to use in clinical trials for NF. Recently, they have provided a list of recommended PRO measures to measure QoL [39]. For paediatric trials, the PedsQL received the highest overall rating and was most recommended by REiNS. The CHQ questionnaire was ranked relatively low in their review due to various reasons, including irrelevance of some items for NF, possible problems with ceiling effects, and poor internal consistency for some subscales. The last two points can also be observed in our data. Following this recommendation, the PedsQL might be a better option if data comparability is anticipated to be an important aspect of a trial, since the recommendation by REiNS may most likely result in more frequent use of the PedsQL questionnaire.

Given the comparable psychometric properties and the results from the PCA, both questionnaires seem to adequately measure generic HRQoL in children with NF1. However, as mentioned previously, generic HRQoL measures do not capture disease-specific problems and symptoms. This is especially a problem in NF1, given the various disease manifestations in all organ systems with varying severity. The complexity of measuring HRQoL in NF1 is reflected in the number of subscales of the only disease-specific HRQoL questionnaire for NF1 in children, the Neurofibromatosis Type 1 module of the PedsQL. This questionnaire has 104 items (distributed over 18 individual scales) that cover a wide range of problems seen in children with NF1, including skin problems, the impact of pain and cognitive functioning [19]. It demonstrated excellent feasibility and good to excellent reliability, but takes longer to complete than the generic PedsQL. Further research is needed to establish whether generic HRQoL measures alone satisfactorily measure (a significant change in) HRQoL in NF1, or whether a more extensive assessment is preferred by adding disease-specific questionnaires.

This study's major strength is the relatively large overall sample size and the nationwide representativeness of the sample. The Sophia Children's Hospital is the main Dutch expertise center for NF1, and coordinates the national NF network in the Netherlands. A large part of the Dutch paediatric NF1 population visits our centre for follow-up, regardless of disease severity. The administration of the questionnaires was part of regular care. A small proportion of parents/caregivers (approximately 10%) did not receive the questionnaires at the first visit due to missing email addresses. A detailed inventory of the first four months of data collection revealed a response rate of 70%. The study sample can be considered representative for the NF1 paediatric population in the Netherlands.

Several limitations must be considered regarding the comparison of the HRQoL scores with the reference population. First, we used the PedsQL questionnaire that assesses HRQoL over the past month, while the study that supplied the data for the reference population of 5–7 year olds used the version that asks about the past week. Second, for the CHQ questionnaire, the reference population consisted of children aged 5–13

years old, while we performed the analysis for the children aged 5–7 years and 8–12 years separately, using this same reference population. The lack of data on the overall disease severity is another limitation. The general severity of NF1 can be assessed using the Riccardi scale [40]. However, this scale is based on the weighted presence or absence of certain clinical characteristics, but lacks information on the perceived disease burden by the patient, again highlighting the need for a validated HRQoL measure for patients with NF1.

Because we used proxy-report forms in this study, reported HRQoL scores might have been influenced by parent-related characteristics like demographics and parental health. In addition, since NF1 is autosomal dominantly inherited with a 50–70% de novo mutation rate [1,41], a significant number of patients with NF1 will have a parent that suffers from NF1 as well. As described in the literature and partly confirmed in this study, familial NF1 may be a protective factor in proxy-reports of QoL for children of all ages [15]. A further evaluation of the impact of parental NF1 status and other parental/caregiver characteristics on reported HRQoL scores should be considered.

5. Conclusions

Proxy-reported HRQoL of children with NF1 is significantly lower compared to the reference population on multiple domains. Both the PedsQL and CHQ show relevant loadings on the two PCA components and adequately measure HRQoL in children with NF1. The PedsQL has slightly better psychometric properties, making it more preferable to use as outcome measure in research. In contrast, the CHQ covers a unique dimension of HRQoL associated with disease impact on parents and family, making it conceivably more preferred if an extensive evaluation of HRQoL is needed, for instance in clinical care.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

Authors Britt Dhaenens, André Rietman and Rianne Oostenbrink conributed to the study concept and design. The data-analysis plan was developed by all authors. Preperation of the data, data analysis and the writing of the first draft of the manuscript were performed by Britt Dhaenens. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Supervision performed by Rianne Oostenbrink.

