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An economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy: An interim analysis

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SUMMARY

Objectives: To gain insight into the cost-effectiveness of the ketogenic (KD) diet compared with care as usual (CAU) in children and adolescents with intractable epilepsy, we conducted an economic evaluation from a societal perspective, alongside a randomized controlled trial.

Methods: Participants from a tertiary epilepsy center were randomized into KD (intervention) group or CAU (control) group. Seizure frequency, quality adjusted life years (QALYs), health care costs, production losses of parents and patient, and family costs were assessed at baseline and during a 4-month study period and compared between the intervention and control groups. The incremental cost-effectiveness ratios (ICERs) (i.e., cost per QALY and cost per responder), and cost-effectiveness acceptability curves (CEACs) were calculated and presented.

Results: In total, 48 children were included in the analyses of this study (26 KD group). At 4 months, 50% of the participants in the KD group had a seizure reduction $\geq 50\%$ from baseline, compared with 18.2 of the participants in the CAU group. The mean costs per patient in the CAU group were €15,245 compared to €20,986 per patient in the KD group, resulting in an ICER of €18,044 per responder. We failed, however, to measure any benefits in terms of QALYs and therefore, the cost per QALY rise high above any acceptable ceiling ratio. It might be that the quality of life instruments used in this study were not sufficiently sensitive to detect changes, or it might be that being a clinical responder is not sufficient to improve a patient's quality of life. Univariate and multivariate sensitivity analyses and nonparametric bootstrapping were performed and demonstrated the robustness of our results.

Significance: The results show that the KD reduces seizure frequency. The study did not find any improvements in quality of life and, therefore, unfavorable cost per QALY ratio's resulted.

KEY WORDS: Cost-effectiveness, Cost-utility, Quality of life, Economic evaluation, Ketogenic diet.

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KEY POINTS

- Children with refractory epilepsy, randomized to the KD group had a significant reduction in seizures compared to children in the CAU group
- The mean costs per patient in the CAU group were €15,245 compared to €20,986 per patient in the KD group, resulting in an ICER of €18,044 per responder
- No benefits in terms of QALYs were found and, therefore, the cost per QALY increase high above any acceptable ceiling ratio

Epilepsy is a major, cost-intensive and global health problem.¹ In The Netherlands, the prevalence of epilepsy is estimated to be 5 per 1,000 of the population; at any one time, about 80,000 individuals have epilepsy.² In 2004, the total costs of epilepsy in Europe were €15.5 billion, indirect costs being the single most dominant cost category (€8.6 billion).³ In 2011, in The Netherlands, the direct medical costs were €248 million, which is 0.3% of the health care budget.⁴ Although in the majority of patients epilepsy is treatable with antiepileptic drugs (AEDs), about 30% of patients have intractable epilepsy.⁵ Patients are diagnosed as having intractable epilepsy when their seizures are not controlled after taking two or more different AEDs. Patients with uncontrolled epilepsy depend heavily on informal care (family and friends), and on health care professionals (neurologists, social workers, psychologists, and so on). Complications due to intractable epilepsy result in frequent hospitalizations, and many of these patients are institutionalized. Living with uncontrolled seizures has a negative impact on the quality of life (QoL) of the child and his or her surroundings.

Patients with intractable epilepsy after failure of AEDs and/or resective surgery can potentially benefit from a ketogenic diet (KD). The KD is a high-fat, low-carbohydrate diet that imitates the metabolic state of fasting while maintaining a normal number of calories. Body energy requirements while on a KD are met by lipolysis and β -oxidation of fatty acids rather than by the breakdown of carbohydrates. The exact anticonvulsant mechanism of action of a KD has not yet been elucidated.⁶ Currently, the scientific and clinical attention directed toward the role of the KD is negligible.⁷ This means that the KD is often overlooked and underutilized as a treatment option for children with intractable epilepsy. An important reason for this is that relatively few children and their parents can comply with the stringent diet. Physicians are, therefore, often reluctant to initiate the diet. The beneficial effect of a KD has been studied in multiple observational studies,^{8–15} reviews,^{16–19} and in two randomized controlled trials.^{20,21} However, none of these studies has researched the cost-effectiveness of the KD.

Because resources are scarce, in current health care decision-making, we need to prove that the effects of the KD are worth the extra costs, to allow decisions to be evidence based.^{22,23} Economic evaluation is a method for examining this trade-off between costs and effects of comparative treatments. Full economic evaluations are necessary to inform the decision makers. Therefore, this trial-based economic evaluation researches the cost-utility and cost-effectiveness of the KD compared with care as usual (CAU) in children and adolescents with intractable epilepsy from a societal perspective.

