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RESEARCH ARTICLE

Multicenter, cross-sectional study of the costs of illness and cost-driving factors in adult patients with epilepsy

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Abstract

Objective: This study was undertaken to quantify epilepsy-related costs of illness (COI) in Germany and identify cost-driving factors.

Methods: COI were calculated among adults with epilepsy of different etiologies and severities. Multiple regression analysis was applied to determine any epilepsy-related and sociodemographic factors that serve as cost-driving factors.

Results: In total, 486 patients were included, with a mean age of 40.5 ± 15.5 years (range = 18–83 years, 58.2% women). Mean 3-month COI were estimated at €4911, €2782, and €2598 for focal, genetic generalized, and unclassified epilepsy, respectively. The mean COI for patients with drug-refractory epilepsy (DRE; €7850) were higher than those for patients with non-DRE (€4720), patients with occasional seizures (€3596), or patients with seizures in remission for >1 year (€2409). Identified cost-driving factors for total COI included relevant disability (unstandardized regression coefficient b = €2218), poorer education (b = €2114), living alone (b = €2612), DRE (b = €1831), and frequent seizures (b = €2385). Younger age groups of 18–24 years (b = −€2945) and 25–34 years (b = −€1418) were found to have lower overall expenditures. A relevant disability (b = €441), DRE (b = €1253), frequent seizures (b = €735), and the need for specialized day-care (b = €749) were associated with higher direct COI, and poorer education (b = €1969), living alone (b = €2612), the presence of a relevant disability (b = €1809), DRE (b = €1831), and frequent seizures (b = €2385) were associated with higher indirect COI.

Significance: This analysis provides up-to-date COI data for use in further health economics analyses, highlighting the high economic impacts associated with disease severity, disability, and disease-related loss of productivity among adult patients with epilepsy. The identified cost drivers could be used as therapeutic and socioeconomic targets for future cost-containment strategies.

KEYWORDS

antiseizure medication, burden of illness, cost containment, HEOR, seizures

1 | INTRODUCTION

In modern health systems, which are subject to increasing economization measures, cost-recovery pressures, and profit motives, the evaluation of illness-specific costs, referred to as the costs of illness (COI), is of central importance.[1] Chronic illnesses and diseases associated with disabilities are of particular interest, because they typically involve long-term expenses for both medical and social care, and determining the profitability of both established and new diagnostic and therapeutic measures can guide treatment decisions.[2] Health economics and outcome research (HEOR) has emerged as a scientific discipline that aims to provide reliable scientific databases for the use of scientists and health care decision-makers worldwide.[3]

Epilepsy is a common, chronic, neurological disorder characterized clinically by the occurrence of recurrent seizures of various semiologies. Aside from a few variants with a self-limiting course, which typically present during childhood and adolescence, most epileptic disorders have a chronic course and are sometimes associated with the development of epileptic encephalopathies or mental or physical disabilities.[4,5] Epilepsy represents a major burden to patients, their families, and health care systems.[6-10] The influence of statutory cost-containment policies on direct epilepsy-specific COI has been demonstrated for the German health care system[11,12]; however, the introduction of new antiseizure medications (ASMs) and other novel therapeutic or diagnostic interventions can be challenging due to the presence of economically motivated obstacles and controversies.[13]

The primary aim of this study was to determine the COI among adult patients with different epilepsy etiologies, severities, and disease courses. The secondary aim was to identify epilepsy-related cost-driving factors to provide therapeutic and socioeconomic targets for future cost-containment strategies.

Key Points

- A comprehensive, multicenter study was carried out to determine epilepsy-specific COI and cost-driving factors
- Mean 3-month COI of €4911, €2782, and €2598 were calculated for focal, genetic generalized, and unclassified epilepsy, respectively
- COI were related to epilepsy severity, with drug-refractory epilepsy accounting for the highest expenditures
- Identified cost drivers were epilepsy severity, seizure frequency, presence of disability, and need for specialized daycare
- This analysis provides up-to-date COI for use in further health economics analyses

2 | MATERIALS AND METHODS

2.1 | Study setting, patients, and design

This analysis was based on data collected during the Epi2020 study, a large, multicenter study focusing on different health care aspects of patients with epilepsy in Germany. Epi2020 enrolled adult patients with epilepsy between October 2020 and December 2020 at four different epilepsy centers: Frankfurt am Main, Greifswald, Marburg, and Münster. All study sites offer specialized inpatient and outpatient care for patients with epilepsy, epileptic encephalopathies, or syndromes associated with epilepsy. Specialized epilepsy centers, such as those where this study was conducted, play a central role in the care of children, adolescents, and adult patients with epilepsy in Germany. Currently, there are 50 centers certified by the German chapter of the International League Against Epilepsy (ILAE) (Deutsche Gesellschaft für Epileptologie e.V., Berlin, Germany), with different focuses in terms of methods (e.g., epilepsy surgery) and age groups (e.g., children and adolescents). In Germany, primary care for epilepsy patients is provided by general practitioners and neurologists in private practice. Patients with unclear, drug-refractory, or potentially surgically treatable epilepsy are usually referred to one of the specialized epilepsy centers. In addition, women who desire to have children are often referred to centers for counseling, as well as pregnant patients for regular monitoring during pregnancy. Although the Epilepsy Center Frankfurt Rhine-Main has a primarily urban catchment area, the epilepsy centers in Greifswald, Marburg, and Münster provide care as the only neurologic departments in their cities and surrounding rural areas, with care for populations of more than half a million each.[14] Due to its representative population structure, the area around Marburg was used earlier for a population-based estimate of the incidence of status epilepticus in Germany.[14] All four hospitals provide the

full range of neurologic care, with expertise in epileptology and intensive care medicine. The study was approved by the ethics committee of Goethe University Frankfurt (reference 19-440) and was registered with the German Clinical Trials Register (DRKS00022024; Universal Trial Number: U1111-1252-5331).

All adult patients (≥18 years old) with confirmed epilepsy diagnoses were eligible for study inclusion. Written consent provided by the patient was mandatory before study enrollment. Patients or, in cases associated with intellectual or physical disabilities, their caretakers were asked to complete a standardized questionnaire designed to systematically record direct and indirect cost components, in addition to sociodemographic and other disease-related information. The cost-assessment questionnaire used in Epi2020 has been validated and established for use in previous HEOR studies.[12,15] For each COI item, the respondents were asked whether the costs were incurred during epilepsy treatment, and only epilepsy-associated costs were used for cost calculations.

2.2 | Cost assessment

Cost calculations were based on current national and international recommendations and followed a well-established and validated, bottom-up approach from the perspective of the statutory health insurance (Gesetzliche Krankenversicherungen).[16-18] Direct costs, such as expenditures for hospitalization, outpatient treatment, rehabilitation, medication, therapeutic measures, and medical auxiliaries, were assessed using a validated questionnaire describing the 3-month period immediately before study entry. Drug costs were obtained from the drug prescription report (Arzeiverordnungsreport 2020),[19] and costs for inpatient care (hospitalization and rehabilitation) were calculated using the current version of the German Diagnosis Related Groups (www.g-drg.de). The costs of outpatient medical consultations, therapies, and diagnostics were calculated using currently valid national benchmarks (Einheitlicher Bewertungsmaßstab, www.kbv.de).[20] Costs for medical auxiliaries were derived from provider price lists for cases in which the costs could not be indicated by the patients. Indirect costs, such as expenditures caused by loss of productivity due to unemployment or disease-related reductions in work hours, days off due to seizures, or epilepsy-related early retirement, were evaluated using the human capital approach for patients younger than 67 years, which corresponds to the retirement age in Germany. According to the German Federal Statistical Office (DeSTATIS, www.destatis.de), the mean gross income in 2020 was €47 700 per year, equaling €3975 per month or €131 per calendar day. The productivity loss attributed to epilepsy was equated as the monetary equivalent of time not worked by patients with epilepsy before reaching the retirement age of 67 years.[15,21,22] Methodically, indirect COI due to premature epilepsy-related death and intangible costs could not be assessed.

