Received: 10 February 2019 | Revised: 21 May 2019 | Accepted: 5 June 2019

DOI: 10.1111/epi.16099

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

A multicenter, matched case-control analysis comparing burden-of-illness in Dravet syndrome to refractory epilepsy and seizure remission in patients and caregivers in Germany

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Abstract

Objective: To compare direct and indirect costs and quality of life (QoL) of pediatric and adult patients with Dravet syndrome (DS), with drug-resistant epilepsy (DRE) and in seizure remission (SR), and their caregivers, in Germany.

Methods: Questionnaire responses from 93 DS patients and their caregivers were matched by age and gender with responses from 93 DRE and 93 SR patients collected in independent studies, and were compared across main components of QoL, direct costs (patient visits, medication use, care level, medical equipment, and ancillary treatments), and indirect costs (quitting job, reduced working hours, missed days).

Results: Mean total direct costs were highest for DS patients (€4864 [median €3564] vs €3049 [median €1506] for DRE [excluding outliers], $P = 0.01$; and €1007 [median €311], $P < 0.001$ for SR). Total lost productivity over 3 months was highest among caregivers of pediatric DS (€4757, median €2841), compared with those of DRE (€1541, $P < 0.001$; median €0) and SR patients (€891, $P < 0.001$; median €0). The proportions of caregivers in employment were similar across groups (62% DS, 63% DRE, and 63% SR) but DS caregivers were more likely to experience changes to their working situation, such as quitting their job (40% DS vs 16% DRE and 9% SR, $P < 0.001$ in both comparisons). KINDL scores were significantly lower for DS patients (62 vs 74 and 72, $P < 0.001$ in both comparisons), and lower than for the average German population (77). Pediatric caregiver EQ-5D scores across all cohorts were comparable with population norms, but more DS caregivers experienced moderate to severe depressive symptoms (24% vs 11% and 5%). Mean Beck Depression Inventory (BDI-II) score was significantly higher in DS caregivers than either of the other groups ($P < 0.001$).

Significance: This first comparative study of Dravet syndrome to difficult-to-treat epilepsy and to epilepsy patients in seizure remission emphasizes the excess burden of DS in components of QoL and direct costs. The caregivers of DS patients have a greater impairment of their working lives (indirect costs) and increased depression symptoms.

KEYWORDS
costs, depression, encephalopathy, quality of life, Severe myoclonic epilepsy of infants

1 | INTRODUCTION

Dravet syndrome (DS) is a severe form of epilepsy, characterized by febrile and afebrile, generalized and unilateral, clonic or tonic-clonic seizures with onset in the first year of life.[1,2] Described as a developmental and epileptic encephalopathy by the International League Against Epilepsy (ILAE), DS is at the severe end of the epilepsy spectrum. Approximately 85% of patients clinically diagnosed with DS have a mutation in the *SCN1A* gene.[3–6] DS is also characterized by symptoms such as behavioral, developmental, and sensory integration disorders.[1] The spectrum and severity of seizure types in DS are distinct from other forms of epilepsy.[1]

Studies evaluating the direct and indirect economic burden of epilepsy have reported a high-resource consumption for drug-resistant epilepsy (DRE) patients, and low costs once patients are in seizure remission (SR).[7–9] The socioeconomic impact for DS patients and their caregivers has been

Key Points

- This is the first analysis to compare quality of life (QoL) and direct/indirect cost burden of Dravet syndrome (DS) with drug-resistant and seizure-remission epilepsy
- QoL for patients with DS was significantly lower than for drug-resistant and seizure-remission epilepsy
- More caregivers of pediatric patients with DS had moderate to severe depressive symptoms than caregivers of drug-resistant or seizure-remission patients
- Care grade and inpatient direct costs are highest for DS and patients with drug-resistant epilepsy
- More caregivers of patients with DS quit their jobs, and mean indirect productivity costs were highest for this cohort

shown to be substantial in several studies.[10–14] However, DS patients have not previously been compared with patients experiencing DRE or in SR.

The objective of this study was to compare direct and indirect costs and caregiver domains of DS patients that were age- and gender-matched with patients with DRE and SR in Germany using datasets derived from a common questionnaire and set of data collection instruments.

2 | METHODS

2.1 | The disease cohort datasets and matching

Three sequential cost-of-illness studies in Germany used a common retrospective questionnaire to evaluate direct and indirect costs, quality of life (QoL), and psychometric impact of DS[12] and epilepsy in the general population.[7,8] The German DS study was completed in 2018 by caregivers of 82 pediatric and 11 adult patients.[12] The EpiPaed study was completed in 2011 by 489 caregivers of children with epilepsy in Hessen and Schleswig-Holstein, who were treated by neuropediatricians, at centers for developmental and social pediatrics and at epilepsy centers.[7,15] The study in adults was completed in 2013 in Hessen, and 292 patients were included.[9,16] Both epilepsy studies included patients irrespective of seizure severity, duration of illness, and epilepsy syndrome.[8] Each patient with DS was matched based on age and sex with one patient with DRE and one in SR for more than 1 year. Patients who were <18 or ≥ 18 were taken from the pediatric and adult studies, respectively. The six cohorts that were generated for the comparative analysis were the three pediatric cohorts ($n = 82$ each) (pediatric DS, pediatric DRE, pediatric SR) and the three adult cohorts ($n = 11$ each) (adult DS, adult DRE, and adult SR). All three studies had an ethics approval, and the DS study was registered at the German Clinical Trials Register (DRKS00011894). The classification of seizure types, epilepsies, and drug resistance was based on the definitions proposed by the ILAE.[17–19] Specifically, the definition of DRE was drawn from Kwan et al,[18] and implied that DRE patients failed at least two adequate trials of tolerated, appropriately chosen, and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. DRE patients experienced at least one seizure per year, whereas SR patients were defined as those who had not experienced a seizure in the last year. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed.[20]

2.2 | Questionnaires and instruments

The data used in this comparative analysis were retrieved from retrospective questions spanning the previous 3 months. Seizure frequency was calculated as the average during the previous 3 months. Patients reporting no seizures for more than 1 year were defined from retrospective questions spanning more than 1 year. The questions used in the German DS study questionnaire were based on the content and terminology from questions presented in both epilepsy studies. The common components seek to understand the diversity of socioeconomic status, the direct and indirect costs for patient and caregiver, and patient and caregiver QoL measures (Table A1 in Appendix).