Ethics approval

This study was approved by the Ethics Committee of the Erasmus MC, Rotterdam (local Institutional Review Board (IRB) identifier MEC-2015-203).

Consent to participate

Informed consent for using routinely collected data was provided by the parents/caregivers of all participants.

Declaration of competing interest

All authors have no relevant financial or non-financial interests to disclose.

Appendix A. Known-groups validity of the PedsQL

PedsQL scale	Familial mutation (n = 44)		De novo mutation (n = 108)		p-value	No plexiform neurofibroma (n = 115)		Plexiform neurofibroma (n = 37)		p-value	No OPG (n = 132)		OPG (n = 20)		p-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Emotional functioning	75.8	18.6	69.9	18.8	0.027	71.5	18.8	71.7	19.3	0.957	72.1	17.9	68.8	23.8	0.538
Social functioning	77.1	21.1	73.2	22.0	0.287	74.4	22.6	73.6	19.7	0.630	74.9	21.1	70.2	25.8	0.466
School functioning	78.0	17.4	75.5	19.6	0.457	75.2	19.0	78.4	19.1	0.258	75.6	19.2	78.4	17.8	0.575
Physical Health Summary score	84.7	16.8	77.8	22.1	0.106	80.5	20.8	77.1	21.5	0.273	80.0	20.4	77.0	24.4	0.654
Psychosocial Health Summary score	76.9	16.0	72.8	17.2	0.082	73.7	17.2	74.6	16.5	0.754	74.1	16.6	72.4	19.4	0.811
Total score	79.7	15.1	74.6	17.1	0.043	76.0	16.9	75.4	16.5	0.702	76.2	16.4	74.0	19.2	0.703
PedsQL scale	**No scoliosis (n = 124)**		**Scoliosis (n = 28)**		**p-value**	**No special needs education (n = 118)**		**Special needs education (n = 34)**		**p-value**	**No ADHD (n = 109)**		**ADHD (n = 43)**		**p-value**
	Mean	**SD**	**Mean**	**SD**		**Mean**	**SD**	**Mean**	**SD**		**Mean**	**SD**	**Mean**	**SD**	
Emotional functioning	73.0	18.6	66.9	18.4	0.066	74.9	17.1	58.1	19.8	**< 0.001**	72.9	18.6	67.9	19.1	0.146
Social functioning	75.2	21.2	71.4	21.7	0.395	78.2	19.4	57.7	23.6	**< 0.001**	77.2	20.2	65.6	24.0	**0.003**
School functioning	76.7	18.7	73.3	20.7	0.474	77.3	19.1	70.8	17.8	0.035	79.3	18.1	66.6	18.3	**< 0.001**
Physical Health Summary score	79.5	21.2	79.6	19.8	0.918	81.6	20.0	71.3	23.0	**0.007**	81.3	20.4	74.7	22.1	0.076
Psychosocial Health Summary score	75.0	16.5	70.5	17.5	0.156	76.8	15.6	62.2	17.4	**< 0.001**	76.5	16.4	66.7	16.7	**< 0.001**
Total score	76.6	16.7	73.7	16.5	0.335	78.5	15.6	65.4	17.3	**< 0.001**	78.2	16	69.5	17.4	**0.002**