2.3 | Epilepsy severity and seizure frequency

All epilepsy diagnoses and medical and seizure terminology used in this study were derived from the latest definitions established by the ILAE.[4,5,23,24] Patients with uncertain epilepsy diagnoses were excluded from the data analysis to increase the data quality and reliability. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[25] guidelines were closely followed during study planning, study conduct, and data analysis.

Epilepsy severity was graduated according to established prognostic categories that have been used in previous health economics evaluations.[26-28] Newly diagnosed epilepsy (NDE) cases were defined as patients with new onset, unprovoked seizures who were presented for the initiation or completion of a diagnostic workup and were diagnosed with epilepsy as a result. Epilepsy in remission (seizures in remission) cases were defined as patients with complete seizure control for ≥12 months at the time of study entry. Patients with persisting seizures who did not require treatment changes were defined as occasional seizure cases. Patients with ongoing seizures were defined as non-drug-refractory epilepsy or drug-refractory epilepsy (DRE) cases, depending on the expected response to ASMs as judged by the treating physician. Seizure frequency was calculated according to the patients' reports for overall seizure frequency and was not divided according to individual seizure semiology.

2.4 | Data entry and statistical analysis

Statistical comparisons were performed using appropriate tests in SPSS (IBM Corporation) or GraphPad Prism 9 (GraphPad Software). Univariate analysis was performed using the Kruskal–Wallis test. Based on the level of measurement, only multiple regression analysis (MRA) using dichotomously dummy-coded variables was found to be suitable for multivariate data exploration. All variables from the univariate analysis, regardless of their significance levels, were included in the MRA, except for the employment situation in the indirect and total COI analyses, as this variable was the basis for the calculation of these values. No adjustments for multiple testing were

made due to the MRA used for the final interpretation of data. The unstandardized regression coefficient (b) was used to illustrate the dynamics of COI for those variables significantly contributing to the MRA. In this context, b indicates the increases or decreases of COI in Euros when the respective predictor was present (e.g., disability). Probability values < .05 were considered significant. Costs have been rounded to full Euro amounts, in keeping with typical convention, and are displayed as the mean, median, minimum, maximum, and 95% confidence interval, which was calculated using the bias-corrected accelerated bootstrapping method,[29] assuming a right-skewed distribution. Sociodemographic data are presented as the mean ± SD, median, minimum, and maximum for continuous variables or as the number and percentage for categorical variables. Figures were created with GraphPad Prism 9 and Pixelmator Pro (Pixelmator Team).

3 | RESULTS

3.1 | Study population

Overall, health economics data were obtained from 486 adult patients enrolled in the present study, with a mean age of 40.5 ± 15.5 years (range = 18–83 years), 58.2% of whom were women (n = 283). Relevant disease-specific and sociodemographic data for the study population are presented in Table 1.

3.2 | Epilepsy-related COI

COI were calculated and stratified for different epilepsy syndromes and according to disease severity and seizure frequency. The average overall COI, without consideration for epilepsy type, severity, or seizure frequency, were calculated as €4203 ± €5473 (median = €1237), ranging from a minimum of €0 to a maximum of €21 667 over a 3-month period. Direct cost components accounted for 32.3% of the total COI, whereas indirect cost components represented 67.7%, with mean expenditures of €1358 ± €1690 (median = €728, range = €0–€13 158) and €2845 ± €4931 (median = €0, range = €0–€11 925), respectively. The proportions of direct and indirect costs and detailed data regarding cost components are presented in Figure 1.

The total COI and potential cost drivers are presented in Table 2, with direct and indirect disease-related expenditures presented in Tables 3 and 4, respectively. No significant differences in direct (p = .798), indirect (p = .213), or total costs (p = .234) were identified between patients recruited at different centers.

TABLE 1 Sociodemographic and disease-related factors for the study population (N = 486)

Factor	Value
Sex, % (n)	
Female	58.2 (283)
Male	41.8 (203)
Age, years	
Mean ± SD	40.5 ± 15.5
Median	38.0
Range	18–83
Epilepsy onset, years	
Mean ± SD	24.0 ± 16.2
Median	20.0
Range	0–79
Epilepsy duration, years	
Mean ± SD	16.1 ± 15.1
Median	12.0
Range	0–71
Epilepsy severity, % (n)	
NDE	1.9 (9)
SR	40.1 (195)
OS	16.3 (79)
NDRE	21.4 (104)
DRE	20.4 (99)
Therapy regimen, % (n)	
0 ASM	4.5 (22)
1 ASM	40.5 (197)
2 ASMs	35.4 (172)
≥3 ASMs	19.5 (95)

Abbreviations: ASM, antiseizure medication; DRE, drug-refractory epilepsy; NDE, newly diagnosed epilepsy; NRDE, non-drug-refractory epilepsy; OS, occasional seizures; SR, seizures in remission.

3.3 | Cost-driving factors

3.3.1 | Univariate analysis

The univariate analysis revealed sex, age, level of education, employment status, marital status, presence of a relevant disability, epilepsy etiology, epilepsy severity, seizure frequency, and ASM regimen as factors significantly associated with increased total COI (Table 2). Sex, age, employment situation, marital status, the presence of a relevant disability, epilepsy etiology, epilepsy severity, seizure frequency, and the number of ASMs being used were significant cost-driving factors for direct COI (Table 3). Age, education, employment situation, presence of a relevant disability, epilepsy etiology, epilepsy severity, seizure frequency, and the number of ASMs being used were also identified as significant factors associated with indirect

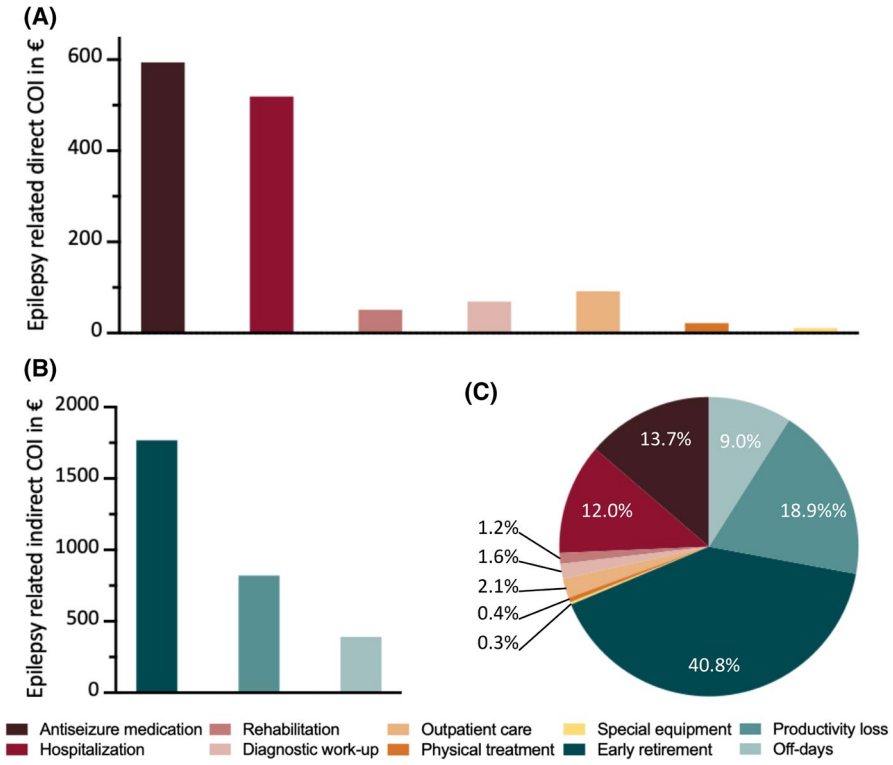

FIGURE 1 Mean epilepsy-related (A) direct and (B) indirect cost components and (C) their shares of total epilepsy-related costs of illness (COI; in Euros)

