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Quality of life and correlating factors in children, adolescents with epilepsy, and their caregivers: A cross-sectional multicenter study from Germany

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ABSTRACT

Purpose: To identify factors correlating with poorer quality of life (QoL) in children and adolescents with epilepsy and regarding QoL and depression of their caregivers in Germany.
Method: A cross-sectional multicenter study on QoL and depression was performed in two representative German states (Hessen and Schleswig-Holstein). Variance analysis, linear regression, and bivariate correlation were used to identify correlating factors for poorer QoL and symptoms of depression.
Results: Data from 489 children and adolescents (mean age 10.4 ± 4.2 years, range 0.5–17.8; 54.0% male) and their caregivers were collected. We identified missing seizure freedom ($p = 0.046$), concomitant diseases ($p = 0.007$), hospitalization ($p = 0.049$), recent status epilepticus ($p = 0.035$), living in a nursing home or with foster parents ($p = 0.049$), and relevant degree of disability ($p = 0.007$) to correlate with poorer QoL in children and adolescents with epilepsy. Poorer QoL of caregivers was associated with longer disease duration ($p = 0.004$), non-idiopathic (mainly structural-metabolic) epilepsy ($p = 0.003$), ongoing seizures ($p = 0.003$), concomitant diseases ($p = 0.003$), relevant disability ($p = 0.003$), or status epilepticus ($p = 0.003$) as well as with unemployment of the primary caretaker ($p = 0.010$). Symptoms of depression of caregivers were associated with non-idiopathic epilepsy ($p = 0.003$), concomitant diseases ($p = 0.003$), missing seizure freedom ($p = 0.007$), status epilepticus ($p = 0.004$), or a relevant disability ($p = 0.004$) of their ward. A poorer QoL value of the children and adolescents correlated with a poorer QoL value of the caregivers ($p < 0.001$).
Conclusions: Epilepsy shows a considerable impact on QoL and symptoms of depression. Early and effective therapy should focus on reduction of seizure frequency and the probability for developing status epilepticus. Furthermore, comprehensive care should pay attention at comorbidities, consequences of disability and dependency on others.

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1. Introduction

Epilepsy is a common, chronic neurological disease with a clinical hallmark of recurrent seizures that places a major burden on patients, their caregivers, and society [1–3]. Moreover, disease-specific restrictions on self-sufficiency, mobility, career choice, family planning, and other social aspects as well as frequent epilepsy-related accidents and injuries have been shown to be associated with a reduced quality of life (QoL) and increased depression scores [4–7]. QoL is a complex and multidimensional construct representing the general "well-being" of individuals by outlining individual negative and positive aspects of life. In this respect, QoL quantifies more than just physical health and includes many different aspects, such as family life, education, employment, wealth, freedom, and environmental aspects as well as personal and financial safety [8,9].

A significant proportion of epilepsies have their onset in childhood [10]. Assuming a mean prevalence of 0.43% of epilepsy in children and adolescents in European countries, it can be surmised that more than 63,000 people aged younger than 18 years suffer from epilepsy in Germany [11]. To date, the available knowledge on QoL is limited in German children and adolescents with epilepsy and their caregivers, but several studies from other countries have suggested the existence of a decreased QoL in these populations, in line with findings in adult patients [12–19]. With more and more individualized anticonvulsant therapies being introduced and a strong trend towards individually tailored therapeutic approaches growing, physicians and therapists should be aware regarding which factors have an influence on the QoL of their epilepsy patients. Similarly, the QoL of the caregivers of these patients should be considered carefully, especially in view of trends towards depression, which has been shown to have a negative influence on their wards [20,21]. Several studies pointed out a high rate of depression for both mothers and fathers of children with epilepsy [22,23]. Moreover, a negatively impact on health related child QoL during the first 24 months after diagnosis has been revealed for maternal depression [24]. As possible reasons for increased prevalence of depression in caregivers, different psychosocial and medical factors have been discussed. Moreover, the importance of this multidirectional relationship of epilepsy, family environment, child and parent health as well as well-being has been strengthened by a large systematic review [7].

