






## RESEARCH ARTICLE

# Trends in resource utilization and cost of illness in patients with active epilepsy in Germany from 2003 to 2020

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## Abstract

**Objective:** This study was undertaken to calculate epilepsy-related direct, indirect, and total costs in adult patients with active epilepsy (ongoing unprovoked seizures) in Germany and to analyze cost components and dynamics compared to previous studies from 2003, 2008, and 2013. This analysis was part of the Epi2020 study.

**Methods:** Direct and indirect costs related to epilepsy were calculated with a multicenter survey using an established and validated questionnaire with a bottom-up design and human capital approach over a 3-month period in late 2020. Epilepsy-specific costs in the German health care sector from 2003, 2008, and 2013 were corrected for inflation to allow for a valid comparison.

**Results:** Data on the disease-specific costs for 253 patients in 2020 were analyzed. The mean total costs were calculated at €5551 ( $\pm$ €5805, median = €2611, range = €274–€21 667) per 3 months, comprising mean direct costs of €1861 ( $\pm$ €1905, median = €1276, range = €327–€13 158) and mean indirect costs of €3690 ( $\pm$ €5298, median = €0, range = €0–€11 925). The main direct cost components were hospitalization (42.4%), antiseizure medication (42.2%), and outpatient care (6.2%). Productivity losses due to early retirement (53.6%), part-time work or unemployment (30.8%), and seizure-related off-days (15.6%) were the main reasons for indirect costs. However, compared to 2013, there was no significant increase of direct costs (−10.0%), and indirect costs significantly increased ( $p < .028$ , +35.1%), resulting in a significant increase in total epilepsy-related costs ( $p < .047$ , +20.2%). Compared to the 2013 study population, a significant increase of cost of illness could be observed ( $p = .047$ ).

**Significance:** The present study shows that disease-related costs in adult patients with active epilepsy increased from 2013 to 2020. As direct costs have remained

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constant, this increase is attributable to an increase in indirect costs. These findings highlight the impact of productivity loss caused by early retirement, unemployment, working time reduction, and seizure-related days off.

#### KEYWORDS

antiseizure medication, cost of illness, economic burden, health care, seizure

## 1 | INTRODUCTION

As health care systems have become increasingly economically oriented, the analysis of trends and changes in disease-specific costs or cost of illness (COI) is increasingly relevant.<sup>1</sup> Chronic diseases are particularly important, because chronic illnesses incur long-term costs compared to monophasic or time-limited diseases and therefore comprise a burden for statutory health care systems.<sup>2</sup> More than 400 000 individuals suffer from epilepsy in Germany, at a prevalence of at least .5 per 1000 inhabitants; approximately 20%–40% of individuals have drug-refractory epilepsy (DRE).<sup>3</sup> Patients with ongoing unprovoked seizures have been shown to be associated with relevant illness-specific costs. Frequent hospitalizations, emergency and regular outpatient visits, and antiseizure medication (ASM) polytherapy are major sources of direct costs, whereas epilepsy-related early retirement, unemployment, and days off due to seizures are the main reasons for productivity losses.<sup>4–6</sup> By comparing health care expenses in patients with active epilepsy in Germany between 2003 and 2013, we were able to show that a significant shift in the distribution of cost components was associated with increased costs for hospitalization and early retirement.<sup>7</sup> Furthermore, decreased ASM costs could be attributed to statutory health care reforms implemented since the early 2000s.<sup>7–9</sup> The impact of surgical treatment options for DRE, such as epilepsy surgery, implantable vagal nerve stimulators, and stereotactic laser thermoablation (SLTA), remains unclear but might decrease disease-specific costs in the long term.<sup>10–12</sup>

The aim of this Epi2020 study was to calculate epilepsy-related direct, indirect, and total costs in adult patients with epilepsy in Germany and to analyze any changes in cost components by comparing the results to studies from 2003, 2008, and 2013.