COI (Table 4). The cost distributions for age, epilepsy severity, and seizure frequency are shown in Figure 2.

3.3.2 | Multivariate analysis

The MRA revealed a model with a significantly improved ability to predict epilepsy-specific total costs relative to any univariate analysis ($p < .001$), with an overall model fit of $R^2 = .306$. The younger age groups of 18–24 years (b = −€2945, $p < .001$) and 25–34 years (b = −€1418, $p = .032$) were associated with significantly lower total COI. Less education (≤10 years, b = €2114, $p = .003$), living alone (b = €2702, $p < .001$), the presence of a relevant disability (b = €2219, $p < .001$), DRE (b = €3150, $p < .001$), and experiencing weekly seizures (b = €3144, $p < .001$) were associated with significantly higher total COI. The MRA also revealed a model with a significantly improved ability to predict epilepsy-specific direct costs relative to any univariate analysis ($p < .001$), with an overall model fit of $R^2 = .194$. The presence of a relevant disability (b = €441, $p = .013$), DRE (b = €1253, $p < .001$), experiencing weekly seizures (b = €735, $p = .014$), and the need for specialized daycare (b = €749, $p = .039$) remained significant variables associated with higher direct costs. All other tested variables remained nonsignificant within the model ($p \geq .05$). Finally, the MRA revealed a model with a significantly improved ability to predict epilepsy-specific indirect costs relative to any univariate analysis ($p < .001$), with an overall model fit of $R^2 = .241$. The younger age groups of 18–24 years (b = −€3169, $p < .001$) and 25–34 years (b = −€1434, $p = .021$) were associated with significantly lower indirect costs, whereas the age group of 55–64 years was associated with higher indirect COI (b = €1626, $p = .035$). Less education (≤10 years, b = €1969, $p = .004$), living alone (b = €2612, $p < .001$), the presence of a relevant disability (b = €1809, $p < .001$), DRE (b = €1831, $p = .037$), and experiencing weekly seizures (b = €2385, $p = .005$) were associated with significantly higher indirect COI.

4 | DISCUSSION

In increasingly economically oriented health care systems, the accurate evaluations of COI and cost-driving factors represent central aspects that guide the implementation of cost-containment measures. This prospective, multicenter study provided detailed COI data for 486 patients with different epilepsy etiologies and severities, and MRA was used to identify potential cost-driving factors that could serve as future targets for cost-containment approaches.

Disease-specific direct, indirect, and overall COI varied significantly between different patient groups (Tables 2–4). In particular, the differences in cost-driving factors according to age groups, disease severity, and seizure frequency were striking (Figure 1). Many other factors found to be significant in the univariate analysis for higher or lower overall, direct, or indirect COI failed to remain significant in the multivariate analysis. For these variables (e.g., patient sex), it can be assumed that they are not independent

TABLE 2 Impacts of sociodemographic and disease-specific factors on total costs of illness in adult patients with epilepsy (in 2020 Euros, $N = 486$)

Factor	(%) *n*	Mean ± SD	Median	Minimum	Maximum	95% confidence interval[a]	*p*[b]
Sociodemographic aspects							
Sex							
Female	58.2 (283)	3657 ± 5155	999	0	21 572	3103–4194	.003[c]
Male	41.8 (203)	4964 ± 5815	1734	0	21 667	4267–5711	
Age, years							
18–24	17.7 (86)	2473 ± 3862	986	0	15 498	1732–3251	<.001[c]
25–34	25.3 (123)	3539 ± 4897	1347	0	18 015	2710–4473	
35–44	21.8 (106)	4737 ± 5765	1675	46	18 733	3729–5853	
45–54	13.9 (67)	5597 ± 6363	1754	0	21 667	4195–7071	
55–64	13.0 (63)	7789 ± 6152	12 053	19	16 630	6316–9269	
≥65	8.4 (41)	653 ± 802	341	0	3241	427–892	
Level of education							
None	4.7 (23)	5728 ± 5406	3840	0	16 805	3746–7916	<.001[c]
≤10 years	17.5 (85)	5857 ± 6236	2712	0	21 667	4622–7178	
11 years	32.3 (157)	4403 ± 5595	1459	25	18 252	3535–5387	
13 years	41.6 (202)	2983 ± 4650	864	0	21 572	2417–3521	
n.a.	3.9 (19)	6272 ± 6293	2771	0	16 423	3395–9078	
Marital status							
Permanent relationship	55.3 (269)	3727 ± 5133	1077	0	21 572	3052–4455	.002[c]
Divorced	4.7 (23)	7297 ± 5914	6724	166	14 593	4596–9711	
Single, living with others	16.5 (80)	4738 ± 6256	1323	0	21 667	3365–6339	
Single, living alone	19.8 (96)	4464 ± 5374	1666	0	18 252	3463–5462	
Widowed	1.9 (9)	2854 ± 5263	103	25	12 317	103–6127	
n.a.	1.9 (9)	4326 ± 6235	1143	523	16 423	916–8554	
Relevant disability							
Yes	58.2 (283)	5742 ± 6060	2438	0	21 667	4984–6453	<.001[c]
No	41.2 (200)	2008 ± 3522	452	0	15 498	1545–2526	
Epilepsy-related aspects							
Epilepsy syndrome							
Focal epilepsy	67.7 (329)	4911 ± 5836	1639	0	21 667	4344–5565	<.001[c]
Temporal lobe epilepsy[c]	32.1 (156)	5085 ± 5695	2005	0	21 667	4193–6021	
Frontal lobe epilepsy[c]	8.0 (39)	3692 ± 5372	1077	30	18 252	2407–5698	
Idiopathic generalized epilepsy	21.2 (103)	2782 ± 4331	599	0	14 421	2067–3639	
Juvenile myoclonic epilepsy[c]	8.4 (41)	2692 ± 4260	636	0	14 421	1519–4032	
Juvenile absence epilepsy[c]	1.9 (9)	2974 ± 4363	1065	46	12 424	679–5848	
Unclassified epilepsy	11.1 (54)	2598 ± 4189	660	0	14 065	1612–3657	

(Continues)

TABLE 2 (Continued)