Three instruments, the Beck Depression Inventory (BDI-II)[21] (completed by caregivers), the EuroQol scale with 5 dimensions and 3 levels (EQ-5D-3L), and the EuroQol visual analogue scale (EQ-VAS)[22] (completed by caregivers,) and the Kiddy-KINDL and Kid-KINDL[23] (completed by caregivers by proxy), were used in the questionnaires. The BDI-II scale (summated scores of 14-19, 20-28, and 29-63 indicate mild, moderate, and severe depressive symptoms, respectively) measured depressive symptoms in caregivers. The EQ-5D-3L measured caregiver QoL and responses were scored according to the German value set derived using the time trade-off with reference points of death (0) and perfect health (1).[22] Responses to the well-established KINDL questionnaires (Kiddy-KINDL for children QoL aged 4-6 years, and the Kid-KINDL in those aged 7-17 years) were age-adjusted and were used to assess childrens' and adolescents' QoL values.[23]

2.3 | Cost calculations

The cost analysis was conducted using a bottom-up approach to evaluate the economic burden of the disease from a societal perspective as well as the statutory health insurer "Gesetzliche Krankenversicherung" (GKV). Direct costs included health care resource use such as inpatient/outpatient hospital visits and medical aids, as well as costs based on care grade level, antiepileptic drug (AED) cost and treatment use. Indirect (productivity) costs were based on both pediatric mothers' and fathers' productivity and considered three components: reduced hours, missed days, and quitting work. Part-time salaries were assumed to be 60% of full-time workers' salaries in Germany. These costs were calculated according to German recommendations for health economic evaluations.[8]

2.4 | Cost comparison

Cost comparisons for orthopaedic, childcare, and supervision costs were not feasible across all three cohorts and were removed from the analysis. For the comparable treatments considered in this paper, a common unit cost was applied across the three cohorts to ensure comparability and to account for inflation from 2011 to 2017. Where there were no data available to apply a cost to adult patients (speech therapy,

occupational therapy, nutritionist, homeopathy, alternative medicine, and child psychiatrist), the average costs from the pediatric patients from each cohort were applied to the adult patients (except for child psychiatrist costs where adult patients were assigned a value of €0).

2.5 | Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics version 25 (SPSS Inc.). For scale variables, means, medians, standard deviations, minima, maxima, and ranges were calculated for each cohort. A 95% confidence interval was calculated using the bootstrap method according to the bias-corrected accelerated approach[24,25] considering that most cost variables are highly skewed. Statistical differences in the means of each cohort were tested using two-tailed independent samples *t* tests. Differences in DS, DRE, and SR cohorts were considered statistically significant at $P < 0.05$.

For categorical variables, frequencies and percentages were calculated for each cohort. Statistical differences in the distribution of each categorical variable between cohorts were calculated using two-tailed Pearson chi-square tests or z-tests for proportions where relevant. Chi-square tests of independence were used to test for relationships between the proportion of DS and DRE, and DS and SR patients in each BDI-II score category, with the null hypothesis that there is no statistically significant relationship between the cohorts.

A regression model was used to establish an effect of seizure frequency on direct health care costs. An ordinary least squares (OLS) regression was used with direct costs as the dependent variable. The independent variables used were seizure frequency, age in months, patient disability ID, parental BDI-II scores, and dummy variables for DS and DRE patients. Other independent variables that are likely to influence direct health care costs (comorbidities, non–seizure-related accidents) were not included due to a lack of comparable data between the three cohorts (DS, DRE, SR).

3 | RESULTS

3.1 | Demographic factors

The groups were well-matched on age and gender, with no statistical differences on these variables across the cohorts (Table A2 in Appendix). The mean ages for the pediatric DS, DRE, and SR cohorts were 8.1 years, 7.6 years, and 8.3 years, and for the adult cohorts, 24.6 years, 23.9 years, and 23.6 years, respectively. The gender distribution was consistent across all cohorts.

Although there was no significant difference in employment status between the caregivers of pediatric patients (62% DS, 63% DRE, and 63% SR in employment), a higher proportion of those caring for patients with DS experienced changes to their working situation (40% DS vs 16% DRE and 9% SR,

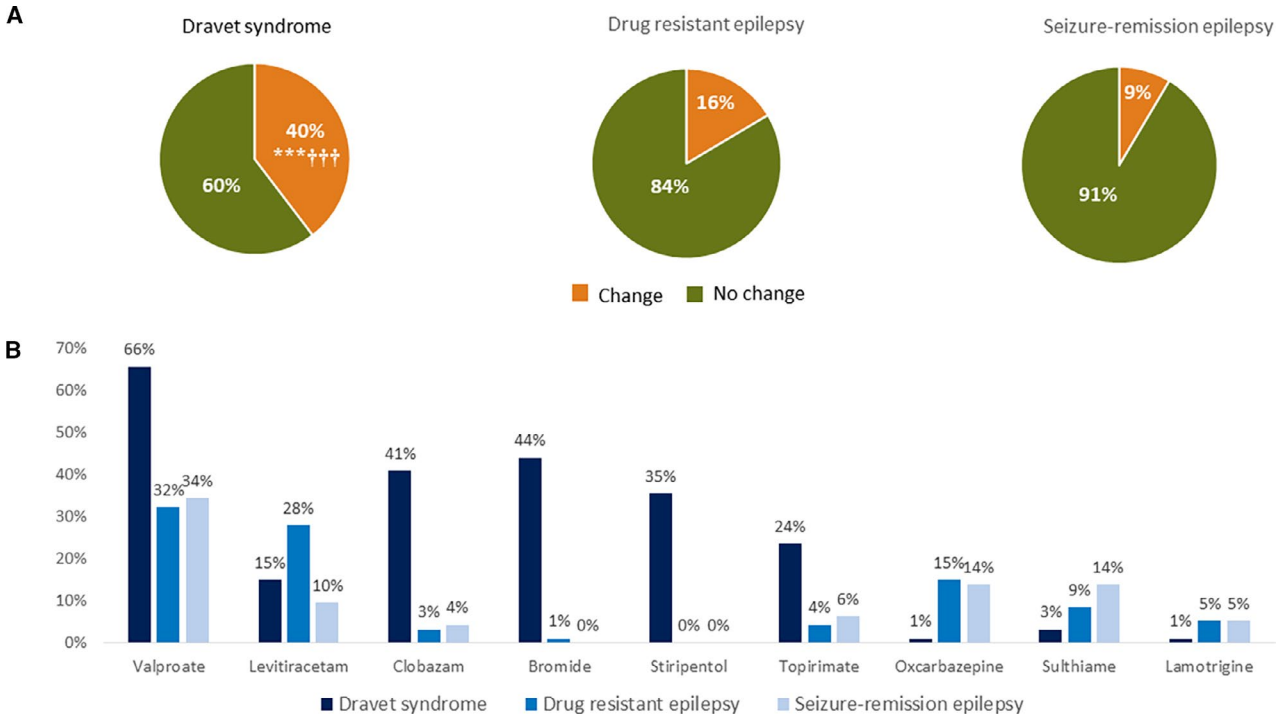

FIGURE 1 A, Proportion of parents (mothers and fathers) reporting a change in working situation in the Dravet syndrome (n = 164), refractory epilepsy (n = 163), and seizure-remission (n = 164) cohorts B, Proportion of patients taking the indicated antiepileptic drug by disease cohort (n = 93 per cohort)