## 2 | MATERIALS AND METHODS

### 2.1 | Study setting, patients, and design

This Epi2020 study was a large multicenter study focusing on different health care aspects of adult patients with

#### Key Points

- This multicenter study used a bottom-up design and human capital approach to calculate disease-related costs in adult patients with active epilepsy
- Epilepsy-specific costs in 2020 were calculated at €5551 per 3 months; direct costs accounted for one third of the total, whereas two thirds of the total were indirect costs
- Direct cost-driving factors were hospitalization and antiseizure medication
- Indirect costs arose mainly from early retirement, days off due to seizures, unemployment, and work-time reduction
- Epilepsy-related indirect costs have increased since 2013, reinforcing the need to preserve the working capability of people with epilepsy

epilepsy in Germany. The study was conducted at epilepsy centers in Frankfurt am Main, Greifswald, Marburg, and Münster between October 2020 and December 2020. The study was approved by the ethics committee of Goethe University (Reference 19-440) and was registered with the German Clinical Trials Register (DRKS00022024; Universal Trial Number: U1111-1252-5331). All study sites offered interdisciplinary, specialized inpatient and outpatient care for patients of all ages with epilepsy, epileptic encephalopathies, or syndromes associated with epilepsy. The design of the Epi2020 study was similar to previous COI studies conducted in 2003, 2008, and 2013 at the epilepsy center in Marburg but was extended to three other sites to allow for multicenter inclusion of patients.<sup>7–9</sup> With written informed consent from the patient, all adult patients aged 18 years or older with active epilepsy (at least one unprovoked seizure in the 12 months before study enrollment) were eligible and consecutively enrolled. Patients were asked to complete a standardized questionnaire that recorded a comprehensive set of direct and indirect cost components over the previous 3 months.<sup>8</sup> In the case of a mild intellectual or relevant physical disability, the support of patients in filling out the questionnaire by their relatives or caregivers

was permitted. Patients who were not able to give their own informed consent were not included in the study. For each item, individuals were asked to indicate whether the cost was incurred for treating epilepsy. Only epilepsy-associated costs were used for cost calculations. Epilepsy diagnoses and medical and seizure terminology were based on the latest definitions from the International League Against Epilepsy.<sup>13,14</sup> Patients with an uncertain epilepsy diagnosis were excluded from the analysis to increase data quality and reliability. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were closely followed during study planning, execution, and data analysis.

## 2.2 | Methods of health economic evaluation

There are various methods available for recording COI. Usually, so-called "top-down" or "bottom-up" approaches are employed. Both of the methods have its own advantages and disadvantages.<sup>2</sup> For the top-down approach, processed data on health care expenditures, for example from insurance companies, are utilized and analyzed for certain diagnoses or groups of diagnoses. This allows the calculation of COI in a large number of patients; however, this analysis lack granularity and usually relies on International Classification of Diseases (ICD)-10 or ICD-9 coding. Moreover, in the case of patients with multiple diseases, individual cost components cannot be reliably assigned to different diseases.<sup>2,15</sup> For the bottom-up approach, costs and cost components are calculated based on data derived directly from well-characterized patients.<sup>2,16</sup> The bottom-up approach allows analysis of individual disease-specific expenses but is time-consuming, and this limits the number of included individuals.<sup>17</sup> Recently, a combination of both top-down and bottom-up approaches for precise COI approximation has been suggested.<sup>18</sup> The "human capital approach" is used to estimate indirect cost due to productivity losses. The value of the human capital loss is calculated using the number of disease-related days off work or work-time reduction based on the average gross income.<sup>2,19</sup>

## 2.3 | Cost assessment

Cost calculations were based on current national and international recommendations and followed a well-established and validated bottom-up design, following the perspective of the statutory health insurance (Gesetzliche Krankenversicherungen).<sup>16</sup> Direct costs, that is, expenditures for hospitalizations, outpatient treatments, rehabilitation, medications, therapeutic

measures, and medical auxiliaries, were assessed with a validated questionnaire examining the 3 months immediately before study entry. Drug costs were obtained from a drug prescription report (Arzneiverordnungsreport 2020),<sup>20</sup> and costs for inpatient care (hospitalization and rehabilitation) were calculated using the current version of the German Diagnosis Related Groups ([www.g-drg.de](http://www.g-drg.de)). Current valid national benchmarks were used to calculate outpatient medical consultations, therapies, and diagnostics (Einheitlicher Bewertungsmaßstab, [www.kbv.de](http://www.kbv.de)).<sup>21</sup> Costs for medical auxiliaries were derived from providers' price lists if they could not be reported by the patients.

Indirect costs, that is, expenditures caused by a loss of productivity due to unemployment, disease-related reduction 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 is the retirement age in Germany. Consequently, all patients below this age limit who reported receiving a pension during the acquisition period were classified as early retired. According to the German Federal Statistical Office (DeSTATIS, [www.destatis.de](http://www.destatis.de)), the mean gross income in 2020 was €47 700 per year, equaling €3975 per month or €131 per calendar day. Productivity loss attributed to epilepsy was equated with the monetary equivalent of hours not worked by patients before the retirement age of 67 years.<sup>22</sup>

To allow for a comparison of disease-related costs and expenditures with those of the 2003, 2008, and 2013 cohorts,<sup>7-9</sup> direct cost components were adjusted for inflation in the medical sector compared to 2020, and indirect cost components were adjusted for differences in gross income compared to 2020 (DeSTATIS, [www.destatis.de](http://www.destatis.de)).