Factor	(%) *n*	Mean ± SD	Median	Minimum	Maximum	95% confidence interval[a]	*p*[b]
Epilepsy severity							
Newly diagnosed epilepsy	1.9 (9)	2546 ± 2243	1847	71	7231	1200–4096	<.001[c]
Seizures in remission	40.1 (195)	2409 ± 4369	399	0	14 928	1770–3038	
Occasional seizures	16.3 (79)	3569 ± 5160	1178	30	18 733	2538–4881	
Non-drug-refractory epilepsy	21.4 (104)	4720 ± 5461	1769	0	21 667	3761–5783	
Drug-refractory epilepsy	20.4 (99)	7850 ± 6065	5726	0	21 572	6587–9103	
Epilepsy duration							
≤2 years	18.7 (91)	3761 ± 4911	1347	0	16 630	2820–4776	.080
3–10 years	22.4 (109)	3659 ± 5511	799	0	21 667	2723–4678	
≥10 years	53.9 (262)	4428 ± 5552	1425	0	21 572	3817–5067	
n.a.	4.9 (24)	5898 ± 6247	2906	0	18 015	3411–8628	
Epilepsy onset							
<18 years of age	29.2 (142)	3679 ± 5112	1073	19	16 805	2848–4522	.278
≥18 years of age	64.6 (314)	4454 ± 5592	1483	0	21 667	3843–5057	
n.a.	6.2 (30)	4050 ± 5852	988	0	18 015	1959–6032	
Seizure frequency							
≥1 seizure per day	4.3 (21)	6183 ± 5730	3472	0	18 252	3754–8935	<.001[c]
≥1 seizure per week	10.1 (49)	8481 ± 5997	8625	0	21 572	6769–10 182	
≥1 seizure per month	17.7 (86)	5105 ± 5528	2384	46	18 015	3977–6314	
≥1 seizure per 6 months	9.3 (45)	5273 ± 6031	2472	185	21 667	3605–6992	
≥1 seizure per 12 months	10.7 (52)	3512 ± 4939	1161	30	16 870	2301–4873	
Seizure-free for ≥12 months	40.7 (198)	2274 ± 4257	405	0	16 630	1685–2881	
Therapy regimen							
No ASM	4.5 (22)	3118 ± 5016	308	0	14 593	1179–5523	<.001[c]
1 ASM	40.5 (197)	2309 ± 4198	425	19	21 572	1768–2945	
2 ASMs	35.4 (172)	4745 ± 5581	1795	74	21 667	3927–3991	
≥3 ASMs	19.5 (95)	7401 ± 6070	4995	218	18 252	6252–8568	

Abbreviations: ASM, antiseizure medication; n.a., not available.

[a]Calculated using the bias-corrected and accelerated method assuming a right-skewed distribution.

[b]Probability value by univariate analysis performed using Kruskal–Wallis test.

[c]Statistically significant.

[d]Subvariables not included in univariate and multivariate analysis.

cost-driving factors for COI in the underlying study population. The mean disease-related expenditures for focal epilepsy were calculated at €1536 over 3 months, corresponding to €6144 per year, €512 per month, and €17 per day. COI of €1044, €4176, €358, and €11 were calculated for genetic generalized epilepsies per quarter, year, month, and day, respectively. These amounts were comparable to the mean annual expenditures of €9256 reported in a recent study examining epilepsy-related COI in Austria, the range of €7318–€9878 ($8412–$11 354) reported by a 2013 USA-based analysis, and the range of €31–€3703 ($40–$4748) reported by a global analysis of the burden of epilepsy in 2006.[9,30,31] The observed increase in recent costs appears to be associated with rising per capita income, inflation, and the rising costs of health care.[11,12]

In line with the present findings, several studies from the USA and Europe identified the lack of seizure freedom associated with recurrent seizures, hospitalization, and seizure-related unemployment and productivity losses as the main cost-driving factors underlying

TABLE 3 Impacts of sociodemographic and disease-specific factors on direct costs of illness in adult patients with epilepsy (in 2020 Euros, $N = 486$)

Factor	(%) *n*	Mean ± SD	Median	Minimum	Maximum	95% confidence interval[d]	*p*[a]
Sociodemographic aspects							
Sex							
Female	58.2 (283)	1209 ± 1565	653	0	13 158	1043–1403	.024[c]
Male	41.8 (203)	1565 ± 1834	866	0	11 854	1355–1802	
Age, years							
18–24	17.7 (86)	1444 ± 2033	716	0	13 158	1732–3251	.008[c]
25–34	25.3 (123)	1412 ± 1745	812	0	11 854	1147–1724	
35–44	21.8 (106)	1323 ± 1444	736	46	6834	1067–1614	
45–54	13.9 (67)	1667 ± 2033	915	0	9742	1272–2140	
55–64	13.0 (63)	1321 ± 1372	668	0	5335	1016–1631	
≥65	8.4 (41)	654 ± 802	341	0	3241	427–892	
Level of education							
None	4.7 (23)	2039 ± 1835	1561	0	7052	1376–2814	.055
≤10 years	17.5 (85)	1495 ± 1910	665	0	9742	1112–1893	
11 years	32.3 (157)	1235 ± 1213	812	25	6834	1048–1453	
13 years	41.6 (202)	1271 ± 1854	651	0	13 158	1060–1513	
n.a.	3.9 (19)	1853 ± 1869	1473	0	6178	3395–9078	
Employment status							
Employed	50.8 (247)	1209 ± 1510	706	0	11 854	1030–1409	<.001[c]
Unemployed	6.2 (30)	2202 ± 2381	1135	90	9742	1451–3108	
Parental leave	4.5 (22)	1183 ± 1032	689	49	3414	777–1648	
In training	8.8 (43)	1343 ± 2285	541	27	13 158	785–2044	
Early retirement	16.0 (78)	1491 ± 1312	948	0	6327	1219–1783	
Retirement	7.8 (38)	688 ± 997	240	0	4155	405–981	
Need for specialized daycare	5.8 (28)	2466 ± 2498	1849	0	9647	1697–3554	
Marital status							
Permanent relationship	55.3 (269)	1247 ± 1591	636	0	11 854	1072–1449	<.001[c]
Divorced	4.7 (23)	1594 ± 1604	1007	166	6724	1053–2281	
Single, living with others	16.5 (80)	1523 ± 2217	648	0	13 158	1077–2074	
Single, living alone	19.8 (96)	1562 ± 1523	1135	0	7052	1282–1870	
Widowed	1.9 (9)	204 ± 309	79	0	971	55–432	
n.a.	1.9 (9)	1571 ± 1445	999	0	4662	784–2537	
Relevant disability							
Yes	58.2 (283)	1614 ± 1710	999	0	9742	1408–1810	<.001[c]
No	41.2 (200)	995 ± 1603	369	0	13 158	802–1234	
Epilepsy-related aspects							
Epilepsy syndrome							
Focal epilepsy	67.7 (329)	1536 ± 1774	971	0	13 158	1380–1709	<.001[c]
Temporal lobe epilepsy[b]	32.1 (156)	1719 ± 2018	1211	0	13 158	1420–2024	
Frontal lobe epilepsy[b]	8.0 (39)	1125 ± 1213	648	30	6327	784–1552	

TABLE 3 (Continued)