$P < 0.001$ in both comparisons; Figure 1A). Possible changes to the work situation were to stop working, accept another job, reduce working hours, or retrain. The impact of DS on adult and pediatric patient work/schooling was significantly higher over a 3-month period than in the other groups, with the average number of missed school/work days reported for DS patients being 7.8 days (median 2.0, standard deviation [SD] 15.5) compared with 0.7 days (median 0, SD 2.1) in DRE and 0.05 days (median 0, SD 0.3) in SR patients ($P < 0.001$ in both comparisons).

The proportion of DS patients (pediatric and adult) with a disability card was significantly higher (83/93, 89.2%) compared with DRE (37/93, 39.8%) and SR (36/93, 38.7%) ($P < 0.001$ in both comparisons). In addition, a higher proportion of DS patients (pediatric and adult) were on higher care grades, especially care levels 2 and 3 compared with the DRE and SR groups (Figure 2A). DS patients were significantly more likely to have a care grade compared to DRE and SR ($P < 0.001$ in both comparisons).

3.2 | Seizure frequency

Patients in the SR cohort had been by definition seizure-free for a year or more. With the exception of four patients in the DS cohort that had experienced no seizures in the past year, patients in the DS and DRE cohort reported experiencing seizures on a half-yearly, monthly, or weekly basis (Table A3 in Appendix 1). More patients in the DS (70/93) than the DRE cohort (47/93) experienced daily, weekly, or monthly seizures ($P = 0.0018$, Pearson chi-square test), whereas more patients in the DRE (42) than the DS cohort (22) experienced seizures on a 6-monthly basis or less frequently (for details, please refer to Table A3 in Appendix).

3.3 | Quality of Life

The Kiddy/Kid-KINDL score for the DS cohort was statistically significantly lower at 62.1 ($P < 0.001$ in both comparisons) than that of the of DRE (74.4) and SR (71.9) paediatric cohorts (Table 1). The latter two scores did not differ significantly from each other or the score of 76.8 for the general population of healthy children and adolescents in Germany. The KINDL subscale scores were lower in DS patients for the domains "friends" ($P < 0.001$), "school" ($P < 0.001$), and "well-being" ($P < 0.05$), compared with patients in DRE and SR cohorts.

Depressive symptoms and QoL (Table 1, Figure 3) of caregivers of pediatric patients were analyzed using data collected from the BDI-II and EQ-5D-3L and EQ-VAS

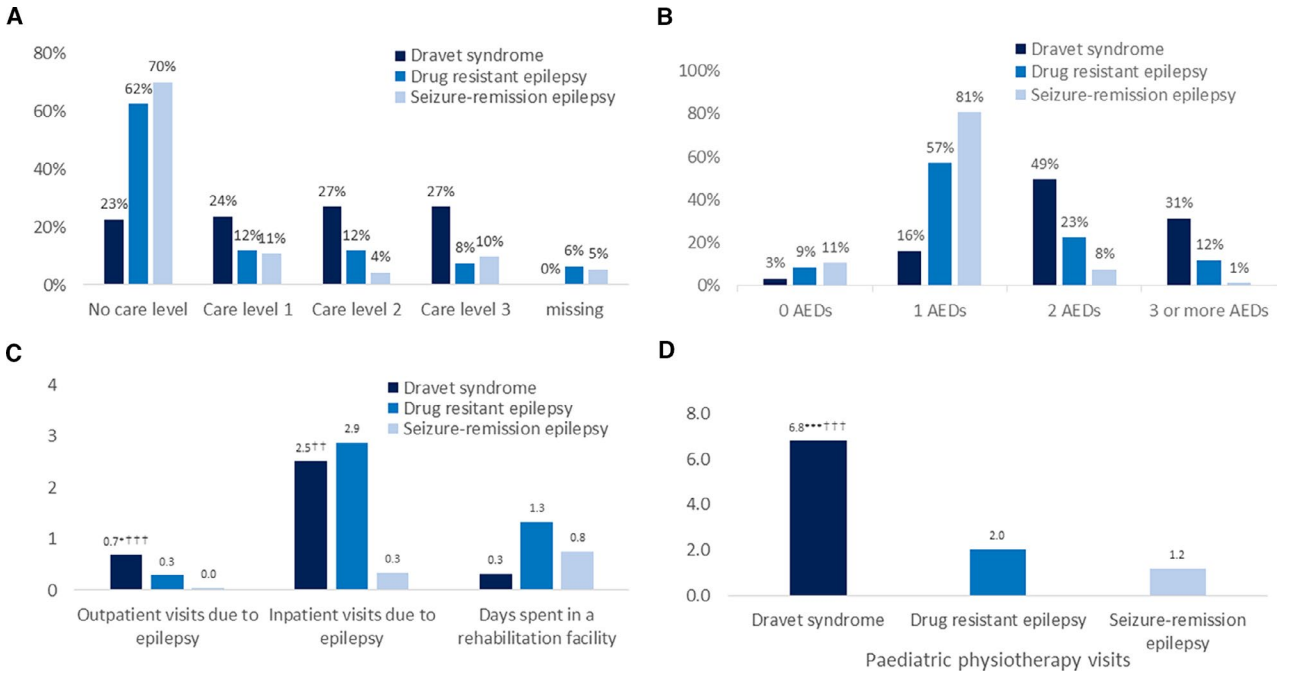

FIGURE 2 A, Percentage of patients (paediatric and adult) in each cohort (n = 93) receiving the indicated care level. *z*-tests for proportions find a statistically significant difference between the proportion of Dravet syndrome (DS) patients with a care grade compared to drug-resistant epilepsy (DRE) ($P < 0.001$) and seizure-remission (SR) ($P < 0.001$). B, Proportion of patients (paediatric and adult) from each cohort (n = 93) taking the indicated number of daily antiepileptic drugs (AEDs). C, Mean days spent in outpatient/inpatients visits (paediatric and adult) and rehabilitation facilities (paediatric patients only) over 3 months * indicates $P < 0.05$ between DS and DRE ** indicates $P < 0.01$ *** indicates $P < 0.001$,† indicates $P < 0.05$ between DS and SR †† indicates $P < 0.01$ ††† indicates $P < 0.001$. D, Mean physiotherapy visits over 3 months (n = 93 per cohort) * indicates $P < 0.05$ between DS and DRE ** indicates $P < 0.01$ *** indicates $P < 0.001$,† indicates $p < 0.05$ between DS and SR †† indicates $P < 0.01$ ††† indicates $P < 0.001$