## 2.4 | Data entry and statistical analysis

Statistical analysis was performed using SPSS Statistics 28 (IBM). Costs are presented as the mean  $\pm$  SD, median, minimum, and maximum. Considering that most cost variables are right-skewed, 95% confidence intervals were provided using the bootstrap method based on the bias-corrected and accelerated approach.<sup>23</sup> Statistical comparisons were performed using appropriate tests, such as chi-squared, Kruskal-Wallis, and one-way analysis of variance, using SPSS or Prism 9 (GraphPad Software). Sociodemographic data are also presented as mean  $\pm$  SD, median, minimum, and maximum or as number and percentage, depending on scaling. Figures were created with GraphPad Prism and Pixelmator Pro (Pixelmator Team).

### 3 | RESULTS

#### 3.1 | Study population

A total of 253 patients were enrolled in the Epi2020 study, with a mean age of 39.5 years ( $\pm 14.2$  years, range = 18–80 years). Of the participants, 57.3% ( $n = 145$ ) were female. Sociodemographic and epilepsy characteristics are shown in Table 1. Comparing the study populations from 2003, 2008, 2013, and 2020 revealed no difference in the distribution of sex (53.5%, 53.6%, 50.5%, and 57.3% female patients, respectively;  $p = .545$ ), age (median = 40.0, 44.0,

39.0, and 38.0 years, respectively;  $p = .706$ ), employment situation (unemployment rate = not available, 11.9%, 12.6%, and 8.7%, respectively;  $p = .171$ ), or different epilepsy syndromes (76.2%, 76.8%, 75.8%, and 73.9% focal epilepsy, respectively;  $p = .577$ ); however, there was a significant difference in epilepsy duration (17.0, 20.0, 9.0, and 12.0 years, respectively;  $p = .027$ ) and mean number of ASMs (median ASMs = 2.0, 1.0, 1.5, and 2.0, respectively;  $p < .001$ ). When comparing the 2013 and 2020 cohorts, only the difference in ASM prescription patterns remained significant (median ASM number = 1.5 and 2.0;  $p = .024$ ).

**TABLE 1** Sociodemographic and disease-related aspects of the 2003, 2008, 2013, and 2020 cohorts

Characteristic	Current Epi2020 study	Previous cohorts			Statistical comparison	
	2020, $N = 253$	2003, <sup>8</sup> $N = 101$	2008, <sup>9</sup> $N = 151$	2013, <sup>7</sup> $N = 198$	To 2003–2013, $p^a$	To 2013, $p^b$
Sex, % ( $n$ )						
Female	57.3 (145)	53.5 (54)	53.6 (81)	50.5 (100)	.545	.150
Male	42.7 (108)	46.5 (47)	46.4 (70)	49.5 (98)		
Age, years						
Mean $\pm$ SD	39.5 $\pm$ 14.2	40.7 $\pm$ 15.7	41.0 $\pm$ 14.9	39.6 $\pm$ 14.0	.706	.941
Range	18–80	18–78	18–82	18–84		
Epilepsy duration, years						
Mean $\pm$ SD	17.0 $\pm$ 15.3	18.1 $\pm$ 15.4	19.4 $\pm$ 15.2	14.6 $\pm$ 14.1	.027 <sup>c</sup>	.088
Range	0–71	0–52	0–68	0–63		
Epilepsy syndrome						
FE	73.9 (187)	76.2 (77)	76.8 (116)	75.8 (150)	.577	.663
IGE	17.8 (45)	19.8 (20)	13.9 (21)	18.2 (36)		
Unclassified	8.3 (21)	4.0 (4)	9.3 (14)	6.1 (12)		
Antiseizure medication, % ( $n$ )						
Mean $n$	2.0 $\pm$ 1.0	1.7 $\pm$ .9	1.8 $\pm$ .8	1.8 $\pm$ .8	<.001 <sup>c</sup>	.024 <sup>c</sup>
0	3.2 (8)	4.0 (4)	5.3 (8)	1.0 (2)		
1	28.1 (71)	39.6 (40)	30.5 (46)	39.9 (79)		
2	40.3 (102)	33.6 (34)	48.3 (73)	37.9 (75)		
$\geq 3$	28.4 (72)	22.8 (23)	15.9 (24)	21.2 (42)		
Employment situation						
Employed	47.0 (119)	n.a.	39.7 (60)	38.4 (76)	.171	.247
Unemployed	8.7 (22)	n.a.	11.9 (18)	12.6 (25)		
In training	8.3 (21)	n.a.	8.6 (13)	6.6 (13)		
Parental leave	4.3 (11)	n.a.	10.0 (15)	7.1 (14)		
Early retirement	18.5 (47)	n.a.	21.8 (33)	16.2 (38)		
Retirement	4.7 (12)	n.a.	7.3 (12)	6.6 (13)		
n.a.	8.3 (21)	n.a.	.7 (1)	9.6 (19)		