This study was performed as an explanatory analysis with the following research questions derived from previous publications: (1) Does QoL in children and adolescents correlate with different sociodemographical and disease specific aspects? (2) Does QoL in caregivers correlate with different sociodemographical and disease specific aspects? (3) Does QoL children and adolescents reciprocally correlate with QoL in their caregivers?

In addition, we quantified symptoms of depression in caregivers of children and adolescents with epilepsy, and determined their age adjusted QoL that was compared to QoL of the general German population.

2. Patients and methods

2.1. Study settings and design

The study was designed as a cross-sectional survey and enrolled patients from two representative German states (Hessen and Schleswig-Holstein, which together have over 8.5 million inhabitants) at multiple sites. Both states offer comparable infrastructural settings with large rural and metropolitan regions and a standardized, comprehensive medical supply. Data acquisition was performed in 2011 by nine neuropediatricians (NP), seven specialized centers for social pediatrics ("Sozialpädiatrische Zentren"; SPZ), and three large epilepsy centers (EC). After receiving written informed consent from the patients' parents or legal guardians, all children and adolescents younger than 18 years of age with medically confirmed epilepsy and their caregivers were deemed eligible, irrespective of seizure severity, duration of illness, and epilepsy syndrome. Participants were excluded when the diagnosis of epilepsy could not be confirmed, or participants had febrile convulsions only. For further details of the study protocol, please refer to Riechmann et al. [25]. The seizure and epilepsy syndrome classifications were adapted to the latest definitions of the International League Against Epilepsy [26,27]. The study had the approval of the local ethics committees.

2.2. Data assessment

The QoL values of children and adolescents were assessed using the age-adjusted and well-established KINDL^R questionnaire [28]. For children aged between four years and 11 years, the questionnaire by proxy was used, while older patients were asked to complete the self-reported version of the KINDL^R questionnaire as recommended [28]. Both versions of the KINDL^R calculate QoL using several items that are weighted and then summed to a score ranging from 0 (poor) to 100 (excellent) [28]. The KINDL questionnaire shows good internal consistency of item responses, factorial validity and invariance, as well as the convergent and known-groups validity of the child-report version and the parent-report version of the questionnaire [29].

The QoL and depression of caregivers was measured using the well-established EQ-5D [30–32] questionnaire and Beck Depression Inventory II (BDI-II) [33,34]. Following the recommendations of the BDI-II manual, caregivers with a BDI-II score of $\geq$13 points were classified as having symptoms of depression, and the subclassifications of minor (score: 13–19 points), moderate (score: 20–28 points), and severe (score $\geq$29 points) symptoms of depression were determined. Patients with a BDI-II score $<$ 13 points were classified as not having symptoms of depression [33,34]. In the case of two or more caregivers existing for the same patient, the most involved/primary caregiver was asked to complete the questionnaire to ensure reliable results. In children aged less than four years QoL could not be determined as KINDL^R questionnaires are not available for this very young age group. The caregivers completed only the BDI-II and EQ-5D questionnaires regarding their QoL and symptoms of depression. To correlate the measured items with sociodemographic- and disease-related aspects, seizure frequency, further chronic comorbidities, disability care situation, and treatment with anticonvulsants were assessed in detail, as described previously [25]. In short, information on the epilepsy syndrome, seizure frequency, anticonvulsant therapy and concomitant diseases were provided by the treating physician. In line with the ILAE guidelines seizure freedom was defined as credible absence of seizures for $\geq$12 month at study entry [26]. Level of disability is given to patients by the social security administration reflecting the overall amount of special needs of a patient. All other information was accessed using an established questionnaire for social and demographic aspects [25].

2.3. Data entry and statistical analysis

Data were entered using the File Maker Pro 8.5 database software (Filemaker Inc., Santa Clara, CA, USA) using a double-entry procedure to minimize possible data input errors. Statistical analyses were performed using the SPSS Statistics 22 software (IBM Corp., Armonk, NY, USA). For more information on the structure and interpretation of KINDL^R, BDI II, and EQ-5D, please refer to the available literature [28,30,31,34]. Variance analysis using a nonparametric Kruskal–Wallis test with post-hoc correction for multiple testing after Benjamini–Hochberg [35,36] was employed to identify potential correlating factors for lower QoL or depression. Linear regression was completed to analyze significant factors from the univariate analysis. Spearman correlation was applied to analyze for possible correlations between the QoL of children and adolescents and that or symptoms of depression of their caregivers. P-values of $<$ 0.05 after correction were regarded as being significant.