TABLE 1 Kiddy-KINDL (children aged 4-6 years) and Kid-KINDL (children aged 7-17 years) component mean scores and total 100 scores, completed in proxy by the caregivers. BDI-II and mean EQ-5D-3L scores completed by pediatric caregivers. All scores provided by disease cohorts (DS, Dravet syndrome; DRE, drug-resistant epilepsy; SR, seizure remission)

	DS	DRE	SR	General population	*P* DS vs DRE	*P* DS vs SR	*P* DRE vs SR
Kiddy/Kid-KINDL component mean scores[a]							
Physical well-being	62.77*,†	72.27	73.88	76.5	0.02	<0.01	0.6
Emotional well-being	75.13	79.82	78.03	80.8	0.1	0.3	0.5
Self-esteem	62.17††	66.47	70.62	68.8	0.2	<0.01	0.2
Family	75.04	80.63	75.75	77.7	0.06	0.8	0.08
Friends	47.55**,*,†††	70.91	70.93	78.0	<0.001	<0.001	1
School	57.85**,*,†††	81.21	74.41	76.0	<0.001	<0.001	0.01
Total 100 scores	62.13**,*,†††	74.39	71.89	76.3	<0.001	<0.001	0.2
BDI-II scores[b]							
Number of caregivers scoring (0)	1 (1%)	9 (11%)	10 (13%)				
No depressive symptoms (0-13)	37 (50%)	59 (75%)	69 (87%)				
Mild depressive symptoms (14-19)	19 (26%)	11 (14%)	6 (8%)				
Moderate depressive symptoms (20-28)	12 (16%)	7 (9%)	3 (4%)				
Severe depressive symptoms (29-63)	6 (8%)	2 (3%)	1 (1%)				
Mean overall score	14.9**,*,†††	9.4	6.9		<0.001	<0.001	0.04
Mean carer EQ-5D scores[a]							
EQ-5D-3L (SD)	0.90†† (0.18)	0.94 (0.10)	0.96 (0.07)	0.9	0.1	<0.01	0.1
EQ-VAS	73††	76	80	77	0.2	<0.01	0.1

Due to rounding, numbers may not add up to 100%.

Abbreviations: BDI-II, Beck Depression Inventory; DS, Dravet syndrome; DRE, drug-resistant epilepsy; EQ-5D-3L, EuroQol scale with five dimensions and three levels; SD, standard deviation; SR, seizure remission

[a]Where * is $P < 0.05$, ** is $P < 0.01$, and *** is $P < 0.001$ between DS and DRE, † is $P < 0.05$, †† is $P < 0.01$, and ††† is $P < 0.001$ between DS and patients in SR.

[b]Chi-square tests of independence were used to test for a relationship between the proportion of DS patients in each BDI score category, with the proportion of DRE and SR patients in each category. No statistically significant relationships were found at a 0.05 significance level in either test.

instruments (time trade-off scores for Germany and self-assessed VAS). A statistically significant difference ($P < 0.01$) in the average BDI-II score was found between caregivers from the DS and the DRE and SR cohorts (mean BDI-II score in the DS group of 14.9 [SD 9.4] vs 9.4 in the DRE group [SD 7.7]; $P < 0.001$, and 6.9 in the SR group [SD 6.6]; $P < 0.001$). Most caregivers of DRE and SR patients (75% and 87% of respondents, respectively) recorded no depressive symptoms (0-13 on the BDI-II) compared with half of DS caregivers (50%). A higher proportion of DS caregivers therefore reported depressive symptoms (50% mild-to-severe) compared with either DRE or SR patients (25% and 13%, respectively; Table 1). Caregiver QoL (EQ-VAS) scores were similar across the cohorts, with DS caregivers reporting a mean of 72.6 [median 75.0, SD 17.7], DRE caregivers a mean of 76.0 [median 80.0, SD 17.1], and SR caregivers a mean of 80.3 [median 80.0, SD 15.8]). These scores were comparable with the average German population score (77.3; Table 1).[22]

3.4 | Treatment and hospital use

Patients with DS used more AEDs (Figure 2B) compared with DRE and SR patients. Eighty percent of DS patients (pediatric and adult) used 2 or more AEDs compared with 34% and 9% of DRE and SR patients, respectively. The mean number of different AEDs taken was also highest for DS patients (paediatric and adult) at 2.2 vs 1.4 and 1.0 AEDs taken by patients with DRE and in SR, respectively ($P < 0.001$ in both comparisons). Valproate was the most common AED taken by all three cohorts, but was more frequently used by DS patients (66%) compared with DRE (32%) and SR (34%)

