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Burden of disease of people with epilepsy during an optimized diagnostic trajectory: costs and quality of life

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ABSTRACT

Background: Diagnosing epilepsy can be lengthy and stressful, potentially leading to increased use of healthcare resources and a reduction in quality of life.

Aim: This study aims to determine cost and quality of life before and after an optimized diagnostic procedure for people suspected of having epilepsy from a societal perspective with a follow-up of 12 months. In addition, this study aims to differentiate between people diagnosed with epilepsy during the follow-up of the study and the people who are diagnosed as not having epilepsy or for whom diagnosis is still uncertain.

Methods: A questionnaire regarding the use of healthcare resources was used accompanied by the EQ-5D-3 L. Multiple imputations by chained equations with predictive mean matching was used to account for missing data. To investigate the uncertainty of the results, non-parametric bootstrapped (1000 times) was used.

Results: In total, 116 people were included in the study. Total average costs per patient made in the previous 3 months had decreased from €4594 before the optimized diagnostic trajectory to €2609 in the 12 months after the optimized diagnostic trajectory. Healthcare costs were the largest expense group (52–66%) and had decreased significantly from baseline measurement to 12 months after baseline (€2395 vs €1581). Productivity costs had decreased from €1367 to €442 per 3 months. Total annual costs were similar between people diagnosed with epilepsy during the follow-up of the study and the people who are diagnosed as not having epilepsy or for whom diagnosis is still uncertain. Quality of Life had significantly increased over the course of 12 months from 0.80 to 0.84 (Dutch tariff).

Discussion: This study indicates that an optimized diagnostic trajectory has positively influenced the use of healthcare resources and the quality of life in people with epilepsy. As chronic care patients make diverse costs, future research should identify the long-term costs after an optimized diagnostic trajectory for patients with epilepsy, possibly identifying patients who are at high risk of becoming high-cost users in the future for early intervention.

1. Background

Correctly diagnosing epilepsy poses a great clinical challenge, as misdiagnosis is common and differentiation is not always a straightforward process (Chadwick and Smith, 2002). The condition has a complicated clinical appearance, as its progression varies per patient. Its symptoms are diverse and often ambiguous (Pugliatti et al., 2007), which makes distinguishing epilepsy from similar disorders a major difficulty in establishing the correct diagnosis (Chadwick and Smith, 2002).
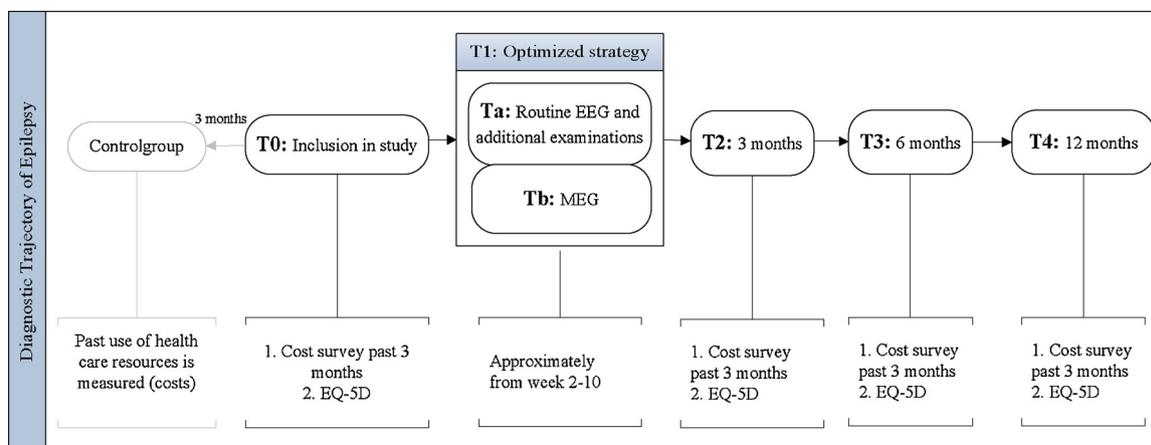

Fig. 1. Diagnostic trajectory of the study with an optimized trajectory.