Factor	(%) *n*	Mean ± SD	Median	Minimum	Maximum	95% confidence interval[d]	*p*[a]
Idiopathic generalized epilepsy	21.2 (103)	1044 ± 1524	440	0	7934	792–1327	
Juvenile myoclonic epilepsy[b]	8.4 (41)	1161 ± 1714	546	0	7934	715–1648	
Juvenile absence epilepsy[b]	1.9 (9)	1605 ± 2458	499	46	7734	472–3313	
Unclassified epilepsy	11.1 (54)	868 ± 1243	424	0	7052	588–1173	
Epilepsy severity							
Newly diagnosed epilepsy	1.9 (9)	1601 ± 952	1792	71	3425	1032–4096	<.001[c]
Seizures in remission	40.1 (195)	681 ± 938	310	0	6311	562–806	
Occasional seizures	16.3 (79)	1394 ± 1623	894	30	7.334	1068–1780	
Non-drug-refractory epilepsy	21.4 (104)	1454 ± 1747	1006	0	11 854	1165–1851	
Drug-refractory epilepsy	20.4 (99)	2538 ± 2162	2301	0	13 158	2131–2966	
Epilepsy duration							
≤2 years	18.7 (91)	1357 ± 2049	741	0	13 158	995–1791	.398
3–10 years	22.4 (109)	1316 ± 1763	470	0	9742	1017–1635	
≥10 years	53.9 (262)	1349 ± 1525	744	0	9647	1178–1541	
n.a.	4.9 (24)	1644 ± 1645	1252	0	6090	1027–2362	
Epilepsy onset							
<18 years of age	29.2 (142)	1303 ± 1510	705	19	7934	1069–1555	.266
≥18 years of age	64.6 (314)	1394 ± 1758	818	0	13 158	1215–1590	
n.a.	6.2 (30)	1241 ± 1807	452	0	6724	680–1861	
Seizure frequency							
≥1 seizure per day	4.3 (21)	2262 ± 1868	2173	0	7052	1571–3011	<.001[c]
≥1 seizure per week	10.1 (49)	2520 ± 2493	1959	0	13 158	1916–3249	
≥1 seizure per month	17.7 (86)	1727 ± 1568	1341	0	6724	1400–2094	
≥1 seizure per 6 months	9.3 (45)	1908 ± 2109	1081	185	9742	1350–2525	
≥1 seizure per 12 months	10.7 (52)	1261 ± 1374	728	30	6178	908–1625	
Seizure-free for ≥12 months	40.7 (198)	734 ± 1182	323	0	11 854	592–915	
Therapy regimen							
No ASM	4.5 (22)	559 ± 1118	46	0	4602	182–1041	<.001[c]
1 ASM	40.5 (197)	758 ± 1143	340	19	9647	607–914	
2 ASMs	35.4 (172)	1607 ± 1782	977	74	11 854	1364–1903	
≥3 ASMs	19.5 (95)	2334 ± 1994	1779	218	13 158	1977–2757	

Abbreviations: ASM, antiseizure medication; n.a., not available.

[a]Calculated using the bias-corrected and accelerated method assuming a right-skewed distribution.

[b]Probability value by univariate analysis performed using Kruskal–Wallis test.

[c]Statistically significant.

[d]Subvariables not included in univariate and multivariate analysis.

TABLE 4 Impacts of sociodemographic and disease-specific factors on indirect costs of illness in adult patients with epilepsy (in 2020 Euros, $N = 486$)

Factor	(%) *n*	Mean ± SD	Median	Minimum	Maximum	95% confidence interval[c]	*p*[d]
Sociodemographic aspects							
Sex							
Female	58.2 (283)	2448 ± 4667	0	0	11 925	1989–2895	.112
Male	41.8 (203)	3399 ± 5239	0	0	11 925	2751–4094	
Age, years							
18–24	17.7 (86)	1029 ± 3063	0	0	11 925	478–1634	<.001[c]
25–34	25.3 (123)	2127 ± 4332	0	0	11 925	1382–2909	
35–44	21.8 (106)	3414 ± 5293	0	0	11 925	2479–4409	
45–54	13.9 (67)	3930 ± 5542	0	0	11 925	2698–5136	
55–64	13.0 (63)	6468 ± 5846	11 925	0	11 925	4957–7942	
≥65	8.4 (41)	0	0	0	0	–	
Level of education							
None	4.7 (23)	3689 ± 5116	523	0	11 925	1864–5823	<.001[c]
≤10 years	17.5 (85)	4363 ± 5677	0	0	11 925	3261–5564	
11 years	32.3 (157)	3168 ± 5120	0	0	11 925	2384–4070	
13 years	41.6 (202)	1712 ± 4032	0	0	11 925	1195–2207	
n.a.	3.9 (19)	4419 ± 5873	0	0	11 925	1912–7045	
Marital status							
Permanent relationship	55.3 (269)	2480 ± 4654	0	0	11 925	1896–3123	.327
Divorced	4.7 (23)	5703 ± 6091	0	0	11 925	3117–7950	
Single, living with others	16.5 (80)	3216 ± 5220	0	0	11 925	2133–4404	
Single, living alone	19.8 (96)	2902 ± 4975	0	0	11 925	1944–3849	
Widowed	1.9 (9)	2650 ± 5258	0	0	11 925	0–5963	
n.a.	1.9 (9)	2755 ± 5156	196	0	11 925	78–6109	
Relevant disability							
Yes	58.2 (283)	4128 ± 5532	0	0	11 925	3477–4785	<.001[c]
No	41.2 (200)	1013 ± 3113	0	0	11 925	598–1486	
Epilepsy-related aspects							
Epilepsy syndrome							
Focal epilepsy	67.7 (329)	3375 ± 5237	0	0	11 925	2834–3980	.014[c]
Temporal lobe epilepsy[a]	32.1 (156)	3367 ± 5207	0	0	11 925	2561–4231	
Frontal lobe epilepsy[a]	8.0 (39)	2838 ± 4866	0	0	11 925	1416–4386	
Idiopathic generalized epilepsy	21.2 (103)	1738 ± 4087	0	0	11 925	1012–2582	
Juvenile myoclonic epilepsy[a]	8.4 (41)	1531 ± 3935	0	0	11 925	474–2777	
Juvenile absence epilepsy[a]	1.9 (9)	1369 ± 3961	0	0	11 925	0–3980	
Unclassified epilepsy	11.1 (54)	1730 ± 3908	0	0	11 925	801–2750	

(Continues)

TABLE 4 (Continued)

Factor	(%) *n*	Mean ± SD	Median	Minimum	Maximum	95% confidence interval[c]	*p*[d]
Epilepsy severity							
Newly diagnosed epilepsy	1.9 (9)	944 ± 1995	0	0	5619	0–2374	<.001[c]
Seizures in remission	40.1 (195)	1728 ± 4105	0	0	11 925	1153–2333	
Occasional seizures	16.3 (79)	2175 ± 4570	0	0	11 925	1201–3368	
Non-drug-refractory epilepsy	21.4 (104)	3267 ± 5085	0	0	11 925	2320–4264	
Drug-refractory epilepsy	20.4 (99)	5312 ± 5776	1307	0	11 925	4135–6529	
Epilepsy duration							
≤2 years	18.7 (91)	2403 ± 4516	0	0	11 925	1552–3339	.148
3–10 years	22.4 (109)	2343 ± 4599	0	0	11 925	1540–3207	
≥10 years	53.9 (262)	3079 ± 5126	0	0	11 925	2505–3684	
n.a.	4.9 (24)	4254 ± 5556	849	0	11 925	2246–6667	
Epilepsy onset							
<18 years of age	29.2 (142)	2377 ± 4604	0	0	11 925	1674–3114	.526
≥18 years of age	64.6 (314)	3061 ± 5056	0	0	11 925	2498–3621	
n.a.	6.2 (30)	2809 ± 5117	0	0	11 925	988–4549	
Seizure frequency							
≥1 seizure per day	4.3 (21)	3921 ± 5273	915	0	11 925	1820–6355	<.001[c]
≥1 seizure per week	10.1 (49)	5961 ± 5622	3920	0	11 925	4420–7485	
≥1 seizure per month	17.7 (86)	3379 ± 5222	0	0	11 925	2396–4448	
≥1 seizure per 6 months	9.3 (45)	3365 ± 5284	0	0	11 925	1880–4911	
≥1 seizure per 12 months	10.7 (52)	2251 ± 4599	0	0	11 925	1066–3532	
Seizure-free for ≥12 months	40.7 (198)	1539 ± 3925	0	0	11 925	1038–2083	
Therapy regimen							
No ASM	4.5 (22)	2558 ± 4824	0	0	11 925	668–4831	<.001[c]
1 ASM	40.5 (197)	1551 ± 3813	0	0	11 925	1049–2124	
2 ASMs	35.4 (172)	3137 ± 5129	0	0	11 925	2396–3991	
≥3 ASMs	19.5 (95)	5067 ± 5782	522	0	11 925	3927–6177	