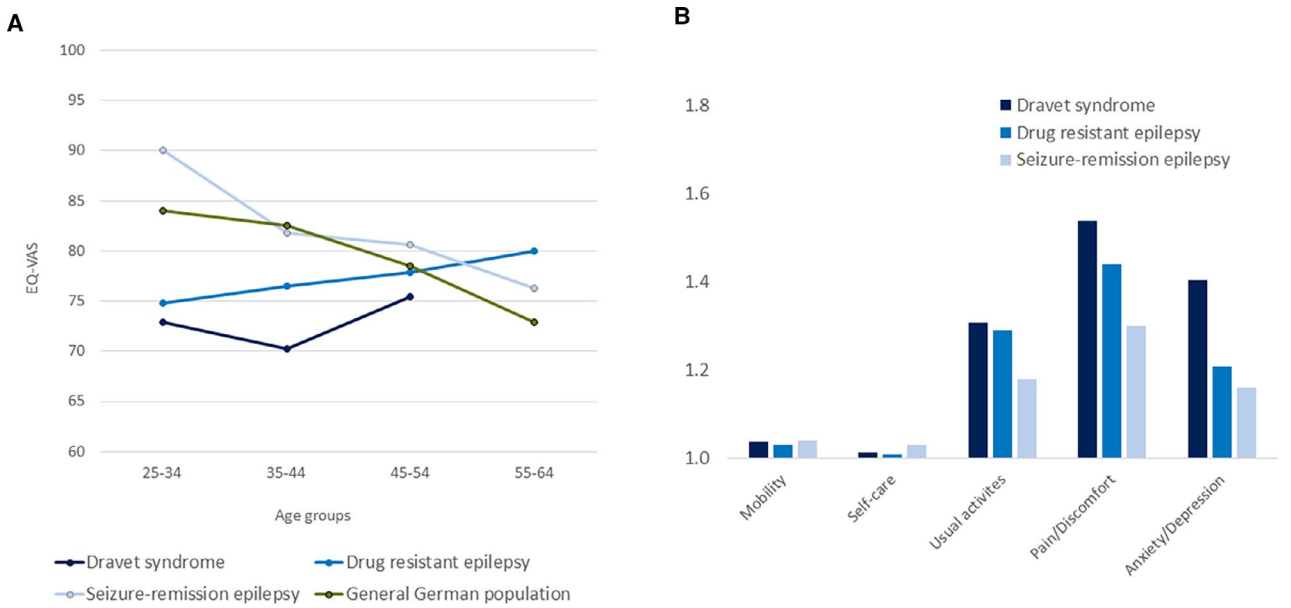

FIGURE 3 A, Average EQ-VAS caregiver score by caregiver age group in each disease cohort B, Mean paediatric EQ-5D component scores by cohort

patients (Figure 1B). DS patients had the highest AED costs (mean €892, median €532, SD €1017) over the 3-month study period followed by patients with DRE (mean €349, median €102, SD €655) and SR (mean €116, median €41, SD €198; Table 2). Mean AED costs in DS patients were significantly higher than those in either of the other groups ($P < 0.001$ in both comparisons).

There was no statistically significant difference in the mean duration of hospital visits over the 3 months between DS (2.5 days) and DRE patients (2.9 days; Figure 2C), both having significantly higher inpatient visits than those in SR (0.3 days; $P = 0.002$ in both comparisons). Adult patients did not use rehabilitation services while, in pediatric patients, they were most frequently used by those with DRE (5%) and least used by DS patients (1%). In this study, rehabilitation refers specifically to days spent in a rehabilitation facility, the charges for which may include ancillary treatments such as physiotherapy. The pediatric DS cohort had a higher mean number of outpatient physiotherapy visits (6.8) compared with the DRE (2.0, $P < 0.001$) and SR cohorts (1.2, $P < 0.001$) over the 3-month study period (Figure 2D). Furthermore, total ancillary treatment visits (speech therapy, occupational therapy, outpatient physiotherapy) were used significantly more by DS cohort than the DRE and SR cohorts. (Table 3)

3.5 | Health care resource costs

Direct costs incurred for the three cohorts (Table 2) were calculated based on health care resource use (hospital costs, medical aids, ancillary treatments, care grade costs, AED costs, doctor visits, and diagnostic tests). The analysis of comparable costs across all cohorts revealed that total mean direct DS costs were €4864 (median €3564, SD €4995), which are significantly higher than those of DRE (mean €3049, median €1506, SD €5022, $P = 0.01$) and of SR patients (mean €1007, median €311, SD €1729, $P < 0.001$). These costs exclude from the analysis two patients in the DRE group who reported spending the entire 90-day survey period in hospital, inflating the estimate of inpatient costs. When including the outliers, the DRE cohort had a mean cost of €4367 (median €1518, SD €10285). Additional costs reported only by DS caregivers were medical aids (reported by 35% of DS caregivers), wheelchairs (8.6%), special beds (6.5%), and helmets (4.3%). In the regression analysis (Table A4 in Appendix), seizure frequency was found to have a significant impact on health care resource use, with each categorical increase in seizure frequency corresponding to an average €730 increment. Patient age and parental BDI-II scores also significantly impacted health care resource use.

3.6 | Indirect (productivity) costs

Caregivers of DS patients were found to have a higher mean number of days missed from work over 3 months at 3 days per caregiver who responded (median 0, SD 10.9) vs 1.30 days for DRE (median 0, SD 7.4, $P = 0.09$) and 0.05 days for those in SR (median 0, SD 0.3, $P < 0.001$). Carers in the DS group were most affected economically during the study

TABLE 2 Total mean and median direct costs per patient and total mean and median indirect (productivity) costs per disease cohort (DS, Dravet syndrome; DRE, drug-resistant epilepsy; SR, seizure remission), for both pediatric and adult patients over 3 months measured in Euros (€)

	Dravet syndrome (DS)		Drug-resistant epilepsy (DRE)		Epilepsy in seizure-remission (SR)		*P*	*P*	*P*	95% CI[d]		
			Mean	Median			DS/DRE	DS/SR	DRE/SR	DS	DRE	SR
	Mean	Median	(including outliers)	(including outliers)	Mean	Median	Excluding outliers			Excluding outliers		
Direct cost components												
Medical aids	283	0	51.6 (50.5)	0 (0)	0	0	0.06	0.02	0.21	124.5-612.4	6.6-308.8	N/A
Hospital and rehabilitation costs[a,††]	1883.4	0	2013.6 (3324.1)	0 (0)	367.8	0	0.90	0.00	0.00			
Rehabilitation	41.3	0	99.5 (245.2)	0 (0)	136	0	0.44	0.37	0.75	0-206.5	11.7-316.6	0-433.6
Inpatient[a,††]	1567.8	0	1794.0 (2961.4)	0 (0)	214.4	0	0.77	0.00	0.00	884.4-2579.5	1143.5-3005.9	60.3-589.6
Outpatien[*,†††]	274.4	0	120.2 (117.6)	0 (0)	17.4	0	0.03	0.00	0.00	191.6-466	75.7-222.5	0-43.6
Ancillary treatments	477.7	394.1	116.0 (118.4)	0 (0)	112.5	0	0.00	0.00	0.92	399.6-577.6	75.4-191.9	74.7-170.2
Diagnostic tests**	37.2	32.2	69.7 (73.3)	37.7 (37.7)	31.1	32.2	0.00	0.36	0.00	28.2-48.6	55.0-95.4	25.4-40.1
Doctor costs**[*,†††]	160.5	110.2	34.9 (40.9)	0 (0)	30.2	0	0.00	0.00	0.58	132.1-200.2	25.9-44.8	19.9-45.9
Care grade cost**[*,†††]	1129.6	1374	414.5 (413.5)	0 (0)	349.2	0	0.00	0.00	0.53	975.7-1284.3	279.3-585.3	229.8-521.4
AED cost**[*,†††]	892.2	532	348.6 (346.0)	101.6 (101.6)	116.5	41.3	0.00	0.00	0.00	709.9-1114.9	243.7-520.0	84.5-164.7
Total direct costs (3 months)[a,*,†††]	4863.7*,†††	3563.5	3049.0 (4366.8)	1506.4 (1518.3)	1007.2	311.0	0.01	0.00	0.00	4005.9-6117.4	2207.5-4389.0	704.5-1493
Indirect (productivity) costs components[b,c]												
DRE and SR: pediatric (n = 82); DS pediatric and adult (93)												
Quit work												
Maternal[*,†††]	3169.7	0	1239.6	0.0	867.7	0.0	0.00	0.00	0.45	2186.0-4044.1	643.4-2197.8	376.5-1714.6
Paternal	109.3	0	0.0	0.0	0.0	0.0	0.32	0.32	N/A	0-327.9	N/A	N/A
Reduced working hours												
Maternal**[*,†††]	732.4	0	39.1	0.0	9.1	0.0	0.00	0.00	0.02	490.7-1136.9	21.1-66.8	3.4-22.4
Paternal[*,†]	121.6	0	0.0	0.0	3.4	0.0	0.03	0.04	0.32	40.7-287.0	N/A	0.0-24.1
Missed days												
Maternal[†]	496.4	0	190.7	0.0	8.2	0.0	0.14	0.00	0.14	277.9-1022.0	58.0-908.8	1.4-26.8
Paternal[††]	127.3	0	72.0	0.0	2.7	0.0	0.26	0.00	0.03	74.5-265.2	27.9-174.5	0.0-8.4
DRE and SR: adult (n = 11)												