Epilepsy has a considerable impact on costs and Quality of Life. It is often paired with psychological states of anxiety and depression, behavioral issues and cognitive dysfunction (Ramaratnam et al., 2008). These associated psychosocial effects as well as the uncertain clinical nature of epilepsy lead to a significant impact on a person's Quality of Life (Baker et al., 1997). Moreover, epilepsy constitutes a considerably high socioeconomic impact in Europe. For example, in 2004, the total costs of epilepsy were estimated at €15.5 billion, constituting 0.3% of the total European healthcare expenditures. Similarly, healthcare costs in the Netherlands have been estimated at €251 million in 2007 (Slobbe et al., 2011). A study by Cockerell et al. shows that the average medical costs per patient with epilepsy decreases with nearly 70% at 2 years after diagnosis (Cockerell et al., 1994).

An adequate diagnosis of epilepsy requires differentiation between seizures and other neurological disturbances (Chadwick and Smith, 2002), for example psychogenic non-epileptic seizures (PNES), which is most frequently misdiagnosed as epilepsy (Benbadis, 2006). In the search for a correct diagnosis, persons may excessively use health care resources, leading to higher health care costs, and experience lower quality of life. As a result, the diagnostic trajectory of epilepsy can be a lengthy process based on trial-and-error, often experienced as stressful and uncomfortable (Noachtar and Rémi, 2009). In addition to this shopping behavior, they can experience stress and anxiety due to uncertainty about their diagnosis, leading to a lower Quality of Life. Determining the correct diagnosis in people suspected of having epilepsy can have great consequences for their health, social behavior and employment (Angus-Leppan, 2008), and can be crucial in minimizing their healthcare consumption and in improving Quality of Life.

No studies up till now have provided insight into which costs people with possible epilepsy make during this diagnostic process and how it influences their Quality of Life, in order to determine how and where efficiency can be increased in the process of diagnosing and treating epilepsy. This study aims to quantify the Burden of Disease, in terms of quality of life and (healthcare) resource use, before and after an optimized diagnostic procedure for people with suspected epilepsy from a societal perspective with a follow-up of 12 months. In addition, this study aims to differentiate between people diagnosed with epilepsy during the follow-up of the study and the people who are diagnosed as not having epilepsy or for whom diagnosis is still uncertain. Assessing the burden of disease will consist of two components: 1) measuring cost of illness, operationalized in costs and use of (healthcare) resources, and 2) measuring health-related quality of life, operationalized in quality-adjusted life years (QALYs).

2. Methods

The study was a Burden of Disease study, which was assessed by two components: measuring the Cost-of-Illness (CoI), operationalized in cost, and measuring the Health-Related Quality of Life (HR-QoL), operationalized in utilities and Quality-Adjusted Life Years (QALYs). A CoI study aims to identify and measure all the costs of a particular disease. The output reflects the total burden of a specific disease to society (Rice, 1994). QALYs are widely used measures for health outcome that combine mortality and morbidity into a single measure (Kind et al., 2009). QALYs are generated by using health utilities, which are preference weights that reflect the value of a certain outcome (Weinstein et al., 2009).

2.1. Design and data collection

The study was a prospective, non-randomized, longitudinal study with a pre-post comparison. In this pre-post design, the same patients were measured before and several times during and after the diagnostic trajectory, i.e. patients serve as their own controls (3-month period before baseline). This study was funded by a healthcare innovation project which enabled access to the optimized diagnostic trajectory.

Data was collected at baseline and after 3, 6 and 12 months. Baseline measures were performed at the start of the diagnostic trajectory (T0). Participants received a questionnaire regarding their use of healthcare resources in the past 3 months and the Dutch EuroQol-5D 3 level version (EQ-5D-3 L) (Van Reenen and Oppe, 2015). The baseline questionnaire also included questions on general characteristics, i.e. date of birth, gender, education, civil status and whether participants autonomously filled in the questionnaire or proxies were used.

Recruited participants were derived from a larger healthcare innovation project in which an optimized diagnostic trajectory was examined that included magnetoencephalography (MEG) in addition to the standard routine diagnostic trajectory. Before the start of the study, the attendant neurologist notified the patient of the request for a routine EEG. During this conversation, the patient was asked to participate in the optimized diagnostic trajectory including the MEG procedure, provided that they met the inclusion criteria. The patient received information about the study and an informed consent form. The patient was given 2 weeks to review and ask questions. Fig. 1 gives an overview of the diagnostic trajectory. At T0, patients were included in the study. After they gave permission, the research nurse provided them with the relevant documents, including the cost questionnaire, the EQ-5D-3 L, and a reply envelope. Subsequently, the routine EEG and MEG were scheduled. During week 2–10 (T1), the optimized diagnostic trajectory took place. After 3, 6, and 12 months (T2-T4), the cost questionnaire and EQ-5D were again administered. The study protocol was approved by the Medical Ethics Committee of Kempenhaeghe.