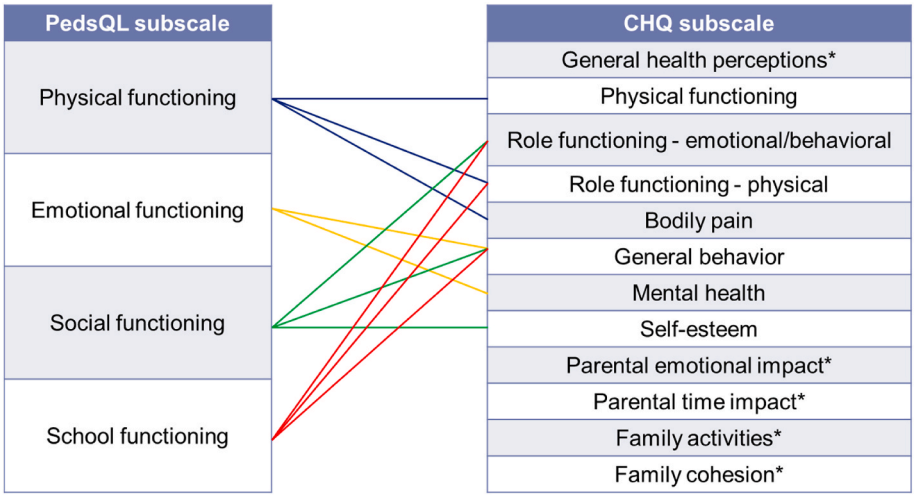
Known-groups validity of the PedsQL as assessed by the Mann Whitney *U* test. Significant p-values in bold. SD = standard deviation, OPG = optic pathway glioma. Bonferroni-adjusted significance level of $\alpha = 0.05/4 = 0.0125$.

Appendix B. Known-groups validity of the CHQ

CHQ-PF50 scale	Familial mutation (n = 44)		De novo mutation (n = 108)		p-value	No plexiform neurofibroma (n = 115)		Plexiform neurofibroma (n = 37)		p-value	No OPG (n = 132)		OPG (n = 20)		p-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
General health perceptions	72.3	18.5	60.1	20.7	**< 0.001**	65.4	20.4	59.8	21.4	0.106	66.6	19.6	48.6	21.0	**< 0.001**
Physical functioning	91.9	11.5	89.4	14.5	0.313	91.1	13.2	87.3	14.5	0.025	90.9	13.2	85.6	15.5	0.049
Role functioning – emotional/ behavioural	94.8	12.4	90.7	19.4	0.239	91.1	19.2	93.7	14.1	0.246	91.7	18.7	92.0	13.6	0.251
Role functioning – physical	95.8	11.3	92.4	15.2	0.092	93.8	14.5	91.5	15.4	0.309	93.0	15.1	94.3	12.0	0.866
Bodily pain	83.3	18.0	73.9	22.5	0.006	78.5	21.6	72.2	21.4	0.048	76.3	21.5	80.3	22.8	0.291
General behaviour	73.7	16.7	73.5	18.2	0.993	72.9	18.5	75.6	15.0	0.497	74.1	16.5	70.7	23.5	0.702
Mental health	79.8	16.3	78.8	14.9	0.506	79.1	15.6	78.7	14.8	0.813	79.2	15.4	77.6	15.8	0.638
Self-esteem	78.7	12.7	79.9	14.3	0.458	79.1	14.1	80.5	13.3	0.677	79.9	13.5	77.2	15.8	0.599
Parental emotional impact	79.3	18.8	73.4	21.9	0.079	75.2	20.5	75.5	22.9	0.677	75.8	21.1	72.1	21.2	0.318
Parental time impact	91.3	16.5	84.7	26.2	0.157	85.8	24.8	90.0	19.8	0.185	87.9	22.2	80.8	30.3	0.328
Family activities	86.0	19.8	82.1	24.1	0.397	83.8	22.7	82.8	23.3	0.788	83.8	22.8	81.8	22.8	0.566
Family cohesion	71.9	20.7	75.7	22.3	0.157	74.2	22.8	75.5	18.4	0.910	74.8	21.6	73.1	23.0	0.820
Physical summary score	52.8	7.0	48.0	9.3	**< 0.001**	50.2	8.4	47.2	9.9	0.031	49.9	8.9	46.8	8.0	0.022