Abbreviations: FE, focal epilepsy; IGE, idiopathic (genetic) generalized epilepsy; n.a., not available.

<sup>a</sup>Calculated using one-way analysis of variance or chi-squared.

<sup>b</sup>Calculated using chi-squared and unpaired  $t$ -test.

<sup>c</sup>Statistically significant.

### 3.2 | Epilepsy-specific direct costs in the 2020 cohort

Mean epilepsy-specific direct costs were calculated at €1861 ( $\pm$ €1905, median = €1276, range = €327–€13 158) per 3 months, resulting in average costs of €7445 per year, €620 per month, or €20.4 per day. At 42.4% (€789), hospitalizations accounted for the largest share of direct epilepsy-related costs, closely followed by expenditures for ASMs at 40.8% (€785). Significantly lower shares of direct costs were incurred for outpatient care (6.2%, €115), outpatient diagnostics (4.3%, €77), rehabilitation (2.7%, €50), physical treatments (1.3%, €25), and special equipment (1.0%, €19; e.g., wheelchairs, helmets, or installation of home emergency call systems). There was no significant difference in the direct costs of the different recruiting centers ( $p = .572$ ). Direct epilepsy-related costs and their individual components are shown in detail in Table 2 and Figure 1A.

### 3.3 | Epilepsy-specific indirect costs in the 2020 cohort

Mean indirect costs were calculated at €3690 ( $\pm$ €5298, median = €0, range = €0–€11 925) per 3 months, resulting in average costs of €14 760 per year, €1230 per month, or €40 per day. At 53.6% (€2121), early retirement accounted for the largest share of indirect

epilepsy-related costs, followed by expenditures for productivity losses (32.7%, €1135) and days off due to seizures (13.7%, €577). The indirect costs were not significantly different between recruiting centers ( $p = .400$ ). Indirect epilepsy-related costs and their individual components are shown in detail in Table 2 and Figure 1B.

### 3.4 | Total epilepsy-specific costs

Indirect and direct cost components totaled to mean total epilepsy-related costs of €5551 ( $\pm$ €5805, median = €2611, range = €274–€21 667) per 3 months, resulting in average costs of €22 204 per year, €1850 per month, or €60 per day. Indirect costs accounted for a larger share (68%) of total epilepsy-related costs than direct costs (32%). The total costs were not significantly different between recruiting centers ( $p = .107$ ). Total epilepsy-related costs and their individual components are shown in detail in Table 2 and Figure 1C.

### 3.5 | Development of epilepsy-related costs from 2003 to 2020

An analysis of mean direct costs revealed no significant difference ( $p = .302$ ,  $-10.0\%$ ) between 2013 and 2020, with significantly lower expenditures for ambulatory