METHODS

The economic evaluation was executed alongside a randomized controlled trial (RCT); details of the trial design can be found elsewhere.²⁴ In short, between July 2010 and September 2014, patients were randomized to either the KD or to CAU after a 1-month baseline period. Patients randomized into the KD group were followed during the 4-month comparative study period and a follow-up period of 12 months. Patients randomized into the CAU group were followed only during the 4-month study period. The time line of the study is graphically presented in Figure 1. This interim analysis reports the cost-effectiveness of the comparative period of the trial, that is, the 4-month study period where direct comparison between KD and CAU is possible. This study has been approved by the ethics committee of the Academic Medical Center Utrecht, The Netherlands.

The economic evaluation was performed from a societal perspective and consisted of a cost-utility analysis with quality adjusted life years (QALYs) as primary outcome and a cost-effectiveness analysis with treatment responder ($\geq 50\%$ seizure reduction) as the primary outcome.

Study population and sample size

Patient were children and adolescents with intractable epilepsy. Patients were eligible to participate if they met the following criteria: aged between 1 and 18 years; having uncontrolled seizures after trying two or more AEDs; not eligible for epilepsy surgery; no fatty acid oxidation disorders and related diseases; no diabetes and hyperinsulinism; no long QT syndrome; no hypercholesterolemia or hypertriglyceridemia; no severe liver, kidney, or pancreas diseases; no renal tubular acidosis; no severe behavioral disorder; no malnutrition; no treatment with topiramate or acetazolamide; and no positive family history or other risk factors for kidney stones or acidosis. Eligible candidates and their parents were referred by their attending physician to the multidisciplinary KD team at epilepsy center Kempenhaeghe in The Netherlands, where they received detailed information about the study before giving their consent.

This study was performed alongside an RCT where seizure frequency was the primary outcome. Based on a minimum detectable difference in success rate of 35% between

Figure 1.
Time line of the study.
Epilepsia © ILAE

the KD group and CAU, and assuming that $\alpha = 5\%$ and power = 80%, we needed 22 children for each group.²⁴

Interventions

Ketogenic diet

Patients assigned to the KD group were admitted to the tertiary epilepsy center for 5 days, whereas KD was introduced by a dietician. The neurologist, pediatrician, and epilepsy nurse visited the child during the 5-day admission, and ketosis was assessed daily in urine (if toilet-trained) and three times in blood by means of a finger puncture. The AEDs used by the children and adolescents at the time of inclusion in the study were continued without changes during the study period (except when medically indicated). The dietician decided together with the parents whether the classical diet, the medium-chain triglyceride (MCT) diet, or a mixture of both diets was introduced. Children who were tube-fed were also treated with KD. The diet was then adjusted to a fluid version.

After the 5-day admission, weekly telephone meetings were planned between parents and the epilepsy nurse, and between parents and the dietician. Ketosis was checked daily by the parents in urine or three times a week in blood via a finger puncture. Furthermore, time points T2 and T3 consisted of a visit to the neurologist, pediatrician, dietician, and epilepsy nurse. At T3, blood and urine samples were taken from the patients in the intervention group. No other protocol-driven care was delivered.

Care as usual

Patients randomized to CAU continued to take their AEDs. The controls were treated and monitored according to good clinical practice. Patients randomized into CAU were seen at time points T2 and T3 by a neurologist, pediatrician, and epilepsy nurse. Weekly telephone meetings were scheduled between parents and the epilepsy nurse. No other protocol-driven care was delivered.

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Outcome measures

Seizure frequency

A daily seizure calendar was used to record seizures continuously. Types of seizures were described and labeled in accordance with the International League Against Epilepsy (ILAE) classification. A patient was labeled as a responder when he or she had a mean reduction in seizures of 50% or more during the last month of the study period (month 4) compared with baseline. Based on previous literature, a cut-off point of $\geq 50\%$ seizure reduction was considered to be a realistic clinical target for patients with intractable epilepsy.

Utilities

QoL of the children and their parents was measured using the EuroQol-Youth (EQ-5D-Y) version for children aged 8 years and older, and the EuroQol (EQ-5D), respectively. The EQ-5D system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, and extreme problems.^{25,26} The EQ-5D health states were converted into a single summary index between 0 and 1 (utility) by applying the Dutch utility-tariff.²⁷ In addition, QoL was assessed by the TAPQOL (TNO-AZL Preschool Children's Quality of Life) for children aged between 1 and 5 years (parent proxy) and the TACQOL (TNO-AZL Children's Quality of Life) for children aged between 6 and 16 years (parent proxy).^{28,29} The TAPQOL has nine domains, all ranging between 0 and 100. The TACQOL has seven domains, two of which have scores ranging between 0 and 32 and two domains between 0 and

16. All domains were given equal weight; a mean score was calculated and transformed into a QoL score between 0 and 1. Utility scores from the EQ-5D, EQ-5D-Y, and QoL-scores from the TAPQOL and TACQOL were measured at time points T0 and T3.