3. Results

3.1. Sociodemographic and clinical aspects of the study population

During the one-year study period, 489 children and adolescents with epilepsy and their caregivers were enrolled. The criterion of a minimum age of four years as a requirement for the KINDL^R questionnaire was met by 447 patients (92.2%), of which 392 (80.8%) provided completed questionnaires. Most patients (n = 253; 51.8%) were treated and enrolled by NP, followed by EC (n = 126; 26.0%) and SPZ (n = 110; 22.3%). Patients treated at SPZ were generally younger and had a shorter epilepsy duration as compared with patients treated at EC ($p < 0.001$, $p = 0.002$) or by NP ($p < 0.001$, $p = 0.012$). The mean age of participants at the time of study entry was 10.4 years (standard deviation: ± 4.2 years, range: 0.5–17.8 years). Additionally, the mean disease duration was 5.7 years (± 4.2 years, range 0–16 years), with a mean epilepsy onset occurring at an age of 4.7 years (± 4.3 years, range 0–17 years). Gender distribution in our study was nearly balanced, with 46% of participants being female and 54% of participants being male. The majority of children and adolescents (96.2%) were found to be living with one (21.1%) or both parents (75.1%), with only 3.8% being taken care of by relatives, foster parents, or in a nursing home. Most patients suffered from symptomatic focal (structural–metabolic) epilepsy (39.5%), followed by idiopathic (genetic) generalized epilepsy (27.2%), idiopathic (self-limited) focal epilepsy (12.7%), or other epilepsies and epileptic syndromes (20.6%). A degree of ≥ 50% of disability according to the definition of the §2 German Code of Social Law, Book IX was reported as being present in 206 patients (44.8%), and 335 (68.5%) participants indicated existing comorbidities. For more details on the sociodemographic- and disease-specific aspects of the present study's patient cohort, please refer to Table 1.

In line with the number of patients, 489 caregivers were enrolled in this study, most of them parents or relatives (97.2%). Mean age of mothers was 39.9 years (± 6.5, range 21–59) and of fathers 43.3 years (± 7.4, range 21–76). The overall employment rate of mothers (60.5%) and fathers (81.2%) was high.

Table 1
Sociodemographic and clinical characteristics of the study population.

Children and adolescents (n = 489)	
Age in years [a]	10.4 ± 4.2 [range: 0.5–17.8]
Sex, % (n)	
Female	46.0 (225)
Male	54.0 (264)
Epilepsy onset in years [a]	4.7 ± 4.3 [range: 0–17]
Epilepsy duration in years [a]	5.7 ± 4.2 [range: 0–16]
Seizures in the past 12 months, % (n)	
Persisting seizures	58.3 (285)
Seizure freedom (≥12 months)	41.7 (204)
Primary caregiver (household with), % (n)	
Both parents	75.1 (367)
One parent	21.1 (103)
Relatives, foster parents, nursing home	3.5 (17)
N/A	7.3 (2)
Epilepsy syndrome, % (n)	
Idiopathic focal epilepsy	12.7 (62)
Symptomatic focal epilepsy	39.5 (193)
Idiopathic generalized epilepsy	27.2 (133)
Symptomatic generalized epilepsy	6.7 (33)
Other generalized epilepsies	11.2 (55)
Other	2.6 (13)
Degree of disability, % (n)[b]	
None or < 50%	55.2 (254)
≥50%	44.8 (206)
Comorbidities	
Yes	68.5 (335)
No	31.5 (154)

N/A = not applicable.
[a] Mean ± standard deviation.
[b] After §2 German Code of Social Law, Book IX, in 29 patients no information available.