(Continues)

TABLE 2 (Continued)

	Dravet syndrome (DS)		Drug-resistant epilepsy (DRE)		Epilepsy in seizure-remission (SR)		*P*	*P*	*P*	95% CI[d]		
			Mean	Median			DS/DRE	DS/SR	DRE/SR	DS	DRE	SR
	Mean	Median	(including outliers)	(including outliers)	Mean	Median	Excluding outliers			Excluding outliers		
Quit work												
Adult patients			924.1	0	0	0			0.34		0.0-4517.8	N/A
Reduced working hours												
Adult patients			0	0	0	0			N/A		N/A	N/A
Missed days												
Adult patients			70.9	0	0	0			0.34		0.0-519.9	N/A
Total indirect costs (3 months)												
Maternal[†††]	4398.6	0.00	1469.4	0	885.0	0	0.00	0.00	0.24	3477.1-5493.9	863.5-2342.2	393.0-1713.2
Paternal*	358.2	0	72.0	0	6.1	0	0.04	0.01	0.03	174.8-742.1	30.9-178.5	1.4-21.3
Adult patients	N/A	N/A	995.0	0	0	0	N/A	N/A	0.3	N/A	0.0-5082.5	N/A

[a]Two patients with DRE were found to have spent the whole 90 d in hospital as an inpatient, which resulted in skewed cost figures. Bracketed figures include the two outlier patients and the figures that are not bracketed exclude outlier patients. Where * is $P < 0.05$, ** is $P < 0.01$, and *** is $P < 0.001$ between DS and DRE patients, † is $P < 0.05$, †† is $P < 0.01$, and ††† is $P < 0.001$ between DS and patients in SR.

[b]Due to differences between the questionnaires, indirect costs for the DS cohort were calculated based on changes to mothers' and fathers' productivity for all 93 of the adult and pediatric patients combined.

[c]For DRE and SR cohorts, the mean total of all patients was calculated by dividing the sum of total paediatric maternal (n = 82), pediatric paternal (n = 82), and adult patient (n = 11) indirect costs by the patient number (n = 93 for both cohorts). For the DS cohort, the mean total of all patients was calculated by dividing the sum of total maternal (adult and pediatric patients) and paternal (adult and pediatric patients) by the patient number (n = 93).

[d]95% confidence intervals were calculated for costs using the bias-corrected accelerated (BCa) bootstrap approach.

TABLE 3 Mean numbers of specialist visits among pediatric patients per disease cohort (DS, Dravet syndrome; DRE, drug-resistant epilepsy; SR, seizure remission)

	DS			DRE			SR			*P*	*P*	*P*
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	DS vs DRE	DS vs SR	DRE vs SR
General practitioner visits	1.62**,††††	1	2.34	0.13	0	0.49	0.12	0	0.4	<0.001	<0.001	0.86
Neurologist/ Neuropaediatrician	1.88**,††††	1	2.09	0.39	0	1.46	0.15	0	0.47	<0.001	<0.001	0.15
Child/Adolescent psychiatrist visits	0.13	0	0.62	0.01	0	0.11	0.09	0	0.48	0.08	0.57	0.18
Alternative medicine and homeopathy visits	0.38*,†	0	0.95	0.22	0	1.02	0.07	0	0.34	0.3	0.01	0.22
Physiotherapy visits	6.82**,††††	2.5	9.24	2.02	0	6.36	1.18	0	3.56	<0.001	<0.001	0.3
Speech therapy visits	3.80**,††††	0	5.26	1.02	0	4.9	1.15	0	3.35	<0.001	<0.001	0.85
Occupational therapy visits	4.49**,††††	0	5.77	0.88	0	0.32	1.12	0	3.36	<0.001	<0.001	0.64

Where * is $P < 0.05$, and *** is $P < 0.001$ between DS and DRE, † is $P < 0.05$, and †††† is $P < 0.001$ between DS and patients in SR.
Abbreviation: SD, standard deviation.

period due to the number of working hours reduced, missed days from work, and by some caregivers quitting work. The overall lost output over the 3 months was estimated to be highest among caregivers of DS patients, at €4756 (median €0, SD €5280), compared with €1541 (median €0, SD €3553) in those with DRE and €891 (median €0, SD €2851) in those in SR (Table 2). Maternal caregivers who had quit work accounted for the largest proportion of total lost output across all three disease cohorts. The proportion of mothers who quit their job was highest among DS carers (28%), compared with DRE and SR groups at 12% and 9%, respectively. Maternal carers of DS patients also had the highest proportion experiencing reduced hours at work (29%) compared with DRE (13%) and SR (7%) groups.

4 | DISCUSSION

Previous studies have reported the direct and indirect economic and humanistic consequences of DS and epilepsy. However, to our knowledge, none has compared the impact of DS on patients and caregivers vs that of DRE and SR. This comparative analysis reports the difference in direct and indirect costs, QoL, and psychometric values of pediatric patients and their caregivers and adult patients across the three patient groups.

The analysis showed that more patients with DS were in possession of disability IDs, received higher care levels, and incurred higher care level costs than the DRE and SR patient populations. This suggests that the impact of disease in the DS population is more severe than in the other two populations and confirms observations that DS is more than a drug-resistant epilepsy syndrome. Indeed, the impact of comorbidities has been shown by Lagae et al[11] and Strzelczyk et al[12] to be a driver of economic cost.