Abbreviations: ASM, antiseizure medication; n.a., not available.

[a]Calculated using the bias-corrected accelerated method assuming a right-skewed distribution.

[b]Probability value by univariate analysis performed using Kruskal–Wallis test.

[c]Statistically significant.

[d]Subvariables not included in univariate and multivariate analysis.

epilepsy-related COI. Although hospitalization predominantly impacts direct COI, productivity loss due to job loss and unemplyoment is most likely to affect indirect COI.[27,30,32,33] The costs of ASMs were not significant within the model, despite having been identified as a relevant cost component affecting direct COI by patients with epilepsy.[27,30,32,33] This outcome is likely attributable to the comparable prices of different ASMs due to statutory cost-containment measures and the correlation between ASM regimens and seizure frequency, treatment response, and epilepsy severity.[11] Therefore, among the current study population, ASMs were not identified as an independent variable affecting COI. These findings distinguish epilepsy from other chronic neurological diseases, such as multiple sclerosis (€44 000–€62 700/year) and chronic inflammatory demyelinating polyneuropathy (€11 333 per 3 months), for which expensive disease-modifying drugs have been identified as cost-driving factors of direct COI.[34,35] Similar to the findings presented by other studies, epilepsy is increasingly associated with indirect

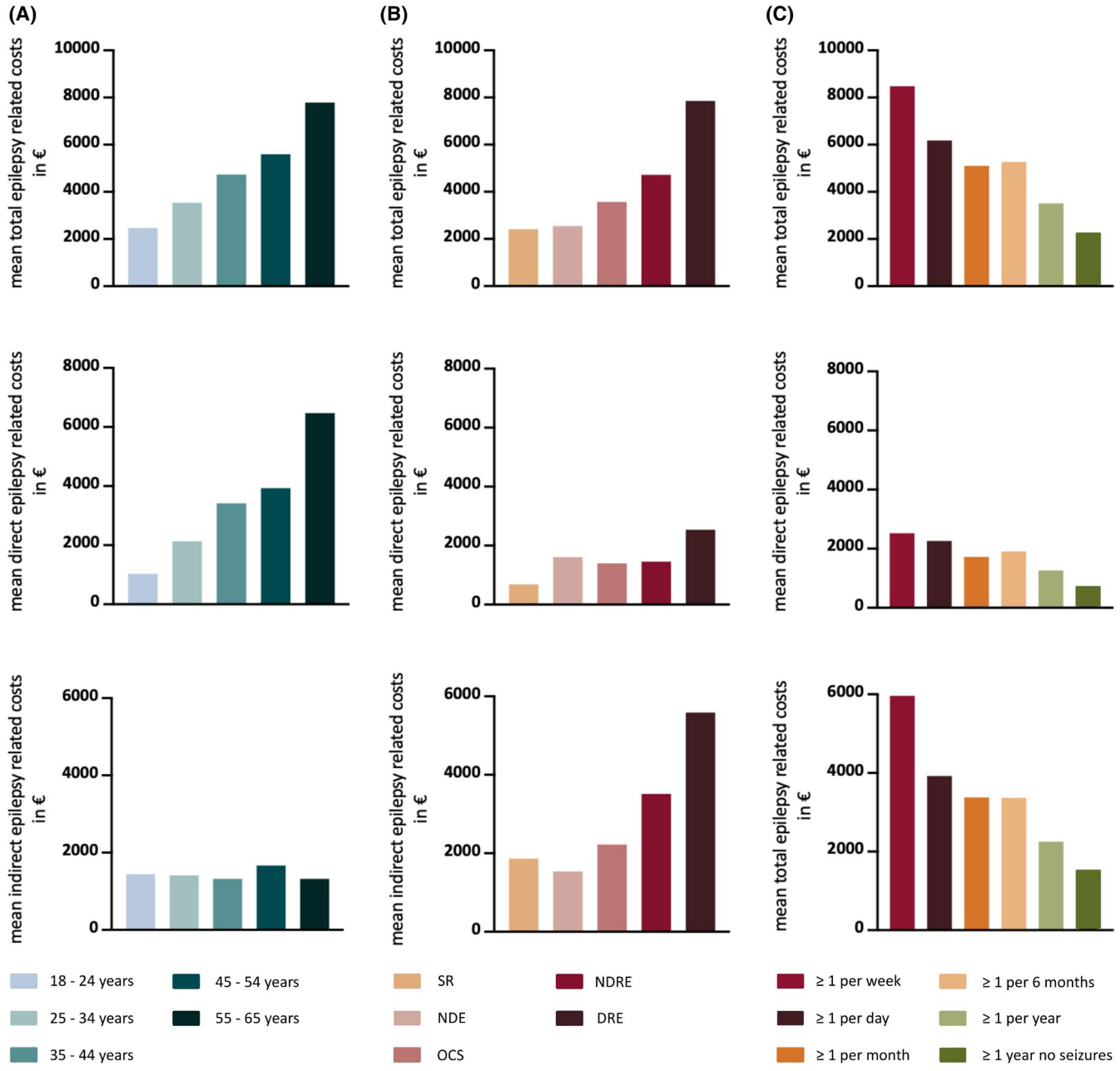

FIGURE 2 Mean epilepsy-related total, direct, and indirect costs of illness (from top to bottom, in Euros), according to (A) age, (B) epilepsy severity, and (C) seizure frequency, displayed as bar charts. DRE, drug-refractory epilepsy; NDE, newly diagnosed epilepsy; NDRE, non-drug-refractory epilepsy; OCS, occasional seizures; SR, seizures in remission

costs due to productivity loss, including absence from work due to seizures or side effects, unemployment, and early retirement.[12,15,30,36] Because employment situations served as the basis for calculating indirect COI and are, therefore, directly included in total costs, these aspects were excluded from the MRA. Therefore, productivity loss was not identified as a sociodemographic risk factor for high COI in the current analysis due to methodological limitations.

An increase in COI with age and the presence of a relevant disability that affects daily living has also been demonstrated in children, adolescents, and adults with epilepsy or other diseases characterized by epilepsy and epileptic seizures, such as Dravet syndrome or tuberous sclerosis complex.[8,37,38,39] NDE has also been shown to be associated with high care costs, although this finding was not reflected in the available data,[40] which may be due to the low number of NDE cases in the present study population. NDE is usually associated with costs for diagnostic procedures, inpatient admission, and days off work upon presentation with a first seizure.