Table 2
Univariate correlation of personal, sociodemographic and disease related aspects with QoL of children and adolescents aged four years and older (n = 392).

	n	KINDL				p-Value*
		Mean	SD	Minimum	Maximum	
Age						
4–10 years	175	71.0	12.3	36.5	95.8	0.888
11–18 years	217	70.6	12.7	33.3	100.0	
Sex						
Male	209	70.0	12.9	33.3	97.9	0.423
Female	183	71.7	12.0	34.4	100.0	
Duration of disease						
0–2 years	107	72.2	12.6	34.4	95.8	0.423
3–10 years	198	71.0	12.0	40.2	100.0	
> 10 years	44	69.7	12.5	44.8	92.7	
Health care sector						
Neuropediatrician	198	69.9	13.0	34.4	100.0	0.422
Specialized center for social pediatrics	83	70.9	12.2	41.3	97.9	
Epilepsy center	111	72.3	11.8	33.3	92.7	
Epilepsy syndrome						
Idiopathic epilepsy	185	71.1	12.1	34.4	97.9	0.888
Non-idiopatic epilepsy	201	70.5	13.0	33.3	100.0	
Seizure freedom (≥ 12 months)						
Age 4–10 years						
Yes	79	72.0	12.1	40.2	95.8	0.652
No	81	69.8	12.7	36.5	95.0	
Age 11–18 years						
Yes	98	73.0	12.3	44.8	100.0	**0.046**
No	130	69.0	12.0	33.3	92.7	
Status epilepticus during the last 12 months						
Yes	30	62.4	14.7	33.3	89.6	**0.035**
No	285	71.3	12.2	34.4	97.9	
Other chronic disease						
Yes	249	68.6	13.2	33.3	95.0	**0.007**
None	143	74.6	10.2	34.4	100.0	
Primary caregiver(s)						
Both parents	290	71.3	12.2	36.5	100.0	0.691
One parent	87	70.4	12.6	34.4	94.8	
Biological parents/ relatives	377	71.1	12.2	34.4	100.0	**0.049**
Foster parents/nursing home	13	62.7	13.7	40.5	89.6	
Hospital stay						
Yes	72	68.0	13.5	33.3	88.9	**0.049**
No	262	72.2	12.6	36.5	100.0	
Level of disability						
None or < 50%	232	72.5	12.3	34.4	100.0	**0.007**
≥50%	139	68.2	12.1	40.5	92.7	

Bold print shows significant p-values < 0.5.
* p-Values were calculated using the Kruskal–Wallis test with post-hoc correction for multiple testing via the Benjamini–Hochberg method.

3.2. Correlating factors of QoL in children and adolescents with epilepsy

The mean QoL of the patients according KINDL^R questionnaire was 70.7 (± 12.5, range: 33–100). A lower QoL was significantly related with missing seizure freedom ($p = 0.046$) in children and adolescents between the ages of 11 years and 18 years. In addition, the presence of concomitant diseases ($p = 0.007$), recent hospitalization ($p = 0.049$), recent status epilepticus ($p = 0.035$), a relevant degree of disability ≥50% ($p = 0.007$), and residence in a nursing home or with foster parents ($p = 0.049$) were significant correlating factors of a lower QoL score. There were no significant differences in QoL with respect to patients' age, sex, duration of disease, etiology, family situation, or enrolling health care sector. For a detailed overview on the tested variables, please refer to Table 2.

A multiple regression analysis was performed for all children and adolescents to search for correlating factors between QoL and the significant findings of the univariate risk factor analysis using disability, status epilepticus, concomitant diseases, recent hospitalization, and the existence of primary caregivers as factors. Concomitant diseases and primary caregivers statistically correlated with QoL ($F = 5.07$, $p < 0.0001$, adjusted $R^2 = 0.068$).