2.2. Optimized trajectory

The study comprised an optimized trajectory, i.e. all patients had been subjected to a routine EEG, any additional examinations, i.e. an EEG after sleep deprivation and/or a 24-hour EEG and/or an MRI, and a MEG. Together they were intended to form an optimized trajectory in order to minimize the burden of epilepsy.

2.3. Sample

The sample consisted of patients enrolled at the Academic Center for Epileptology, Kempenhaeghe, located in Heeze, the Netherlands. Participants eligible for the study were patients suspected of having epilepsy for whom a standard EEG was requested for the first time by the attending neurologist. As the sample originated from research on the effectiveness of MEG, some exclusion criteria were established. Patients were excluded if they were under the age of 6, if there was a high suspicion of non-epileptic seizures, if they were either un-cooperative or claustrophobic, and/or in case of presence of intracranial metal.

2.4. Cost analysis

The following cost categories were identified (Hakkaart-van Roijen et al., 2015); healthcare costs, patient and family costs, and costs in other sectors (Drummond et al., 2005). Self-administered retrospective questionnaires were used to measure costs. If desired, a copy of the questionnaire can be requested from the corresponding author.

Healthcare costs were determined by measuring the amount of consultations with healthcare professionals, the use of diagnostic methods, and the frequency of inpatient stay and outpatient treatment was measured. These costs were derived from the Dutch guidelines (Hakkaart-van Roijen et al., 2015). Additionally, the use of AEDs and other drugs was measured. To determine the costs of these drugs, the website of the Dutch healthcare institute for the cost of pharmaceuticals (www.medicijnkosten.nl) was used. These costs were calculated per unit and subsequently multiplied with the reported dosage.

Patient and family costs, including the use of formal care, informal care, and medical devices, were determined according to the Dutch guidelines (Hakkaart-van Roijen et al., 2015). The costs for informal care were valued using the proxy good method. This method values the time spent on informal care at the labor price of a close market substitute. Consequently, the hourly wage of informal care amounted to €14.08 (Hakkaart-van Roijen et al., 2015). When standard prices of devices were not available, market prices applied.

Costs in other sectors, i.e. productivity losses due to absence from work, were measured using standard prices for productivity costs for paid work. The Dutch guidelines recommend using the friction cost method to determine productivity losses, which implies that long-term absent employees can be replaced. Hence, productivity costs were calculated based on the average period an employer needs to replace a sick employee, which is the friction period. In accordance with the Dutch guidelines, a friction period of 85 days and hourly wages of €3496 were applied in this study (Hakkaart-van Roijen et al., 2015).

To correct for the effects of inflation, all costs were converted and applied to 2015 by use of the Consumer Price Index (www.statline.cbs.nl).

2.5. HR-QoL analysis

To measure the HR-QoL among respondents, utilities were used. Utilities reflect morbidity or quality of a particular health state in a number ranging from 0 to 1 (Kind et al., 2009; Drummond et al., 2005). The EQ-5D-3 L was used to measure these utilities. This multi-attribute instrument is intended for self-completion by respondents and contains 5 dimensions of HR-QoL. Each dimension could be rated at three levels:

no problems, some problems, and major problems (Van Reenen and Oppe, 2015). For each health state of the EQ-5D, utility values were calculated using the Dutch tariff (Lamers et al., 2005). This tariff is derived from preferences elicited from the general population. The EQ-5D also includes a Visual Analogue Scale (VAS), ranging from zero (worst imaginable health state) to 100 (best imaginable health state) (Van Reenen and Oppe, 2015).

Using the generated utilities, QALYs could be calculated by calculating the area under the curve.