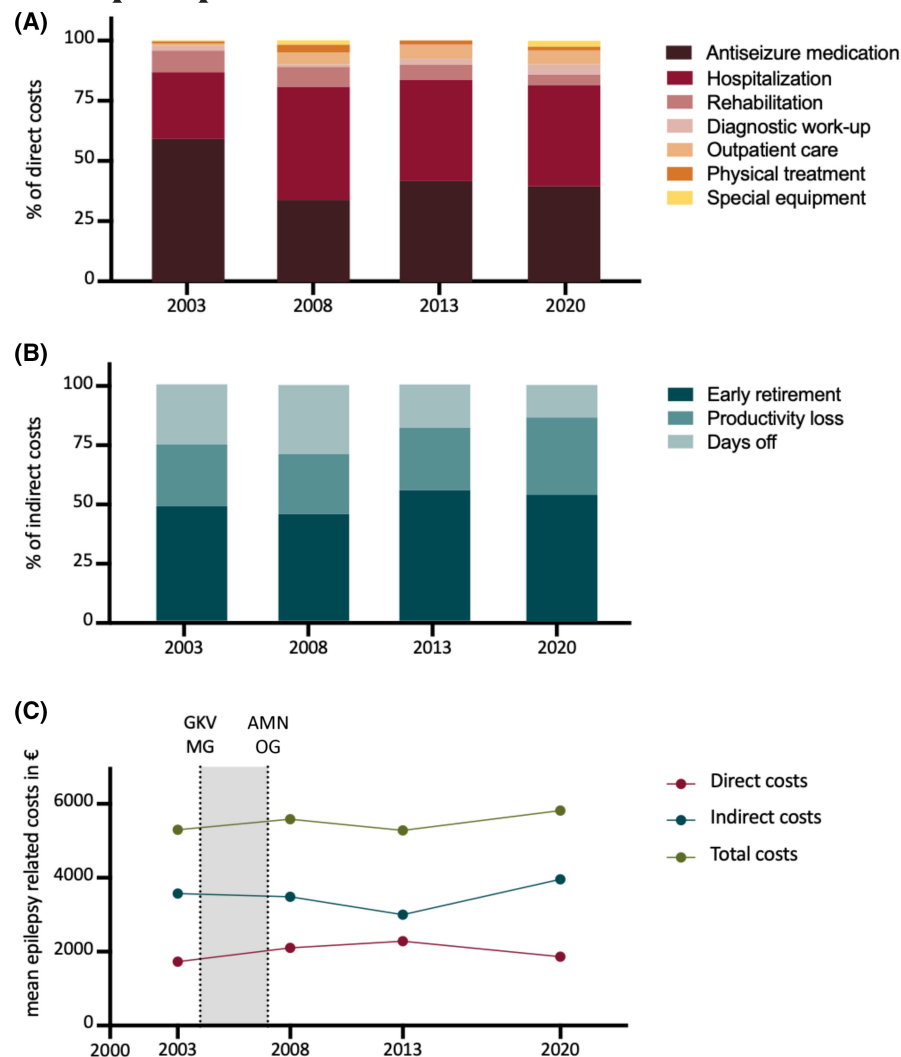
**TABLE 2** Calculation of epilepsy-related direct and indirect costs per 3 months in 2020 Euros ( $N = 253$ )

Cost component	Mean $\pm$ SD <sup>a</sup>	Minimum <sup>a</sup>	Median <sup>a</sup>	Maximum <sup>a</sup>	95% CI <sup>a</sup>
Direct cost components					
Antiseizure medication	785 $\pm$ 969	47	438	7809	680–892
Hospitalization	789 $\pm$ 1291	42	34	9421	636–958
Rehabilitation	50 $\pm$ 425	0	0	4763	5–103
Diagnostic workup	77 $\pm$ 127	0	30	955	63–95
Outpatient care	115 $\pm$ 163	21	70	1383	97–134
Physical treatment	25 $\pm$ 107	0	0	844	13–40
Special equipment	19 $\pm$ 252	0	0	3993	1–53
Total direct costs	1861 $\pm$ 1905	327	1276	13 158	1633–2101
Indirect cost components					
Early retirement	2121 $\pm$ 4569	0	0	11 925	1652–2639
Productivity loss due to part-time work/unemployment	1135 $\pm$ 3473	0	0	11 925	758–1517
Off days due to seizures	577 $\pm$ 1944	0	0	11 925	378–804
Total indirect costs	3690 $\pm$ 5298	0	0	11 925	3131–4284
Total disease-related costs	5551 $\pm$ 5805	274	2611	21 667	5406–6166

Abbreviation: CI, confidence interval using the bootstrap bias-corrected and accelerated method.

<sup>a</sup>Calculated using bootstrapping with the BCa method (bias-corrected and accelerated), assuming a right-skewed distribution.





**FIGURE 1** Breakdown of disease-specific costs of the 2003, 2008, 2013, and 2020 study populations of adult patients with active epilepsy into direct (A) and indirect (B) cost components in percent. (C) In addition, the development of the disease-specific costs per quarter is shown based on the individual study populations from 2003 to 2020, with correction for inflation and changes in gross income to 2020. AMNOG, Pharmaceuticals Market Reorganization Act (Arzneimittelmarkt-Neuordnungsgesetz); GKVMG, Health Care Modernization Act (Gesetz zur Modernisierung der gesetzlichen Krankenkasse)

diagnostic workups in the 2020 cohort ( $p = .040$ , +48.1%). Expenditures for ASMs and hospitalization were also lower in 2020 compared to 2013 but did not reach a level of significance in statistical comparison. Indirect costs increased significantly, growing by 35.3% between 2013 and 2020 ( $p < .028$ ), with significantly higher COIs for productivity losses due to unemployment or work reduction ( $p = .039$ , +59.4%). This resulted in a 20.2% increase in mean total disease-related costs from 2013 to 2020 ( $p < .047$ ). The development of epilepsy-related costs and their individual direct and indirect cost components from 2013 to 2020 are shown in detail in Table 3 and Figure 1C.