3.3. QoL and symptoms of depression in caregivers

The QoL of caregivers was analyzed using both the index value (n = 462) and visual analogue scale (VAS, n = 366) of the EQ-5D score. For both items, longer disease duration (both: p = 0.004), non-idiopathic epilepsy (index: p = 0.003, VAS: p = 0.025), missing seizure freedom (both: p = 0.003), presence of concomitant diseases (both: p = 0.003), a relevant disability (index: p = 0.003, VAS: p = 0.046), recent status epilepticus (index: p = 0.003, VAS: p = 0.012), and unemployment of the primary caretaker (index: p = 0.010, VAS: p = 0.010) were significantly associated with lower QoL. EQ5-D VAS results were used to compare age group-specific QoL values with data from a healthy German population. Here, mean QoL was 81.5 (± 13.2, range: 50–100, n = 18) for caregivers in the age range of 20 years to 29 years; 76.1 (± 17.0, range: 10–100, n = 130) for caregivers in the age range of 30 years to 39 years; 76.3 (± 16.9, range: 20–100, n = 182) for caregivers in the age range of 40 years to 49 years; 77.0 (± 16.5, range: 40–100, n = 25) for caregivers in the age range of 50 years to 59 years; and 66.0 (± 22.6, range: 50–80, n = 2) for caregivers in the age range of 60 years to 69 years. For a comparison between the QoL of caregivers in our study population and that of a healthy German cohort, please refer to Fig. 1.

To better characterize the poor QoL in caregivers each single dimension of EQ-5D score was calculated to allow a differentiated interpretation of the results, p-values were corrected for multiple testing. The dimension “pain/discomfort” was the most relevant constrain being significant in 6 of 7 analyzed aspects (longer disease duration, non-idiopathic epilepsy, active epilepsy, history of status epilepticus, other chronic disease, and level of disability of 50% and more). The dimensions “anxiety/depression” were affected in 5 out of 7 analyzed aspects, “usual activities” in 4 out of 7, and “mobility” in 3 out of 5, for details please refer to Table 3. The dimension “self-care” did not contribute to the poor QoL in caregivers.

Symptoms of depression in primary caregivers were assessed using the BDI-II questionnaire. In 28.1% (n = 133) of caregivers, a BDI-II score of 13 points or more representing suspected depression was calculated, with 85 cases (18.0%) having mild, 37 cases (7.8%) having moderate, and 11 cases (2.3%) having severe symptoms of depression,

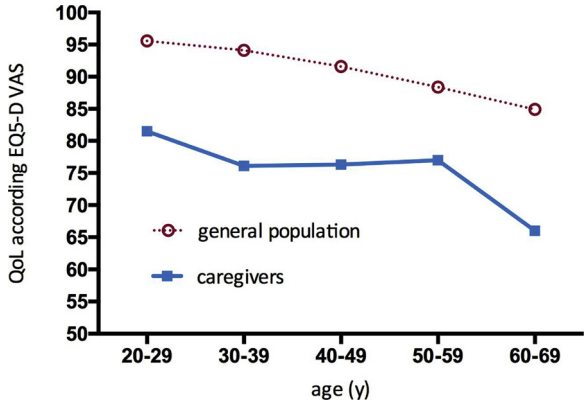

Fig. 1. QoL in caregivers of children and adolescents with epilepsy. As compared with a healthy German population [39], the QoL of caregivers of children and adolescents with epilepsy is lower in all age groups (measured using the VAS of the EQ5-D questionnaire).

respectively. The presence of a non-idiopathic epilepsy (p = 0.003), concomitant diseases (p = 0.004), missing seizure freedom (p = 0.007), status epilepticus (p = 0.004), and/or a relevant disability of the ward (p = 0.004) were associated with significantly increased symptoms of depression among caregivers. In contrast, disease duration, living in a one-parent household, and unemployment of the primary caretaker did not show a significant influence on the QoL of caregivers. For detailed information on the analyzed variables regarding QoL and symptoms of depression in caregivers, please refer to Table 3. As a measure for internal reliability, bivariate correlation between BDI-II score and the EQ5-D item “anxiety/depression” was performed. All calculated measures for correlation were highly significant (Spearman-Rho 0.001, Person 0.01, Kendall-Tau-b 0.01).

A multiple regression was run for all children and adolescents to search for correlating factors between QoL and depression from the significant findings of the univariate risk factor analysis. For QoL, duration of disease, epilepsy syndrome, seizure freedom, status epilepticus, concomitant diseases, disability, and unemployment were used. Disability and unemployment of the primary caregiver significantly correlated with a lower QoL ($F = 4.916$, $p < 0.0001$, adjusted $R^2 = 0.1$). For depression, epilepsy syndrome, seizure freedom, status epilepticus, concomitant diseases, and disability were analyzed. Presence of concomitant diseases in the patient was a correlating factor for caregiver depression ($F = 7.707$, $p < 0.0001$, adjusted $R^2 = 0.1$).