2.6. Statistical analysis

All analyses were conducted using SPSS© (version 23) and STATA 14. The intention-to-treat principle was used, in which all participants of whom baseline data were available were analyzed. It is important to notice that with regards to cost, participants' missing values may imply that they did not use a particular resource rather than having forgotten to fill in the options. Hence, missing values of people who had skipped an entire section were imputed using mean imputation. For completely missing observation (i.e. people did not return the questionnaire) we used multiple imputations by chained equations with predictive mean matching to account for the missing data. This technique was used to account for non-normality of the cost and utility data. Using predictive mean matching "real" observed values from similar cases are imputed instead of imputing regression estimates (Grittner et al., 2011; Horton and Lipsitz, 2001). Moreover, the use of this technique may avoid bias associated with complete case analyses and makes optimally use of available data. Imputations were based on age, gender, marital status, education, and whether people had a paid job. Annual costs were calculated by assuming the last observation carried backwards from 12 months follow-up.

To identify difference in utilities over time, a (generalized) linear mixed model was used to account for the hierarchical structure of the data (e.g. repeated measurements). This model constitutes the recommended approach to longitudinal designs as estimates are based on all available data. Random- and repeated effects were determined based on model fit, (a-priori implemented with random intercepts and slopes for individuals). Utilities were entered as dependent variable, and time point (i.e., 3 months, 6 months, 12 months), gender, age, civil status, education, employment (> 12 h), and eventual diagnosis of epilepsy were added as independent variables. Given the non-normality of the data, non-parametric bootstrapping (1000 replications) was performed in order to investigate the uncertainty around the cost and utilities, and to compute 95% confidence intervals (CI) based on the 2,5th and 97,5th percentiles. Subgroup analyses were performed in which people who were diagnosed as having epilepsy during the follow-up of the study were compared to people who were diagnosed as not having epilepsy or for whom diagnosis was still uncertain after 12 months.

3. Results

In total, 116 participants were included in the study between August 2013 and March 2016 and were able to fill in the baseline questionnaire. Their mean age was 37 (7–77). Nearly 52% of participants were male. The majority of participants were either married or cohabiting, and had finished secondary school. See Table 1 for group characteristics. After 12 months follow-up, 76 people (69.7%) were diagnosed as having epilepsy and 33 people (30.3%) were diagnosed as not having epilepsy or the diagnosis was still uncertain, 7 people dropped-out and hence, no information was available.

3.1. Costs

The mean total costs per participant at baseline were €4594 per three months (see Table 2). The largest expenses throughout the study were healthcare costs (52–66%). The largest cost item within the

Table 1
Group characteristics at baseline (N = 116).

Characteristics		% (N)[a]
Gender	Male	51.8 (59)
	Female	48.2 (55)
Age	7–20	18.8 (21)
	21–40	36.6 (41)
	41–60	31.3 (35)
	> 60	13.4 (15)
Civil status	Married/cohabiting	69 (78)
	Living alone	14.2 (16)
	Living with parents or guardians	7.1 (8)
	Other	9.7 (11)
Education	No education	0.9 (1)
	Primary school	11.7 (13)
	Pre-vocational secondary school	9 (10)
	Secondary school	52.3 (58)
	Higher education	20.7 (23)
	Special education	5.4 (6)
Employment (> 12 h)	Employed	49.6 (56)
	Unemployed	50.4 (57)
Absenteeism	Has been absent from work	66.1 (37)
	Has not been absent from work	33.9 (20)
Questionnaire completed by	Participant themselves	78.1 (89)
	Parent/caregiver	15.8 (18)
	Other	6.1 (7)
Additional EEG	1 additional EEG	84 (77)
	2 additional EEGs	2 (2)
	No additional EEG	23 (21)
EEG after sleep deprivation	Yes	31 28)
	No	78 (72)
24h-EEG	Yes	42 (39)
	No	67 (61)
Other additional examinations	Yes	15 (14)
	No	94 (86)

[a] Number of missing values per characteristic: gender: 2; age: 4; civil status: 3; education: 5; employment: 3; questionnaire completed by: 2.

healthcare costs throughout the entire study was diagnostic procedures, followed by consultations and inpatient stay. All costs except for the costs related to diagnostic procedures had ultimately decreased after 12 months. Significant decreases were found in healthcare costs and patient and family costs. Patient and family costs decreased from €832 at baseline to €585 at the end of the study (Table 2). Overall, the 3-monthly total costs decreased to €2609 at the end of the study. The average annual costs per patient were €13,216 (Table 2). Productivity losses decreased overtime from €1376 at baseline to €442 at 12 months follow-up. At baseline, there was a considerable difference between people who were eventually diagnosed as having epilepsy and those for whom diagnosis was still uncertain or who were not diagnose as having epilepsy (€5057 for the group with epilepsy compared to €3722 (see Table 3). Total annual costs were similar between both groups.