## 4 | DISCUSSION

The primary objective of this multicenter Epi2020 study was to determine the cost of illness for adult patients with active epilepsy based on a questionnaire-based survey conducted at four epilepsy centers in Germany. We used a validated, bottom-up approach to calculate a

comprehensive set of direct cost components and applied a human capital approach to address different sources of indirect costs.<sup>9,22,24</sup> Mean epilepsy-specific total costs amounted to €22 204 per year, corresponding to €1850 per month or €61 per day.

These COIs appear realistic in the context of recent studies that report annual epilepsy-related costs for heterogeneous cohorts of seizure-free and non-seizure-free patients of €5163 in Denmark and \$4536 in the United States.<sup>25,26</sup> The individual cost components also seem realistic, as indicated by reported annual hospitalization costs of AUD 10 333 in New South Wales, Australia (approximately €6600 per year or €550 per month).<sup>27</sup> When comparing these studies, it is important to remember that the COI of patients with active epilepsy is approximately 2–4 times higher than the COI of patients with epilepsy in remission.<sup>28</sup> Unfortunately, only a few methodologically comparable COI studies in epilepsy patients have been published in Europe, the United Kingdom, the United States, or other countries with comparable health care systems. Due to significant differences in health care

**TABLE 3** Comparison of mean epilepsy-related costs as well as direct and indirect cost components of patients with active epilepsy per 3 months from 2003 to 2020

Cost component	2003 cohort, <sup>8</sup> N = 101		2008 cohort, <sup>9</sup> N = 151		2013 cohort, <sup>7</sup> N = 198		2020 cohort, N = 253, in 2020 €		Statistical comparison to 2013
	In 2003 €	Mean <sup>a</sup>	In 2008 €	Mean <sup>a</sup>	In 2013 €	Mean <sup>a</sup>	In 2020 €	Mean ± SD	
Direct cost components	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		<i>p</i> <sup>b</sup>
Antiepilepsy medication	600 ± 610	738	576 ± 538	640	786 ± 778	865	785 ± 969	785 ± 969	.344
Hospitalization	280 ± 1150	344	795 ± 1755	882	785 ± 1878	864	789 ± 1291	789 ± 1291	.616
Rehabilitation	90 ± 890	111	140 ± 836	155	118 ± 754	130	50 ± 425	50 ± 425	.155
Diagnostic workup	20 ± 50	25	16 ± 46	18	47 ± 129	52	77 ± 127	77 ± 127	.040 <sup>c</sup>
Outpatient care	10 ± 50	12	84 ± 137	94	109 ± 155	120	115 ± 163	115 ± 163	.741
Physical treatment	10 ± 40	12	55 ± 155	61	33 ± 167	36	25 ± 107	25 ± 107	.371
Special equipment	3 ± 10	4	30 ± 207	33	1 ± 9	1	19 ± 252	19 ± 252	.316
Total direct costs	1010 ± 1600	1242	1696 ± 2290	1883	1879 ± 2331	2067	1861 ± 1905	1861 ± 1905	.302
Indirect cost components	Mean ± SD	Mean <sup>a</sup>	Mean ± SD	Mean <sup>a</sup>	Mean ± SD	Mean <sup>a</sup>	Mean ± SD	Mean ± SD	<i>p</i> <sup>e</sup>
Early retirement	780 ± 2690	1407	849 ± 2567	1443	994 ± 2893	1510	2121 ± 4569	2121 ± 4569	.101
Productivity loss due to part-time work/ unemployment	420 ± 1360	757	477 ± 1879	811	475 ± 2064	712	1135 ± 3473	1135 ± 3473	.039 <sup>c</sup>
Off days due to seizures	410 ± 1820	739	551 ± 1704	937	326 ± 125	495	577 ± 1944	577 ± 1944	.554
Total indirect costs	1610 ± 3460	2904	1847 ± 3291	3140	1795 ± 3524	2.727	3690 ± 5298	3690 ± 5298	.028 <sup>c</sup>
Total disease-related costs <sup>c</sup>	2610 ± 4200	4146 ± 3532	4360	5.023	3674 ± 4438	4.618	5551 ± 5805	5551 ± 5805	.047 <sup>c</sup>