3.4. Correlation between the QoL of patients and the QoL and depression of caregivers

Spearman correlation revealed a significant positive correlation between the QoL of children and adolescents ($KINDL^R$) and the EQ-5D VAS ($r = 0.221$, $p < 0.001$) as well as between the $KINDL^R$ score and EQ-5D index ($r = 0.215$, $p < 0.001$) of their caregivers. A negative correlation was found between the QoL of patients ($KINDL^R$) and the depression of their caregivers (BDI-II: $r = -0.321$, $p < 0.001$). In addition, a negative correlation between depression (BDI-II) and QoL in caregivers was present (EQ-5D index: $r = -0.539$, $p < 0.001$; EQ-5D VAS: $r = -0.583$, $p < 0.001$).

4. Discussion

The present study was designed to identify factors correlating with poor QoL in children and adolescents with epilepsy as well as regarding QoL and depression of their caregivers in Germany. Therefore, a cross-sectional representative study population of children and adolescents was recruited by NP, SPZ, and EC. Age-specific established questionnaires were used to assess the chosen parameters and to help in the analysis for correlating factors.

The mean QoL of children and adolescents with epilepsy of ages four years to 17 years in our study population was 70.7 (± 12.5, range: 33–100). As compared with reference values from other studies conducted involving healthy German children with a mean QoL of 76.3 or 76.9, respectively [37,38], the patients with epilepsy in our study demonstrated poorer QoL. Within the study population, concomitant diseases, recent hospitalization, status epilepticus, and disability correlated with a lower QoL. In addition, missing seizure freedom was associated with a significantly lower QoL, but only in older children (i.e., those aged 11–18 years), a finding that may be attributed to the increasing importance of social acceptance, autonomy, and mobility in the pubescent adolescent population. These results are in line with those of a previous meta-analysis that identified comorbidity, active epilepsy, focal epilepsy, and seizure severity among others as relevant factors for decreased QoL [13]. In contrast to previous publications, however, we were not able to detect any significant influences of gender, age, or disease duration on the QoL of children and adolescents in our study population [13,37,38]. As possible reasons for this, either the time lag between both studies (2003–2006 vs. 2011) with different

Table 3
Univariate correlation of sociodemographic and disease related factors with QoL and depression of caregivers.

	EQ-5D Dimension p-value*					EQ-5D Index				EQ-5D VAS				BDI-II			
	Mobility	Self-Care	Usual Activities	Pain, Discomfort	Anxiety, Depression	n	Mean	SD	p-Value	n	Mean	SD	p-Value	n	No depression n (%)	Depression n (%)	p-Value
Duration of disease																	
0–2 years	0.105*	0.098*	0.126*	**0.004**	**0.031**	141	0.93	0.10	**0.004***	149	77.7	16.1	**0.004***	143	126 (88.1)	17 (11.9)	0.226
3–10 years						213	0.91	0.15		224	77.3	17.7		221	198 (89.6)	23 (10.4)	
> 10 years						64	0.87	0.16		67	69.9	16.4		64	52 (81.2)	12 18.8()	
Caregiver																	
Both parents	0.900*	0.364*	0.212*	0.204*	0.911*	354	0.92	0.14	0.243*	367	76.9	16.5	0.442*	355	315 (88.7)	40 (11.3)	0.237
Single parent						93	0.91	0.14		102	73.9	19.3		101	85 (84.2)	16 (15.8)	
Epilepsy syndrome																	
Idiopathic epilepsy	0.312*	0.254*	**0.006***	**0.004***	**0.004***	187	0.94	0.10	**0.003***	195	78.4	16.2	**0.025***	188	176 (93.6)	12 (6.4)	**0.003**
Non-idiopathic epilepsy						267	0.9	0.16		286	76.4	17.4		277	231 (83.4)	46 (16.6)	
Seizure frequency																	
Seizure remission	0.968*	0.966*	0.057*	**0.006***	**0.006***	105	0.91	0.10	**0.003***	285	79.3	16.2	**0.003***	198	184 (92.9)	14 (7.1)	**0.007**
Active epilepsy						357	0.92	0.15		204	70.4	17.6		275	231 (84.0)	44 (16.0)	
Status epilepticus																	
Yes	0.105*	0.173*	**0.004***	**0.049***	**0.030***	30	0.84	0.20	**0.003***	30	65.6	20.2	**0.012***	28	19 (67.9)	9 (32.1)	**0.004**
No						347	0.92	0.14		347	76.8	17.1		338	301 (89.1)	37 (10.9)	
Other chronic disease																	
None	**0.004***	0.126*	**0.004***	**0.004***	0.097*	147	0.96	0.07	**0.003***	154	82.6	12.7	**0.003***	149	143 (96.0)	6 (4.0)	**0.004**
Yes						315	0.90	0.16		335	73.5	18.1		324	272 (84.0)	52 (16.0)	
Level of disability																	
None or < 50%	**0.019***	0.160*	**0.004***	**0.004***	**0.004***	241	0.94	0.11	**0.003***	254	79.9	15.1	**0.046***	245	228 (93.0)	17 (7.0)	**0.004**
≥ 50%						196	0.88	0.16		206	72.6	18.5		202	163 (80.7)	39 (19.3)	
Employment status of primary caretaker																	
Not working	**0.000***	0.254*	0.900*	0.086*	0.623*	152	0.89	0.18	**0.010***	152	72.8	18.4	**0.010***	152	107 (70.4)	45 (29.6)	0.582
Working						302	0.94	0.09		302	77.9	16.2		302	220 (72.8)	82 (27.2)	