In contrast with the present findings, previous studies did not identify associations between low education levels or marital status and disease-related COI.[41] The finding that both factors were significantly associated with higher COI in the present study may indicate the potential benefits of disease-specific educational and counseling services, which have previously been demonstrated to improve health-related quality of life and patient satisfaction.[42-44] Different disease-specific and sociodemographic factors were found to have significant influences on epilepsy-specific COI, and these factors may represent ideal targets for the future treatment of epilepsy and cost-containment measures from both medical and economic perspectives.

This study has several methodical limitations that may bias the results and restrict the generalizability of the findings. The study design relied on patients and their caregivers providing complete and truthful information, and post hoc data verification was not possible except for plausibility checks. In this study, COI were recorded retrospectively over a period of 3 months; hence, indirect costs due to epilepsy-related premature death (e.g., due to sudden unexpected death in epilepsy patients) or due to seizure-related trauma (fatal injuries and accidents) could not be assessed. Likewise, intangible costs could not be captured for methodological reasons. The use of mean daily doses to assess drug costs does not allow for the consideration of differences in the drug prices established by different manufacturers, which, although unlikely due to the large sample size, could lead to bias in the estimated ASM costs. Despite the multicenter recruitment of patients, regional characteristics in drug prescriptions or the provision of other medical services could also affect the comparability and generalizability of the data. Moreover, the recording of COI at epilepsy centers may have led to an upward bias of the cost results. In addition, reductions in both elective inpatient and outpatient medical care imposed in response to the SARS-CoV-2 pandemic may also have influenced the data.[45] In line with previous German COI studies, the proportion of female patients in the present study population was higher than in the general population (51% vs. 58%, www.destatis.de). Due to a lack of gender-specific inclusion bias, this seems to be mainly due to a higher willingness of patients to participate in the study[46] and possibly to more female patients being assigned to the centers (e.g., counseling for female patients with the desire to have children). However, the multicenter study design and the close consideration of STROBE guidelines should reduce the potential impacts of these limitations to an acceptable minimum.

In conclusion, epilepsy generates relevant COI, and the levels of direct, indirect, and total costs depend on various sociodemographic and disease-specific factors. Although some of these factors cannot be influenced, disease-specific factors reveal potential intervention targets for further cost containment. In particular, reductions in seizure frequency and adequate therapy for patients with DRE appear to be central factors that should be targeted. Based on the previously reported high demand for and acceptance of specialized epilepsy counseling services in contrast to their very limited availability and uneven distribution among German federal states,[42,47,48] the present findings suggest that the timely referral of patients with DRE or high seizure frequency to specialized counseling centers, specialized resident neurologists, or epilepsy centers could be advantageous. Providing specific counseling for patients and family members and access to advanced diagnostics and therapeutic options, these facilities could help to reduce indirect COI and also direct cost components.

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CONFLICT OF INTEREST

L.L. reports speaker's honoraria from Eisai, GW pharmaceuticals, and Biogen. S.K. reports research funding from Biogen. I.I. reports honoraria from Arvelle Therapeutics and UCB Pharma. F.v.P. is on the speakers bureau of Bial, Desitin Arzneimittel, Eisai, GW Pharmaceuticals, Arvelle Therapeutics, Angelinipharma, Zogenix, and UCB Pharma and reports personal fees and grants from Bial, Desitin Arzneimittel, Eisai, GW Pharmaceuticals, Arvelle Therapeutics, Angelinipharma, Zogenix, and UCB Pharma. F.v.P. reports personal fees and grants from Bial, Desitin Arzneimittel, Eisai, GW Pharmaceuticals, Arvelle Therapeutics, Angelinipharma, Zogenix, and UCB Pharma. F.R. reports personal fees from Arvelle Therapeutics, Desitin Arzneimittel, Eisai, GW Pharmaceuticals, Novartis, Medtronic, and UCB and grants from the Detlev-Wrobel-Fonds for Epilepsy Research, the Deutsche Forschungsgemeinschaft, the LOEWE Program of the State of Hesse, and the European Union. A.S. reports personal fees and grants from Angelini Pharma/Arvelle Therapeutics, Desitin Arzneimittel, Eisai, GW Pharmaceuticals, Marinus Pharma, UCB, UNEEG medical, and Zogenix. None of the other authors has any conflict of interest to disclose. 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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REFERENCES

1. Finkelstein E, Corso P. Cost-of-illness analyses for policy making: a cautionary tale of use and misuse. Expert Rev Pharmacoecon Outcomes Res. 2003;3:367–9.
2. Jo C. Cost-of-illness studies: concepts, scopes, and methods. Clin Mol Hepatol. 2014;20:327–37.
3. O'Donnell JC. Personalized medicine and the role of health economics and outcomes research: issues, applications, emerging trends, and future research. Value Health. 2013;16(6):S1–3.
4. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30.
5. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017;58:531–42.
6. Allers K, Essue BM, Hackett ML, Muhunthan J, Anderson CS, Pickles K, et al. The economic impact of epilepsy: a systematic review. BMC Neurol. 2015;15:245.
7. Strzelczyk A, Griebel C, Lux W, Rosenow F, Reese JP. The burden of severely drug-refractory epilepsy: a comparative longitudinal evaluation of mortality, morbidity, resource use, and cost using German health insurance data. Front Neurol. 2017;8:712.
8. Strzelczyk A, Kalski M, Bast T, Wiemer-Kruel A, Bettendorf U, Kay L, et al. Burden-of-illness and cost-driving factors in Dravet syndrome patients and carers: a prospective, multicenter study from Germany. Eur J Paediatr Neurol. 2019;23:392–403.
9. Strzelczyk A, Reese JP, Dodel R, Hamer HM. Cost of epilepsy: a systematic review. Pharmacoeconomics. 2008;26:463–76.
10. Willems LM, Schubert-Bast S, Grau J, Hertzberg C, Kurlemann G, Wiemer-Kruel A, et al. Health-related quality of life in children and adolescents with tuberous sclerosis complex and their caregivers: A multicentre cohort study from Germany. Eur J Paediatr Neurol. 2021;35:111–22.
11. Willems LM, Hamer HM, Knake S, Rosenow F, Reese JP, Strzelczyk A. General trends in prices and prescription patterns of anticonvulsants in Germany between 2000 and 2017: analysis of national and cohort-based data. Appl Health Econ Health Policy. 2019;17:707–22.
12. Willems LM, Richter S, Watermann N, Bauer S, Klein KM, Reese JP, et al. Trends in resource utilization and prescription of anticonvulsants for patients with active epilepsy in Germany from 2003 to 2013—a ten-year overview. Epilepsy Behav. 2018;83:28–35.
13. Staab TR, Walter M, Mariotti Nesurini S, Dintsios CM, Graf von der Schulenburg JM, Amelung VE, et al. "Market withdrawals" of medicines in Germany after AMNOG: a comparison of HTA ratings and clinical guideline recommendations. Health Econ Rev. 2018;8:23.
14. Kortland LM, Alfter A, Bähr O, Carl B, Dodel R, Freiman TM, et al. Costs and cost-driving factors for acute treatment of adults with status epilepticus: a multicenter cohort study from Germany. Epilepsia. 2016;57:2056–66.
15. Strzelczyk A, Haag A, Reese JP, Nickolay T, Oertel WH, Dodel R, et al. Trends in resource utilization and prescription of anticonvulsants for patients with active epilepsy in Germany. Epilepsy Behav. 2013;27:433–8.
16. Schöffski O, von der Schulenburg JM. Gesundheitsökonomische Evaluationen. 4th edition. Berlin, Germany: Springer; 2012.
17. Graf von der Schulenburg JM, Greiner W, Jost F, Klusen N, Kubin M, Leidl R, et al. German recommendations on health economic evaluation: third and updated version of the Hanover Consensus. Value Health. 2008;11(4):539–44.
18. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). Technical document on cost estimation. https://www.iqwig.de/en/about-us/methods/. Accessed October 09, 2008.
19. Schwabe U. Antiepileptika. In: Schwabe U, Ludwig W-D, editors. Arzneiverordnungs-Report 2020. Berlin, Heidelberg, Germany: Springer-Verlag; 2020:365–78.
20. Krauth C, Hessel F, Hansmeier T, Wasem J, Seitz R, Schweikert B. Empirical standard costs for health economic evaluation in Germany—a proposal by the working group Methods in Health Economic Evaluation. Gesundheitswesen. 2005;67:736–46.
21. Strzelczyk A, Bergmann A, Biermann V, Braune S, Dieterle L, Forth B, et al. Neurologist adherence to clinical practice guidelines and costs in patients with newly diagnosed and chronic epilepsy in Germany. Epilepsy Behav. 2016;64:75–82.
22. Strzelczyk A, Nickolay T, Bauer S, Haag A, Knake S, Oertel WH, et al. Evaluation of health-care utilization among adult patients with epilepsy in Germany. Epilepsy Behav. 2012;23:451–7.
23. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512–21.
24. Levira F, Thurman DJ, Sander JW, Hauser WA, Hesdorffer DC, Masanja H, et al. Premature mortality of epilepsy in low- and middle-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia. 2017;58:6–16.
25. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335:806–8.
26. Beghi E, Garattini L, Ricci E, Cornago D, Parazzini F, EPICOS Group. Direct cost of medical management of epilepsy among adults in Italy: a prospective cost-of-illness study (EPICOS). Epilepsia. 2004;45:171–8.
27. Strzelczyk A, Reese JP, Oertel WH, Dodel R, Rosenow F, Hamer HM. Costs of epilepsy and their predictors: cross-sectional study in Germany and review of literature. Epileptology. 2013;1:55–60.
28. Tetto A, Manzoni P, Millul A, Beghi E, Garattini L, Tartara A, et al. The costs of epilepsy in Italy: a prospective cost-of-illness study in referral patients with disease of different severity. Epilepsy Res. 2002;48:207–16.
29. Desgagne A, Castilloux AM, Angers JF, LeLorier J. The use of the bootstrap statistical method for the pharmacoeconomic cost analysis of skewed data. Pharmacoeconomics. 1998;13:487–97.