The KINDL survey results illustrate the seizure- and non–seizure-related impact of DS on the QoL of patients, compared with the scores close to population norms reported by DRE and SR patients. The KINDL survey contributes in granularity to existing studies on the impact of the disease on the QoL of the patient. Lower physical well-being scores from the KINDL survey align with higher care levels and resource use by DS patients.

Based on a comparison of KINDL scores, QoL in DS pediatric and adolescent patients is lower than that of DRE or SR patients and lower than the average German score of a healthy child or adolescent. In particular, the "school," "friends," and "self-esteem" elements were comparatively low, indicating a higher social isolation experience by DS patients. Whether this is due to their seizure frequency, cognitive, behavioural, speech, or motor impairments is yet to be established.

Parental depressive symptoms and reduced QoL in general epilepsy have been reported in several previous studies.[7]

However, a comparison of BDI-II scores reveals much higher levels of depressive symptoms in DS caregivers compared with caregivers of the other two cohorts. The levels of depressive symptoms in the DS cohort are reminiscent of other rare diseases such as Rett syndrome, with 30.6% (BDI-II score ≥29) of caregivers reporting severe depressive symptoms.[26]

In an open response survey conducted by Villas et al[27] nearly two-thirds of DS caregivers have depressive symptoms according to the author's interpretation, which has also been confirmed in the results of the German DS study, with 23%, 16%, and 8% of caregivers reporting mild, moderate, and severe depressive symptoms, respectively.[12] These detailed psychometric data have been provided in a more granular format than ever before, assessing the severity of pediatric caregiver depressive symptoms using the BDI-II instrument. The burden of genetic findings, its influence on further family planning, and the significantly increased sudden unexpected death in epilepsy (SUDEP) incidence in DS[28] may have an influence on caregivers' QoL, but an analysis of these factors as a predictor of QoL is outside the scope of the current study.

In this study, lost productivity for caregivers of patients with DS was significantly higher than that of caregivers of DRE and SR patients. This may be due to the higher levels of care required for DS patients, and the several comorbidities associated with the disease, forcing carers to miss or quit work.

Of direct costs, hospital and rehabilitation visits were the most important component across the disease groups. Both DS and DRE groups had higher inpatient costs compared to SR patients. It is suspected that DS patients also supplement many inpatient treatments with home care. Some support for this has been found in our study's high patient spend in the DS group on specialist equipment, as well as high use of rescue medication.[29] Furthermore, two pediatric DRE patients were reported to have spent the entire 3-month duration of the study in hospital, which caused a significant increase in the direct costs of this patient group and served to illustrate the heterogeneity in this group.

Ancillary treatments were one of the main direct costs in pediatric patients with general epilepsy,[7] and no study has yet quantified and compared the direct cost of ancillary treatments (speech therapy, acupuncture, occupational therapy, physiotherapy, nutritionists, homeopathy) with the DS population. This analysis revealed that DS patients had the greatest use of ancillary treatments while physiotherapist visits accounted for the highest proportion of visits to all ancillary specialists across the three groups. This aligns with the DISCUSS survey, which reported that physiotherapy accounted for the highest non–seizure-related mean cost per patient in Germany.[11]

Medical equipment expenses were highest for the DS patient cohort and may be linked to the range of comorbidities associated with the disease.[4,11] Wheelchairs, special beds, and helmets were more commonly purchased among DS patients than for the DRE and SR cohorts, confirming the added burden to the everyday lives of DS patients and caregivers.

This analysis utilizes a distinctive approach from other studies, developing comparable questionnaires and using direct age- and gender-matching, providing a high level of data specificity across the three disease cohorts. Through this comparative analysis, we have been able to identify the key differences in direct and indirect cost components in patients with DS, DRE, and in SR, and explored the impact of these differences on patient and caregiver QoL.

This study did not explore in detail whether the differences between DRE and DS patients can be explained by a difference in seizure frequency, seizure semiology or seizure duration (status epilepticus),[30] or by DS patients having more additional symptoms. Although more patients in the DS cohort experienced seizures at a shorter frequency, whether and to what extent this accounts for the higher socioeconomic impact of the disease is beyond the scope of this comparative analysis (matching of patients by seizure frequency would not be possible because of the small sample sizes). Nevertheless, a recent study conducted by Lagae et al on a large cohort of 584 DS patients showed that excluding medication, non–seizure-related costs dominated costs of care, suggesting that the higher costs incurred by patients with DS compared with DRE in this study could be explained in part by the higher burden of their additional symptoms.[11]

4.1 | Limitations

Although question-by-question matching was used in the design of the comparative analysis, differences in wording may have affected the way in which the question is perceived by the patient or caregiver responding to the survey.

Due to the rarity of DS, the overall sample size in this comparative analysis was low, especially for the adult sample, with only 11 patients vs 82 in the pediatric cohort. Therefore, the outcome is more pediatric-focused and the low sample size may have limited the statistical power of the tests. It is also important to note that the studies were performed several years apart and guidelines in treatment and health care may have changed, impacting factors such as the duration/location of patient stay (eg, inpatient vs rehabilitation center), use of AEDs, and other resources used for patients with epilepsy. However, longitudinal studies have not shown any major difference in epilepsy costs or distribution of cost components during the last decade.[16,31] Although the study highlights the cost and QoL burden associated with DS, DRE, and epilepsy in SR, its noninterventional nature means that it is not possible to draw conclusions about the best ways of tackling the disease burden experienced by patients and caregivers.

5 | CONCLUSION

The high QoL and monetary burden associated with DS caregivers and patients is apparent and reinforces existing research. Moreover, DS patients were demonstrated to have a generally higher burden than both SR and DRE patients. Efforts should focus on identifying reasons for areas of high health care resource use in order to focus activity to decrease monetary impact and to improve QoL of patients and caregivers.

ACKNOWLEDGMENTS

The authors would like to thank all patients and caregivers who contributed to this survey and the German patient advocacy group Dravet-Syndrome.V. (www.dravet.de) for their help with recruiting participants. This study was sponsored by Zogenix International Limited.