3.2. Quality of life

The average utilities significantly increased from 0.80 before to 0.84 one year after an optimized diagnostic procedure (after three 3 months, p = 0.36; after 6 months, p = 0.31; after 12 months, p = 0.00). The results show that immediately after the optimized diagnostic procedure there is already a (non-significant) increase in utilities. The overall QALY during the course of the study was 0.81 (Table 4). Moreover, people eventually diagnosed as having epilepsy had a slightly higher utility at baseline. However, the group diagnosed as not having epilepsy or for whom diagnosis was still uncertain demonstrated larger increases overtime. Hence, overall QALY was lower for the people diagnosed with epilepsy (0.81 compared to 0.83).

4. Discussion

The aim of this study was to quantify the Burden of Disease for people with possible epilepsy before and after an optimized diagnostic trajectory. The mean costs per patient made in the previous three months had decreased from €4594 before vs. €2609 in the 12 months after the optimized diagnostic trajectory. Healthcare costs and costs in other sectors had significantly decreased within 12 months of the study. At 3 months follow-up, the healthcare costs increased, which can be explained by the optimized diagnostic trajectory that took place between the baseline and 3-month-after measurement, which led to extra costs. Annual total costs were similar between people eventually diagnosed as having epilepsy and those that were diagnosed as not having epilepsy or for whom diagnosis was still uncertain. However, total costs per 3 months decreased earlier in the group who was diagnosed as having epilepsy, mainly due to a steep reduction in healthcare costs. This is likely to be explained by additional examinations in the other group.

Overall the utility had increased during the course of the study (0.80 vs. 0.84) using the Dutch tariff. The Quality of Life had directly increased after the optimized diagnostic trajectory occurred. This may suggest that the trajectory has had a positive effect on Quality of Life. However, utilities were slightly lower in the group eventually diagnosed as having epilepsy, ultimately leading to a lower overall QALY for this group.

A prospective Cost-of-Illness study for epilepsy in Italy found similar results regarding medication and hospital admission (Tetto et al., 2002). Furthermore, a study among privately insured people examined the burden of epilepsy in the United States and found average annual direct costs per patient with epilepsy to be $10,258 in 2005 (approx. €8,000–10,000 in 2016), which is comparable to the annual healthcare cost demonstrated in this study (€8138). The study demonstrated similar average annual indirect costs per person (Ivanova et al., 2010).

To the best of our knowledge, there is no literature available on how a correct diagnosis influences the Quality of Life in people with epilepsy. However, few studies report an increase of Quality of Life due to certain interventions for epilepsy patients (Dodrill and Morris, 2001; Hosseini et al., 2016; Caller et al., 2016).

Several studies reported similar scores for Quality of Life, also using the EQ-5D. A study on the HR-QoL of patients before and after epilepsy surgery established an improvement in utilities from 0.81 at baseline to 0.91 at follow-up, consistent with our baseline findings. As this trial included an intervention, follow-up utilities can only be compared to a certain extent (Selai et al., 1999). Furthermore, a recent cross-sectional study on coping styles and Quality of Life in patients with partial epilepsy showed an average utility score of 0.80 among patients, identical to our findings at baseline (Westerhuis et al., 2011). Likewise, a study using a similar multi-attribute instrument found a mean value of 0.88 for the 15D utility (Stavem et al., 2001).

4.1. Strengths and limitations

A first strength of this study is that it lives up to scientific standards, as academic guidelines and reliable instruments were used (Hakkaart-van Roijen et al., 2015). Second, the study takes a broad perspective on the Burden of Disease, as many cost items were covered, especially costs related to informal care and productivity losses. This can be seen as an asset compared to other European studies, which often solely take healthcare costs into account. Last, this study applied a bottom-up approach, since the patients' perspective was adopted in collecting and quantifying data, which contributed to thoroughness of the results.