<sup>a</sup>Mean adjusted for an increase in the gross income to 2020.<sup>b</sup>Statistical comparison between 2003 and 2013 using an unpaired *t*-test after testing for a normal distribution with a D'Agostino–Person test.<sup>c</sup>Statistically significant.<sup>d</sup>Mean adjusted for inflation in the gross income to 2020.<sup>e</sup>Approximate calculation based on published data.

systems, costs of living, and methodologies, epilepsy-specific COIs from recent studies in Africa, India, and Asia do not seem to be comparable.<sup>29</sup> In contrast to the lack of COI studies conducted with a bottom-up method, several studies based on insurance data have used a top-down approach.<sup>30–32</sup> This development is regrettable, because the top-down approach, although easier to implement, is methodologically inferior to the bottom-up approach, as indirect costs are underestimated in the top-down method.<sup>18,33</sup>

The calculated costs also seem comparable in view of studies on patients with other chronic diseases associated with epilepsy or epilepsy syndromes, such as tuberous sclerosis complex (€1650 per month)<sup>34,35</sup>; however, costs calculated in this study were significantly lower than costs of other chronic neurological diseases such as multiple sclerosis (MS; €3358 per month) and developmental and epileptic encephalopathies such as Dravet syndrome (DS; €3819 per month).<sup>4,36</sup> These COI differences seem to be primarily attributable to the absence of progressive physical and mental disabilities in most patients with epilepsy compared to the frequent occurrence of disability in patients with MS or DS.<sup>37,38</sup> The total annual economic burden due to epilepsy has been estimated at €1.6 billion for Germany, whereby this is distributed over approximately 600 000 patients.<sup>39</sup> The total sum is comparable to €1.7 billion for patients with MS; however, this applies to 188 000 patients in Germany.<sup>40</sup> This seems likely to be due to the high cost of immunomodulatory MS therapies, which far exceed the cost of therapy with ASMs.<sup>41,42</sup> Another cost-driving factor identified in MS patients is the inability to work and the need for care associated with progressive disability, which compared to epilepsy affect a much higher number of patients during the course of the disease.<sup>40</sup> Moreover, epilepsy surgery as well as neuromodulatory therapies such as vagal nerve stimulation are only performed on a small number of patients, and thus contribute relatively little to total costs.<sup>7,43</sup> Acute complications and worsening in the course of epilepsy are responsible for high inpatient costs. This was shown for episodes of status epilepticus that are associated with costs between €4063 to €32 706 based on the refractoriness of status epilepticus, whereas a mean cost of €2500 was calculated for acute MS relapse.<sup>44,45</sup> These aspects illustrate how differently individual cost-driving factors are distributed among different chronic neurological diseases, highlighting the complexity of health economic analysis.<sup>46</sup>

In line with our findings, a methodologically comparable COI study from Austria, whose health care system is comparable to Germany's, determined unemployment to be a cost-driving factor for total epilepsy-related costs.<sup>47</sup> Moreover, several other studies from Europe<sup>31,48</sup> and from

countries outside of Europe with differently organized health care systems highlight the impact of productivity losses on indirect COI components for epilepsy patients. This is reflected in the current evaluation, in particular in the finding that the rate of patients retiring early due to epilepsy, at 18.5%, is by far higher than the general early retirement rate in Germany, which was stable at .9% in relation to the working-age population between 2018 and 2020.<sup>49</sup> The large share of indirect costs and the composition of direct and indirect cost components are in line with previous studies.<sup>7,50,51</sup>

The second objective of this study was to compare the 2020 COI with methodologically comparable costs from 2003, 2008, and 2013.<sup>7–9</sup> After adjusting the direct and indirect cost factors for inflation and the increase in gross income (Figure 1C), the epilepsy-specific COI appeared to be stable between 2003 and 2020. However, a statistical comparison between the 2013 and 2020 datasets revealed a significant increase in total epilepsy-specific costs caused by an isolated increase in indirect cost factors alongside largely constant direct costs (Table 3). Productivity losses made a relevant contribution to the increase in the total COI, and all analyzed indirect cost components were higher in 2020 compared to 2013; however, only the difference in epilepsy-related unemployment or work-time reduction was statistically significant. These findings align with other publications highlighting unemployment among epilepsy patients as a main cost-driving factor<sup>7,47,52</sup> and illustrate the critical need to improve efforts to keep epilepsy patients employed or find suitable alternative jobs through occupational retraining.<sup>53,54</sup> Moreover, productivity loss due to premature epilepsy-related loss of life has been identified as a relevant health-related economic factor in an Australian productivity-based analysis, highlighting the potential impact of a reduced seizure burden<sup>55</sup> and the prevention of sudden unexpected death in epilepsy on COI.