Psychosocial summary score	51.7	8.7	51.0	10.1	0.919	50.7	10.1	52.6	8.3	0.415	51.4	9.3	49.9	11.8	0.886
CHQ-PF50 scale	**No scoliosis (n = 124)**		**Scoliosis (n = 28)**		**p-value**	**No special needs education (n = 118)**		**Special needs education (n = 34)**		**p-value**	**No ADHD (n= 109)**		**ADHD (n = 43)**		**p-value**
	Mean	**SD**	**Mean**	**SD**		**Mean**	**SD**	**Mean**	**SD**		**Mean**	**SD**	**Mean**	**SD**	
General health perceptions	64.8	20.7	61.7	18.7	0.333	66.0	19.1	56.0	25.1	0.030	64.8	20.2	61.9	22.2	0.403
Physical functioning	90.5	13.7	89.2	13.1	0.308	91.6	12.4	84.3	16.8	0.014	90.6	13.1	89.0	14.9	0.630
Role functioning – emotional/ behavioural	91.5	18.6	92.4	16.6	0.486	93.9	15.4	82.9	24.6	**< 0.001**	94.3	14.0	84.8	24.7	0.006
Role functioning – physical	93.4	14.9	91.9	14.8	0.455	94.5	14.2	88.0	15.7	**0.001**	94.7	11.6	89.2	20.5	0.178
Bodily pain	77.7	21.5	72.3	22.8	0.168	77.2	21.5	75.6	22.6	0.682	77.7	21.0	74.6	23.5	0.487
General behaviour	74.5	16.8	71.7	20.6	0.485	76.6	15.0	61.3	22.1	**< 0.001**	76.6	16.4	65.6	18.6	**< 0.001**
Mental health	80.0	14.9	76.4	16.7	0.270	60.7	14.7	71.2	16.3	**0.003**	80.2	14.6	75.8	17.1	0.103
Self-esteem	79.6	13.2	78.9	16.9	0.900	81.3	12.9	72.2	15.3	**0.001**	81.1	13.8	75.1	13.1	0.005
Parental emotional impact	76.7	20.4	71.0	22.8	0.177	78.0	19.7	63.9	22.6	**< 0.001**	78.8	20.2	65.7	20.5	**< 0.001**
Parental time impact	87.7	22.8	87.3	19.3	0.567	91.6	18.1	67.5	32.5	**< 0.001**	89.4	21.5	80.0	27.7	0.014
Family activities	84.0	22.9	81.9	23.4	0.561	88.1	18.0	64.7	32.5	**< 0.001**	87.5	18.5	72.9	29.2	**< 0.001**
Family cohesion	74.9	21.9	74.3	21.6	0.846	76.9	20.4	65.0	24.6	0.005	76.8	19.8	68.6	25.5	0.052
Physical summary score	49.7	8.8	48.3	9.1	0.168	50.2	8.3	46.4	10.2	0.026	49.9	8.2	48.3	10.4	0.641
Psychosocial summary score	51.7	9.3	50.3	10.9	0.594	52.9	8.1	44.1	12.3	**< 0.001**	52.8	8.8	46.8	10.6	**< 0.001**