This study also has some limitations. First, due to the longitudinal design of the study, loss to follow-up of participants was common, threatening the validity of the study. However, multiple imputation was used to account for this loss and to make optimal use of the available data. A second limitation of the study is the fact that Kempenhaeghe is a

Table 2
Mean costs per participant expressed in costs per 3 months, measured before and up to 12 months after an optimized diagnostic procedure in Euros calculated for 2015.

	Baseline[f]	3 months after	6 months after	12 months after	Total annual costs after[e]
N	116	78	80	67	
Healthcare costs[a,d]	**2395 (52%)**	**2989 (66%)**	**1987 (57%)**	**1581 (61%)**	**8138 (62%)**
95% CI	2078–2737	2514–3463	1625–2348	1387–1775	7252–9025
Consultations	613	495	291	315	
GP	63	41	31	29	
Neurologist	250	195	114	79	
Paramedics	34	27	26	28	
Mental health	41	47	18	66	
Alternative care	20	14	5	30	
Occupational health	67	80	41	24	
Other specialists	138	90	56	59	
Diagnostic procedures	988	1360	1503	1072	
Routine EEG	215	246	240	237	
EEGsd	145	176	214	185	
24-h EEG	336	401	504	405	
MRI	144	149	155	151	
Other	147	183	390	93	
MEG[c]		213			
Cost of AEDs	52	53	48	34	
Cost of other drugs	14	10	13	14	
Inpatient stay	466	632	186	199	
Epilepsy centre	292	547	105	106	
General hospital	163	63	17	93	
Academic hospital	1	17	65	0	
Revalidation centre	0	6	0	0	
Nursing home	0	0	0	0	
Outpatient treatment	263	203	24	54	
Epilepsy centre	152	153	17	50	
General hospital	53	18	7	4	
Academic hospital	58	32	0	0	
Patient and family costs[d]	**832 (18%)**	**946 (21%)**	**1066 (30%)**	**585 (22%)**	**3182 (24%)**
95% CI	395–1310	561–1332	601–1531	47–1122	1653–4711
Cost of formal care	443	274	311	315	
Cost of informal care	387	639	700	450	
Devices	1	4 (	4 (	3	
Costs in other sectors[b,d]	**1367 (30%)**	**562 (12%)**	**448 (13%)**	**442 (17%)**	**1896 (14%)**
95% CI	836–1991	271–853	175–722	131–755	1149–2643
Productivity losses	1367	610	297	405	
Total cost[d]	**4594**	**4497**	**3501**	**2609**	**13,216**
95% CI	3814–5454	3681–5313	2828–4173	1943–3275	11089–15343

[a] Significant differences found in categories between baseline and 12 months after.
[b] Significant differences found in categories between baseline and 6 months after.
[c] MEG is only performed within 3 months prior to the 3-month measurement.
[d] Mean costs are based on multiple imputations using predictive mean matching (N = 116).
[e] Calculated with the last observation carried backwards to reflect costs during 12 months.
[f] Assessment at baseline covered the period of three months before inclusion in the study and hence before start of the diagnostic trajectory.

Table 3
Mean costs per participant (in Euros; 2015) and 95% confidence intervals for main cost categories separately for people diagnosed with epilepsy and people diagnosed as not having epilepsy (or for whom it is still uncertain).

	Baseline	3 months after	6 months after	12 months after	Total annual costs[b]
Healthcare costs[a]					
No epilepsy or uncertain (95%CI)	2235 (1778–2692)	2903 (1838–3967)	2476 (1415–3536)	1626 (1352–1900)	8630 (6643–10,618)
Diagnosed with epilepsy (95%CI)	2401 (2002– 2799)	3026 (2461 –3590)	1766 (1522–2010)	1575 (1304–1847)	7942 (692–8964)
Patient and family costs[a]					
No epilepsy or uncertain (95%CI)	427 (110 – 744)	914 (192–1636)	730 (285–1175)	355 (0–754)	2354.805 (980–3730)
Diagnosed with epilepsy (95%CI)	1070 (379 –1761)	912 (398 –1425)	1234 (544–1924)	702 (0–1522)	3550 (1234–5867)
Costs in other sectors[a]					
No epilepsy or uncertain (95%CI)	1059 (1–2118)	523 (0–1052)	981 (100–1861)	178 (0–408)	1859.024 (733–2985)
Diagnosed with epilepsy (95%CI)	1586 (810 –2361)	567 (212–923)	248 (92–405)	352 (167–537)	1520 (974–2067)
Total cost[a]					
No epilepsy or uncertain (95%CI)	3722 (2494 –4949)	4340 (2607 –6073)	4187 (2728–5645)	2159 (1574 - 2744)	12,844 (9827–15,862)
Diagnosed with epilepsy (95%CI)	5057 (3913 –6200)	4505 (3508–5502)	3248 (2426 – 4071)	2630 (1735–3525)	13,013 (10,128–15,898)