30. Pirker S, Graef A, Gachter M, Baumgartner C. Costs of epilepsy in Austria: unemployment as a primary driving factor. Seizure. 2021;89:24–9.
31. Begley CE, Durgin TL. The direct cost of epilepsy in the United States: a systematic review of estimates. Epilepsia. 2015;56:1376–87.
32. Cramer JA, Wang ZJ, Chang E, Powers A, Copher R, Cherepanov D, et al. Healthcare utilization and costs in adults with stable and uncontrolled epilepsy. Epilepsy Behav. 2014;31:356–62.
33. Peña P, Sancho J, Rufo M, Martínez S, Rejas J, LINCE Study Collaborative Group. Driving cost factors in adult outpatients with refractory epilepsy: a daily clinical practice in clinics of neurology in Spain. Epilepsy Res. 2009;83:133–43.
34. Mengel D, Fraune L, Sommer N, Stettner M, Reese JP, Dams J, et al. Costs of illness in chronic inflammatory demyelinating polyneuropathy in Germany. Muscle Nerve. 2018;58:681–7.
35. Flachenecker P, Kobelt G, Berg J, Capsa D, Gannedahl M, European Multiple Sclerosis Platform. New insights into the burden and costs of multiple sclerosis in Europe: results for Germany. Mult Scler. 2017;23:78–90.
36. Foster E, Chen Z, Zomer E, Rychkova M, Carney P, O'Brien TJ, et al. The costs of epilepsy in Australia: a productivity-based analysis. Neurology. 2020;95:e3221–31.
37. Riechmann J, Strzelczyk A, Reese JP, Boor R, Stephani U, Langner C, et al. Costs of epilepsy and cost-driving factors in children, adolescents, and their caregivers in Germany. Epilepsia. 2015;56(9):1388–97.
38. Grau J, Zöllner JP, Schubert-Bast S, Kurlemann G, Hertzberg C, Wiemer-Kruel A, et al. Direct and indirect costs and cost-driving factors of tuberous sclerosis complex in children, adolescents, and caregivers: a multicenter cohort study. Orphanet J Rare Dis. 2021;16:282.
39. Zöllner JP, Grau J, Rosenow F, Sauter M, Knuf M, Kurlemann G, et al. Direct and indirect costs and cost-driving factors in adults with tuberous sclerosis complex: a multicenter cohort study and a review of the literature. Orphanet J Rare Dis. 2021;16:250.
40. Quintana M, Fonseca E, Sanchez-Lopez J, Mazuela G, Santamarina E, Abraira L, et al. The economic burden of newly diagnosed epilepsy in Spain. Epilepsy Behav. 2021;125:108395.
41. Taylor RS, Sander JW, Taylor RJ, Baker GA. Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. Epilepsia. 2011;52:2168–80.
42. Willems LM, Kondziela JM, Knake S, Schulz J, Neif B, Schade B, et al. Counseling and social work for people with epilepsy in Germany: a cross-sectional multicenter study on demand, frequent content, patient satisfaction, and burden-of-disease. Epilepsy Behav. 2019;92:114–20.
43. Leenen LAM, Wijnen BFM, Kessels AGH, Chan H, de Kinderen RJA, Evers S, et al. Effectiveness of a multicomponent self-management intervention for adults with epilepsy (ZMILE study): a randomized controlled trial. Epilepsy Behav. 2018;80:259–65.
44. May TW, Pfäfflin M. The efficacy of an educational treatment program for patients with epilepsy (MOSES): results of a controlled, randomized study. Modular Service Package Epilepsy. Epilepsia. 2002;43:539–49.
45. Willems LM, Balcik Y, Noda AH, Siebenbrodt K, Leimeister S, McCoy J, et al. SARS-CoV-2-related rapid reorganization of an epilepsy outpatient clinic from personal appointments to telemedicine services: a German single-center experience. Epilepsy Behav. 2020;112:107483.
46. Markanday S, Brennan SL, Gould H, Pasco JA. Sex-differences in reasons for non-participation at recruitment: Geelong Osteoporosis Study. BMC Res Notes. 2013;6:104.
47. Kondziela JM, Schulz J, Brunst B, Fuchs S, Gerlinger S, Neif B, et al. Acceptance, demand, reasons for consultation and outcome of counseling on epilepsy in Hesse and Lower Franconia. Nervenarzt. 2019;90:832–9.
48. Schnabel S, Neininger MP, Bernhard MK, Merkenschlager A, Kiess W, Bertsche T, et al. Epilepsy: a cross-sectional study of paediatricians and general practitioners on their experiences, knowledge and handling of the disease. Epileptic Disord. 2019;21:197–205.

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