Known-groups validity of the CHQ as assessed by the Mann Whitney *U* test. Significant p-values in bold. SD = standard deviation, OPG = optic pathway glioma Bonferroni-adjusted significance level of $\alpha = 0.05/12 = 0.0042$.

Appendix C. Visual representation of content mapping results



Appendix D. Spearman correlation coefficient between PedsQL and CHQ subscales

		CHQ												PedsQL			
		General health perceptions	Physical functioning	Role functioning – emotion/beh	Role functioning – physical	Bodily pain	General behaviour	Mental health	Self-esteem	Change in health	Parental emotional impact	Parental time impact	Family activities	Family cohesion	Physical functioning	Emotional functioning	Social functioning	School functioning
CHQ	General health perceptions	1.000																
	Physical functioning	0.477*	1.000															
	Role functioning – emotional/ behavioural	0.262*	0.260*	1.000														
	Role functioning – physical	0.365*	**0.527***	0.472*	1.000													
	Bodily pain	0.394*	0.342*	0.114	0.278*	1.000												
	General behaviour	0.321*	0.209*	**0.500***	0.324*	0.187*	1.000											
	Mental health	0.291*	0.246*	0.453*	0.357*	0.319*	**0.642***	1.000										
	Self-esteem	0.268*	0.343*	0.355*	0.293*	0.267*	**0.553***	**0.563***	1.000									
	Change in health	0.118	0.073	0.060	0.201*	0.182*	0.145*	0.063	0.216*	1.000								
	Parental emotional impact	0.495*	0.426*	0.460*	0.412*	0.290*	**0.615***	**0.534***	0.466*	0.204*	1.000							
	Parental time impact	0.381*	0.393*	**0.569***	0.467*	0.235*	0.474*	0.433*	0.371*	0.122	**0.550***	1.000						
	Family activities	0.417*	0.266*	**0.512***	0.447*	0.315*	**0.698***	**0.537***	0.472*	0.125	**0.611***	**0.650***	1.000					
	Family cohesion	0.121	0.125	0.226*	0.246*	0.207*	**0.515***	0.466*	0.388*	0.161*	0.361*	0.224*	0.407*	1.000				
PedsQL	Physical functioning	0.478*	**0.609***	0.337*	0.475*	0.493*	0.380*	0.372*	0.365*	0.016	0.459*	0.414*	0.444*	0.185*	1.000			
	Emotional functioning	0.372*	0.287*	**0.507***	0.419*	0.314*	**0.647***	**0.696***	0.439*	0.093	**0.558***	0.414*	**0.555***	0.364*	0.499*	1.000		
	Social functioning	0.407*	0.417*	0.487*	0.434*	0.165*	**0.564***	**0.529***	**0.523***	0.043	**0.537***	0.434*	**0.556***	0.307*	**0.562***	**0.596***	1.000	
	School functioning	0.263*	0.310*	0.444*	0.449*	0.174*	**0.560***	0.392*	0.430*	0.103	**0.502***	0.420*	0.432*	0.280*	0.498*	0.491*	**0.534***	1.000

Spearman correlation coefficients of the subscales of the PedsQL and the CHQ. Correlations flagged with * are $p < 0.05$. Correlations larger than 0.500 in bold. Emotion/behav = emotional/behavioural.

References

[1] D.G. Evans, E. Howard, C. Giblin, T. Clancy, H. Spencer, S.M. Huson, F. Lalloo, Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service, Am. J. Med. Genet. 152A (2) (2010) 327–332.

[2] M. Lammert, J.M. Friedman, L. Kluwe, V.F. Mautner, Prevalence of neurofibromatosis 1 in German children at elementary school enrollment, Arch. Dermatol. 141 (1) (2005) 71–74.

[3] M. Poyhonen, S. Kytölä, J. Leisti, Epidemiology of neurofibromatosis type 1 (NF1) in northern Finland, J. Med. Genet. 37 (8) (2000) 632–636.

[4] E. Uusitalo, J. Leppävirta, A. Koffert, S. Suominen, J. Vahtera, T. Vahlberg, M. Pöyhönen, J. Peltonen, S. Peltonen, Incidence and mortality of neurofibromatosis: a total population study in Finland, J. Invest. Dermatol. 135 (3) (2015) 904–906.

[5] D. Viskochil, A.M. Buchberg, G. Xu, R.M. Cawthon, J. Stevens, R.K. Wolff, M. Culver, J.C. Carey, N.G. Copeland, N.A. Jenkins, et al., Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus, Cell 62 (1) (1990) 187–192.

[6] M.R. Wallace, D.A. Marchuk, L.B. Andersen, R. Letcher, H.M. Odeh, A.M. Saulino, J.W. Fountain, A. Brereton, J. Nicholson, A.L. Mitchell, et al., Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients, Science 249 (4965) (1990) 181–186.

[7] J.O. Blakeley, S.R. Plotkin, Therapeutic advances for the tumors associated with neurofibromatosis type 1, type 2, and schwannomatosis, Neuro Oncol. 18 (5) (2016) 624–638.

[8] B.R. Korf, Neurofibromatosis, Handb. Clin. Neurol. 111 (2013) 333–340.

[9] D.H. Gutmann, R.E. Ferner, R.H. Listernick, B.R. Korf, P.L. Wolters, K.J. Johnson, Neurofibromatosis type 1, Nat. Rev. Dis. Prim. 3 (2017), 17004.