CONFLICT OF INTERESTS

A.S. reports personal fees and grants from Desitin Arzneimittel, Eisai, GW Pharmaceuticals, LivaNova, Marinus Pharmaceuticals, Medtronic, Sage Therapeutics, UCB Pharma, and Zogenix. S.S.B. reports personal fees from UCB, Desitin Arzneimittel, Novartis, Zogenix, LivaNova, and Eisai. T.B. reports fees from Desitin Arzneimittel, GW Pharma, and Zogenix. H.M.H. has served on the scientific advisory board of Cerbomed, Desitin, Eisai, GW Pharma, Novartis, and UCB Pharma. He served on the speakers' bureau of or received unrestricted grants from Amgen, Ad-Tech, Bial, Bracco, Cyberonics, Desitin, Eisai, Hexal, Nihon Kohden, Novartis, Pfizer, and UCB Pharma. K.M.K. reports personal fees from UCB pharma, Novartis Pharma AG, Eisai, and GW Pharma. G.K. reports personal fees from UCB Pharma, Desitin Arzneimittel, Zogenix, LivaNova, Eisai, GW Pharma, Bial, Dibropharma, Novartis, Biogen, Actelion. R.T. reports personal fees and grants from Novartis, Desitin Arzneimittel, UCB Pharma, and Pfizer. A.W.-K. reports personal fees from Desitin Arzneimittel, Dr. Schär, Novartis, Nutricia, Vitaflo, and UCB Pharma. J.C. and C.P. are employed by Wickenstones Ltd and received support from Zogenix International Limited to complete this study. F.R. reports personal fees from Eisai, UCB Pharma, Desitin Arzneimittel, Novartis, GW Pharma, Medtronic, Cerbomed, and Shire; grants from the European Union, Deutsche Forschungsgemeinschaft, the federal state Hessen through the LOEWE programme, and the Detlev-Wrobel-Fonds for Epilepsy Research. None of the other authors reported any related conflicts of interest. This study was sponsored by Zogenix International Ltd. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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How to cite this article: Strzelczyk A, Schubert-Bast S, Bast T, et al. A multicenter, matched case-control analysis comparing burden-of-illness in Dravet syndrome to refractory epilepsy and seizure remission in patients and caregivers in Germany. *Epilepsia*. 2019;00:1–14. https://doi.org/10.1111/epi.16099

APPENDIX

TABLE A1 Questions from the pediatric studies evaluated in the comparative analysis

Socioeconomic Status (Parent caregivers)	Direct costs	Indirect costs (caregiver)	Quality of life	
			Patient	Caregiver
Does not live in the household	Medical aids	Quit work	Kiddie-KINDL (4-6 y)	BDI-II
Employed	Hospital and rehabilitation[a]	Reduced working hours	Kid-KINDL (7-17 y)	EQ-5D-3L
Jobless/unemployed	Ancillary treatments[b]	Missed days		EQ-VAS
Housewife/husband /home-educator	Diagnostic tests[c]			
Training/retraining/civilian service	Doctor visits[d]			
Occupational disability pension	Care grade			
Retirement pension/widows' pension	Medication			

[a]Includes: inpatient rehabilitation, inpatient hospital treatment, medical aids: protective helmet, special bed, wheelchair
[b]Includes: speech therapy, acupuncture, occupational therapy, physiotherapy, nutritionist, homeopathy, alternative medicine.
[c]Includes: computed tomography, radiography, MRI, blood test.
[d]Includes: dentist, child psychiatrist, neurologist, general practitioner
Abbreviations: BDI-II, Beck Depression Inventory; EQ-5D-3L, EuroQol scale with 5 dimensions and 3 levels; EQ-VAS, EuroQol visual analogue scale.

TABLE A2 Demographic factors of the Dravet syndrome (DS), drug-resistant epilepsy (DRE) and epilepsy in seizure-remission (SR) cohorts

	DS		DRE		SR		*P*	*P*	*P*
Demographics	**Mean**	**Median**	**Mean**	**Median**	**Mean**	**Median**	**DS vs DRE**	**DS vs SRE**	**DRE vs SRE**
Age: paediatric	8.1	7.4	7.6	7.0	8.4	7.0	0.5	0.7	0.3
Age: adult	24.6	23.3	23.9	23.0	23.6	23.0	0.7	0.6	0.9
Caregivers' employment status	62%		63%		63%				
Patients' missed school/work days	7.8	2.0	0.7	0.0	0.05	0.00	<0.001	<0.001	0.002
Percentage of cohort									
Females: paediatric	45%		46%		43%		0.0	0.0	0.0
Females: adult	64%		64%		64%		*		
Proportion of patients with a disability card	89%		40%		39%		<0.01	<0.01	0.6

*Statistical tests on proportions cannot be reported here as all proportions are the same.

TABLE A3 Frequency of seizures recorded over several time durations by the three disease groups, Dravet syndrome (DS), drug-resistant epilepsy (DRE) and epilepsy in seizure remission (SR) (paediatric and adult)

	Dravet syndrome (% of cohort)	Drug-resistant epilepsy (% of cohort)	Seizure-remission epilepsy (% of cohort)	DS/DRE *P*[*]
At least once a day	21 (23)	11 (12)	0	0.0018
At least once a week	20 (22)	12 (13)	0	
At least once a month	29 (31)	24 (26)	0	
At least once every 6 months	15 (16)	31 (33)	0	
At least once a year	3 (3)	11 (12)	0	
No seizures for over a year	4 (4)	0	92 (99)	
Missing	1 (1)	4 (4)	1 (1)	
Total	93	93	93	

*Chi-squared tests comparing DS with DRE patients regarding occurrence of daily, weekly or monthly seizures vs seizures at least every 6 months or less. Chi-squared tests comparing SR with either of the other two groups cannot be reported as all SR patients are found in one group.

TABLE A4 Ordinary least squares (OLS) regression model exploring the effect of seizure frequency on health care costs (all patients, n = 279)

	Coefficient	Standard error	*t*	*P* > *t*	95% CI	
Dependent variable: Total direct health care costs						
Age in months	−83.8	38.1	−2.20	0.029	−159.0	−8.7
Seizure frequency (Categorical[*])	730.2	238.3	3.06	0.002	260.8	1199.7
Disability ID (Yes/No)	309.3	552.1	0.56	0.576	−778.4	1397.0
BDI-II	111.5	28.9	3.86	0.000	54.6	168.4
Dravet syndrome (Yes/No)	340.0	1014.7	0.34	0.738	−1659.0	2339.0
Drug-resistant epilepsy (Yes/No)	−517.4	875.0	−0.59	−0.59	−2241.3	1206.5
Constant	183.0	663.1	0.28	0.28	−1123.3	1489.4

*Seizure frequency was measured using six mutually exclusive categories: 1-No seizures for over a year, 2-Seizures at least once a year, 3-Seizures at least once every 6 months, 4-Seizures at least once a month, 5-Seizures at least once a week, 6-Seizures at least once a day.