The stability of direct costs is likely attributable to statutory health care reforms in Germany over the past two decades, for instance, the Pharmaceuticals Market Reorganization Act (Arzneimittelmarkt-Neuordnungsgesetz) and the Health Care Modernization Act (Gesetz zur Modernisierung der gesetzlichen Krankenkasse). In particular, the introduction of a case rate-based reimbursement system for hospital services, statutorily regulated drug discounts, and uniform reimbursement for outpatient therapies and diagnostics helped contain costs in the health care system.<sup>42</sup> High-cost therapeutic options and diagnostic procedures such as invasive video-electroencephalographic monitoring, SLTA, and epilepsy surgery are only performed for a small number of epilepsy patients per year. Therefore, costs for these therapies



and procedures are not captured in our study. However, these therapies and procedures have been shown to have an overall cost advantage and to be cost-effective from a health economic point of view.<sup>56–58</sup> The significant reduction in outpatient diagnostic costs in 2020 compared with 2013 could alternatively be explained by the SARS-CoV-2 pandemic, which significantly reduced the availability and utilization of specialized outpatient care.<sup>59</sup>

In 2020, the SARS-CoV-2 pandemic hit health and economic systems around the world hard, and it seems possible that the pandemic could have had an influence on our study. In terms of indirect costs, the unemployment rate in Germany increased slightly by 1% for October, November, and December 2020 (5.9%–6.0%), whereas this number remained stable in 2018 (4.8%–4.9%), 2019 (4.8%–4.9%), and again in 2021 (5.1%–5.2%). Moreover, the number of people who were in early retirement due to health-related problems remained constant at 1.8 million between 2017 and 2020, and there was no increase in the number of early retirements between 2019 and 2020.<sup>60,61</sup> This is probably because during the SARS-CoV-2 pandemic, the salaries of workers whose companies had to close due to the pandemic (e.g., restaurants, cultural institutions, stores) were comprehensively subsidized by the German government.<sup>62</sup> Regarding direct costs, an impact of the SARS-CoV-2 pandemic is more likely due to a reduced availability and utilization of medical services.<sup>59,63,64</sup> Further studies in the years after the pandemic will have to show whether the observed changes in COI correspond to the previously observed general trend since 2003 or are attributable to the pandemic.

In addition to the mentioned possible influence of the SARS-CoV-2 pandemic, this study may suffer from several other limitations that could influence the results and transferability to other populations. For instance, the analysis relied on the assumption that questionnaires were filled out conscientiously, completely, and truthfully, as a post hoc check of the data was not reasonably possible. Even if the results can be assumed to be transferable within Germany due to the multicenter design, comparing the data with data from other health systems is only possible to a limited extent. Although the bottom-up design and the human capital method used to determine the COI were carried out according to current recommendations for calculating health care costs, these methods can only provide approximate values. In addition, the inclusion of patients at specialized epilepsy centers, which tend to provide care for more severely affected patient subgroups, may have biased costs toward higher COIs. However, through a cautious interpretation of the data and consideration of STROBE guidelines, potential biases were kept to a minimum.

In conclusion, this Epi2020 study highlights the impact of COI for adult patients with epilepsy. Compared to methodologically similar studies from 2003, 2008, and 2013, an increase in the COI was demonstrated, which can be attributed to an increase in productivity losses. These results further underline the need to expand existing efforts to help patients with epilepsy continue working in their intended or trained occupations or to enable them to work in other occupational environments compatible with epilepsy through targeted counseling and retraining programs.

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#### CONFLICT OF INTEREST

J.P.Z. reports speaker's honoraria from Desitin Arzneimittel, Eisai, and GW Pharmaceuticals. L.L. has received honoraria for lecturing from Eisai, Biogen, and GW Pharmaceuticals. S.Ko. reports research funding from Biogen. S.Kn. reports speaker's honoraria from Arvelle, Eisai, Epilog, and UCB. F.v.P. is on the speakers bureaus 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. H.M.H. has served on the scientific advisory board of Angelini, Corlieve, Eisai, GW Pharmaceuticals, Sandoz, UCB Pharma, and Zogenix. He has served on the speakers' bureaus of or received unrestricted grants from Ad-Tech, Bracco, Desitin, Eisai, GW Pharmaceuticals, Micromed, Nihon Kohden, Novartis, Pfizer, 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 Fund 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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