[10] R.E. Ferner, The neurofibromatoses, Practical Neurol. 10 (2) (2010) 82–93.

[11] C. Lu-Emerson, S.R. Plotkin, The neurofibromatoses. Part 1: NF1, Rev. Neurol. Dis. 6 (2) (2009) E47–E53.

[12] R.E. Ferner, S.M. Huson, N. Thomas, C. Moss, H. Willshaw, D.G. Evans, M. Upadhyaya, R. Towers, M. Gleeson, C. Steiger, A. Kirby, Guidelines for the diagnosis and management of individuals with neurofibromatosis 1, J. Med. Genet. 44 (2) (2007) 81–88.

[13] The world health organization quality of life assessment (WHOQOL): development and general psychometric properties, Soc. Sci. Med. 46 (12) (1998) 1569–1585.

[14] K. Haraldstad, A. Wahl, R. Andenæs, J.R. Andersen, M.H. Andersen, E. Beisland, C. R. Borge, E. Engebretsen, M. Eisemann, L. Halvorsrud, T.A. Hanssen, A. Haugstvedt, T. Haugland, V.A. Johansen, M.H. Larsen, L. Løvereide, B. Løyland, L.G. Kvarme, P. Moons, T.M. Norekvål, L. Ribu, G.E. Rohde, K.H. Urstad, S. Helseth, L. network, A systematic review of quality of life research in medicine and health sciences, Qual. Life Res. 28 (10) (2019) 2641–2650.

[15] A.M. Vranceanu, V.L. Merker, E.R. Park, S.R. Plotkin, Quality of life among children and adolescents with neurofibromatosis 1: a systematic review of the literature, J. Neuro Oncol. 122 (2) (2015) 219–228.

[16] L.C. Krab, R. Oostenbrink, A. de Goede-Bolder, F.K. Aarsen, Y. Elgersma, H.A. Moll, Health-related quality of life in children with neurofibromatosis type 1: contribution of demographic factors, disease-related factors, and behavior, J. Pediatr. 154 (3) (2009) 420–425, 425 e421.

[17] R. Oostenbrink, K. Spong, A. de Goede-Bolder, J.M. Landgraf, H. Raat, H.A. Moll, Parental reports of health-related quality of life in young children with neurofibromatosis type 1: influence of condition specific determinants, J. Pediatr. 151 (2) (2007) 182–186, 186 e181-182.

[18] D.L. Patrick, R.A. Deyo, Generic and disease-specific measures in assessing health status and quality of life, Med. Care 27 (3 Suppl) (1989) S217–S232.

[19] K. Nutakki, J.W. Varni, N.L. Swigonski, PedsQL Neurofibromatosis Type 1 Module for children, adolescents and young adults: feasibility, reliability, and validity, J. Neuro Oncol. 137 (2) (2018) 337–347.

[20] J.W. Varni, M. Seid, C.A. Rode, The PedsQL: measurement model for the pediatric quality of life inventory, Med. Care 37 (2) (1999) 126–139.

[21] J.M.A. Landgraf, Child Health Questionnaire (CHQ) : a User's Manual, Landgraf & Ware, Boston, Mass, 1999.

[22] Neurofibromatosis, Natl Inst Health Consens Dev Conf Consens Statement 6 (12) (1987) 1–7.

[23] L. Haverman, V. Engelen, M.A. van Rossum, H.S. Heymans, M.A. Grootenhuis, Monitoring health-related quality of life in paediatric practice: development of an innovative web-based application, BMC Pediatr. 11 (2011) 3.

[24] J.W. Varni, M. Seid, P.S. Kurtin, PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations, Med. Care 39 (8) (2001) 800–812.

[25] V. Engelen, M.M. Haentjens, S.B. Detmar, H.M. Koopman, M.A. Grootenhuis, Health related quality of life of Dutch children: psychometric properties of the PedsQL in The Netherlands, BMC Pediatr. 9 (2009) 68.

[26] J.M. Landgraf, E. Maunsell, K.N. Speechley, M. Bullinger, S. Campbell, L. Abetz, J. E. Ware, Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results, Qual. Life Res. 7 (5) (1998) 433–445.