* p-Values calculated using the Kruskal–Wallis test with post-hoc correction for multiple testing via the Benjamini–Hochberg method.

improvements in AEDs, ambulatory care and seizure control, the number of enrolled subjects (2863 vs. 489) or differences in the surveyed population could be attributed (representative choice of a large national survey vs. regional multicenter-survey). However, there was also no difference in QoL regarding different health care sectors (i.e., NP, SPZ, EC).

Consistent with the findings in the children and adolescents, the results from caregivers revealed a remarkably poorer QoL in the VAS (study population: 76.2 versus reference: 84.3) of the EQ-5D questionnaire as compared with healthy controls [39].

In line with other studies [13,40], non-idiopathic (i.e. focal or generalized symptomatic, mainly structural-metabolic according to newest ILAE classification) epilepsy, missing seizure freedom, a concomitant disease, a relevant disability, incidence of status epilepticus, and unemployment of the primary caregiver were identified as potential risk factors for poorer QoL in the caregiver. Interestingly, a longer disease duration was associated with a poorer QoL in caregivers, but not so in patients themselves, which has already been described by Ferro et al. [13]. Though the exact reasons for this finding remain unclear, habituation and a different time perception in children and adolescents may contribute to this phenomenon [41]. Looking at the single items of the EQ-5D questionnaire, a differentiated pattern of significant sub scores for every factor correlating with a poorer QoL in caregivers became visible. For most tested categories, the item of "anxiety/depression" reached levels of significance, which underlines the strong effect of epilepsy on the mood of caregivers, which has been extensively shown for mothers and fathers in previous studies [22–24]. The item "Self-care" did not reach any level of significance in all analyzed factors, which might be explained by the fact that parents are usually not suffering from chronic illnesses themselves. Furthermore, the self-sacrifying behavior with unaccomplished desires and lifegoals has been already described in parents of children with epilepsy [42]. A recent publication showed a strong correlation between seizure severity and caregiver QoL in patients with medically intractable epilepsy, which could not be verified in the present study due to missing information on individual seizure semiology and severity [43]. QoL of children and adolescents positively correlated with QoL of their caregivers, in line with prior publications [13].

As an additional parameter for the epilepsy-related burden on caregivers, symptoms of depression were analyzed using BDI-II score. Overall, 28.1% (n = 133) of the caregivers met the criterion for depression, having a BDI-II score ≥ 13 points, which is low in comparison with other research that has reported depression rates of up 49% in caregivers [14]. BDI-II score and EQ-5D item "anxiety/depression" showed a significant correlation, which underlines the validity of both measurements.