[a] Mean costs are based on multiple imputations using predictive mean matching. Number of people diagnosed as having epilepsy N = 76; number of people diagnosed as not having epilepsy or uncertain N = 33).
[b] Does not include baseline costs.

Table 4
Mean utilities and health scores per patients related to HR-QoL measured before and 12 months after an optimized diagnostic procedure.

	Baseline[b]	3 months after	6 months after	12 months after	Overall[a]
Total sample					
Utilities	0.80	0.81	0.80	0.84	0.81[a]
No epilepsy or uncertain					
Utilities	0.77	0.84	0.82	0.86	0.83
Diagnosed with epilepsy					
Utilities	0.81	0.79	0.79	0.84	0.81

[a] Reflects the average annual QALY during the year of the study based on area under the curve method.
[b] Assessment at baseline covered the period of three months before inclusion in the study and hence before start of the diagnostic trajectory.

specialized epilepsy center, and is likely to treat more severe or complicated cases. This could impede the generalizability of the results, as these cases are already more likely to use healthcare resources. Third, the EQ-5D is a tool for assessing the HR-QoL of a general population. As other literature indicated, the EQ-5D might not be an appropriate instrument to measure HR-QoL in epilepsy patients, since it does not cover chronic difficulties to which the patient has adapted (Selai et al., 1999; Wijnen et al., 2017). A solution to this would be to use a more disease-specific tool such as the Quality of Life in Epilepsy Inventory to increase sensitivity (QOLIE) (Cramer et al., 1999). Fourth, as the study used self-report instruments, recall-bias by the respondents, or proxies, is likely. Nevertheless, a recall period from 1 to 4 months has been established as an acceptable period to maintain the validity of results related to resource consumption (Evans and Crawford, 1999). Fifth, given the static design of this study with measurements at fixed time points and the continuous reevaluation of patients' health status after additional examinations, we were not able to investigated the immediate impact of a diagnosis on a patients' quality of life. However, it is likely that most patients have completed most of their diagnostic trajectory at 6 months after baseline.

Furthermore, as shown in the results section, costs related to diagnosis had not decreased. This can be explained by the inability of patients to specify appliances. Hence, patients may have wrongly indicated that they had been subjected to one or more given procedures, leading to an overestimation of costs. For example, a similar study found that patients reported implausible estimates of diagnostic procedures which they had undergone, such as MEG and EEG (Wijnen et al., 2014). In addition, the use of healthcare devices may be under-represented because the questionnaire item was a voluntary, open-ended question. Lastly, travel costs, as well as costs of unemployment, incapacity, and mortality were not taken into account, as they were too difficult to measure. To resolve these issues, future research should include more specific items focusing on traveling costs and use of medical devices.

4.2. Conclusion

To conclude, significant reductions in costs and improvements in quality of life were observed which might be attributable to the optimized diagnostic trajectory especially in the early phase. The average 3-monthly costs per patient had decreased towards the end of the study, where costs in other sectors (i.e. productivity losses) had decreased the most drastically. Healthcare costs were the largest expenses and had significantly decreased at the end of the study. As chronic care patients make diverse costs, future research should identify the long-term costs after an optimized diagnostic trajectory for patients with epilepsy, possibly identifying patients who are at high risk of becoming high-cost

users in the future. Moreover, an assessment of the incremental cost-effectiveness of this optimal diagnostic treatment would be needed in order to draw firm conclusions regarding its cost-effectiveness.

Our findings are roughly similar to other studies and can be seen as complementary given that there are no identical studies that are oriented on the influence of diagnosis on the burden of disease of epilepsy, differentiating between people diagnosed with epilepsy during the follow-up of the study and the people who are diagnosed as not having epilepsy or for whom diagnosis is still uncertain. The current study offers promising insights on the effects of diagnostic improvements on decreasing the burden of disease of epilepsy or similar neurological conditions.

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