[27] H. Raat, G.J. Bonsel, M.L. Essink-Bot, J.M. Landgraf, R.J. Gemke, Reliability and validity of comprehensive health status measures in children: the Child Health Questionnaire in relation to the Health Utilities Index, J. Clin. Epidemiol. 55 (1) (2002) 67–76.

[28] Varni, J. W. Scaling and Scoring of the Pediatric Quality of Life Inventory (PedsQL): Mapi Research Trust.

[29] J. Cohen, Statistical Power Analysis for the Behavioral Sciences, L. Erlbaum Associates, Hillsdale, N.J., 1988.

[30] A. Hijkoop, C.A. Ten Kate, M.J. Madderom, I.J. H, J.A. Reuser, H. Koopman, J. van Rosmalen, A.B. Rietman, Sex differences in children's health status as measured by the Pediatric Quality of Life Inventory (PedsQL)™: cross-sectional findings from a large school-based sample in The Netherlands, BMC Pediatr. 21 (1) (2021) 580.

[31] S.A. Schepers, H.A. van Oers, H. Maurice-Stam, J. Huisman, C.M. Verhaak, M. A. Grootenhuis, L. Haverman, Health related quality of life in Dutch infants, toddlers, and young children, Health Qual. Life Outcome 15 (1) (2017) 81.

[32] J.M. Bland, D.G. Altman, Cronbach's alpha, Br. Med. J. 314 (7080) (1997) 572.

[33] B.W. Hair Jf, B.J. Babin, R.E. Anderson, Multivariate Data Analysis: A Global Perspective, 10 ed., Pearson Education, Hoboken, NJ, 2010.

[34] M.M. Garwood, J.M. Bernacki, K.M. Fine, K.R. Hainsworth, W.H. Davies, B. P. Klein-Tasman, Physical, Cognitive, and Psychosocial Predictors of Functional Disability and Health-Related Quality of Life in Adolescents with Neurofibromatosis-1, 2012, Pain Res Treat, 2012, 975364.

[35] A. Graf, M.A. Landolt, A.C. Mori, E. Boltshauser, Quality of life and psychological adjustment in children and adolescents with neurofibromatosis type 1, J. Pediatr. 149 (3) (2006) 348–353.

[36] A. Roy, J.L. Roulin, C. Gras-Le Guen, M.L. Corbat, S. Barbarot, Executive functions and quality of life in children with neurofibromatosis type 1, Orphanet J. Rare Dis. 16 (1) (2021) 420.

[37] Y. Gilboa, S. Rosenblum, A. Fattal-Valevski, N. Josman, Application of the international classification of functioning, disability and health in children with neurofibromatosis type 1: a review, Dev. Med. Child Neurol. 52 (7) (2010) 612–619.

[38] J.W. Varni, T.M. Burwinkle, M. Seid, D. Skarr, The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity, Ambul. Pediatr. 3 (6) (2003) 329–341.

[39] P.L. Wolters, A.M. Vranceanu, H.L. Thompson, S. Martin, V.L. Merker, A. Baldwin, C. Barnett, K.S. Koetsier, C.M. Hingtgen, C.J. Funes, J.H. Tonsgard, E.K. Schorry, T. Allen, T. Smith, B. Franklin, S. Reeve, R.E.I. Collaboration, Current recommendations for patient-reported outcome measures assessing domains of quality of life in neurofibromatosis clinical trials, Neurology 97 (7 Suppl 1) (2021) S50–S63.

[40] V.M. Riccardi, B. Kleiner, Neurofibromatosis: a neoplastic birth defect with two age peaks of severe problems, Birth Defects Orig. Artic. Ser. 13 (3C) (1977) 131–138.

[41] R. van Minkelen, Y. van Bever, J.N. Kromosoeto, C.J. Withagen-Hermans, A. Nieuwlaat, D.J. Halley, A.M. van den Ouweland, A clinical and genetic overview of 18 years neurofibromatosis type 1 molecular diagnostics in The Netherlands, Clin. Genet. 85 (4) (2014) 318–327.