In line with other publications, we identified missing seizure freedom, status epilepticus, presence of concomitant diseases, and a relevant disability of the ward as factors associated with depression among caregivers [14,44]. However, family circumstances like unemployment of the primary caregiver or living in a single-parent family did not show a significant impact on the existence of depression of caregivers, which is in contrast to the findings of other studies on this subject [14]. Here, especially regional and national differences, such as statutory social aids and unemployment compensation, could have had an influence on the particular results. In line with most other publications, though [20,21], our data show a significant negative correlation between the QoL of patients and symptoms of depression in caregivers, which underlines the secondary impact of the diseases of their wards on caregivers that has been shown to exist for many chronic neurological and non-neurological diseases in both adult and pediatric patients [45–49].

Despite the careful study design, this QoL study suffers from certain limitations inherent to such investigations. The chosen study design of a cross-sectional study does only allow to highline correlations, but no causal relationships can be drawn between the analyzed sociodemographical or disease related aspects. Furthermore the value of R^2 was low and might point to a high variation in answers. In addition, it should be noted that, as in the case of most regionally performed studies, unapparent regional or national factors could have led to bias in our analysis. Moreover, more cognitively restricted children may not have been able to answer the questionnaire by themselves. Given that disabled children have a lower QoL [50], the answering of the questionnaire by proxy may not accurately reflect the QoL of these patients. Furthermore, analysis of QoL in children was only possible in those 4 years of age and older, which decreased the numbers for correlation analysis. However, the design of the present study, which included a large population enrolled from multiple sites covering all health care sectors and which maintained consideration of the primary caregiver, should reduce the impact of possible biases to a minimum. Another limitation of this study refers to the transferability of its results to other publications on this topic from abroad due to different cultural acceptance and perception of depression. However, due to similar sociocultural aspects, our results should be comparable to other studies from Europe, the UK or Northern America. In contrast to the mentioned limitations, especially the high number of participants, the multi-center design and the use of established tools and questionnaires represent individual strengths of the present study. To further address the question of a causal relationship between different disease specific, social as well as demographical factors with QoL of children and adolescents with epilepsy as well as their caregivers, a longitudinal study is needed, which should be ideally based on a cohort with newly diagnosed epilepsy.

5. Conclusion

Taken together, the results of our study underline the burden of epilepsy on children and adolescents as well as their caregivers with respect to psychosocial consequences like QoL and depression. Especially in younger patients, diagnostic and therapeutic strategies often must be exhausted in an early stage of the disease so as to reach a sufficient seizure control, decrease the risk of status epilepticus, and reduce the frequency of inpatient admissions. In addition, a second focus should be set on the improvement of concomitant diseases and training or the acceptance of physical or cognitive disabilities to improve the QoL of patients and caregivers.

Conflicts of interest

R. Boor reports personal fees from Desitin Arzneimittel.

M. Kieslich reports personal fees from Bial, Desitin Arzneimittel, Eisai, Proveca and Shire.

S. Knake reports honoraria for speaking engagements from Desitin and UCB as well as educational grants from AD Tech, Desitin Arzneimittel, Eisai, GW, Medtronic, Novartis, Siemens and UCB.

S. Schubert-Bast reports personal fees from UCB, Eisai, Desitin Pharma, LivaNova and Zogenix.

F. Rosenow reports personal fees from Eisai, UCB, Desitin Arzneimittel, Novartis, Medtronic, Cerbomed, Sandoz, GW-Pharma, BayerVital and Shire, grants from the European Union, Deutsche Forschungsgemeinschaft and the Detlev-Wrobel-Fonds for Epilepsy research.

H.M. Hamer has served on the scientific advisory board of cerbomed, Desitin, Eisai, GW, Novartis, and UCB Pharma. He served on the speakers' bureau of or received unrestricted grants from Amgen, AdTech, Bial, Bracco, Cyberonics, Desitin, Eisai, Hexal, Nihon Kohden, Novartis, Pfizer, and UCB Pharma.

A. Strzelczyk reports personal fees and grants from Desitin Arzneimittel, Eisai, GW pharma, LivaNova, Medtronic, Sage Therapeutics, UCB Pharma and Zogenix.

None of the other authors have any conflict of interest to disclose.

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