Quality adjusted life years (QALYs) were calculated by means of the “under the curve method,” in which the time in a certain health state was multiplied by the utility of this health state.²²

Costs

Costs were calculated from a societal perspective; therefore, protocol-driven intervention costs, other health care costs, patient and family costs, and productivity losses of the parent(s) were measured. Costs were expressed in Euros and were converted to the price year 2013 based on the relevant consumer price index. Due to the time horizon of 4 months, no discounting was performed.

Other (epilepsy-related) health care costs and patient and family costs were measured by a monthly cost diary completed by the patient’s parent(s).³⁰ Because there are no institutional records tracking information on the type, frequency, and magnitude of resource use in the cost sectors “other health care costs” and “patient and family costs,” data must be obtained through a self-report “resource use measure,” such as questionnaires and diaries. In comparison with questionnaires, diaries have been reported to provide information prospectively over a period of time, resulting in minimum recall bias.³⁰ Additional costs consisted of parents’ productivity losses, based on the hours absent from work due to their child’s epilepsy or their own health-related problems. Parents’ productivity costs were taken into account because parents are (sometimes) forced to be absent from work to provide care for their child or because of their own health problems that may be indirectly caused by their child’s disease (e.g., due to increased stress levels).

Costs were estimated using a bottom-up approach, in which information on each element of service used was multiplied by an appropriate standardized unit cost and summed to provide an overall total cost.²² Where possible, unit costs were based on standardized costs from the Dutch guidelines for cost research.³¹ Real tariffs or costs were used when no standardized unit costs were available. Cost of medication was calculated using guideline prices.³¹ An addition for prescription charges for prescribed medication was taken into account. When data on medication were diverse, lowest cost prices for the specific medication were used. The cost of informal care was calculated using shadow pricing. For this, the general hourly minimum wages were applied.³¹ Productivity costs were calculated on the basis of the friction cost method (FCM), following the Dutch guidelines.³¹ The FCM is based on the assumption that an organization needs a certain time span (friction period) to replace the absent worker by another worker. The definitive number of days absent from work is then limited to the duration of

the friction period, which was determined in The Netherlands to be 23 weeks in 2010.³¹ Unit prices are presented in Table 1.

Data analyses

The economic analyses were carried out on an intention to treat (ITT) protocol. Mean imputation was used to impute missing (N = 5) and cost data within the treatment group (N = 1). For incomplete cases, last observation was carried forward (n = 4). Due to the relative low proportion of

Table 1. Unit prices

	€ (2013)
Intervention costs (4 months)	
KD group	4,311.81 ^a
CAU group	1,548.60 ^a
Diet costs (4 months)	
Classical diet	0
MCT diet	2,491.20 ^a
Tube diet	3,476.40 ^a
Mixture	1,246.60 ^a
Ketosis check	
Finger puncture device	21.73 ^a
In blood (finger puncture)	2.02 ^a
In urine	0.14 ^a
Health care costs	
GP visit	30.48 ^b
Specialist visit	140.42 ^b
Epilepsy nurse visit	109.65 ^a
Blood sample	24.77 ^a
Physiotherapist visit	39.19 ^b
Speech therapist visit	35.92 ^b
Dietician visit	29.39 ^b
Other paramedic visit	23.95 ^b
Psychologist visits	87.08 ^b
Psychiatrist visit	112.12 ^b
Routine EEG	273.55 ^a
24-h EEG	779.65 ^a
MRI	179.84 ^a
General hospital (day)	473.50 ^b
Academic hospital (day)	625.89 ^b
Epilepsy center (day)	208.25 ^a
Inpatient disabled care (day)	208.25 ^a
Day care	273.21 ^b
Home care (hour)	70.75 ^b
Social services (hour)	70.75 ^b
Prescribed medication	Variable ^c
Patient and family costs	
Informal care (hour)	13.61 ^b
Child care	Variable ^a
Housekeeping (hour)	13.61 ^b
Medication (OTC)	Variable ^c
Activities	Variable ^a
Transport (per kilometer)	0.20 ^b
Other costs	
Production losses (hour)	32.68 ^b

^a(Calculated from) respective providers or professional organizations.

^bDutch guidelines for costing studies.

^cDutch Pharmaceutical Therapeutic Compass.

missing values, less sophisticated methods were used to handle missing data.

Data were analyzed using IBM SPSS Statistics version 22. Baseline differences in costs and utilities between groups were checked with nonparametric bootstrapping, based on 1,000 bootstrap replications, as the data did not comply with the underlying assumptions of parametric tests.

Furthermore, the arithmetic mean and 95% nonparametric confidence intervals were calculated (1,000 bootstrap replications) for differential costs and QALYs during the study period.

In addition, bootstrapping with Microsoft Excel 2010 was used to quantify the uncertainty around the incremental cost-effectiveness ratio (ICER) (5,000 bootstrap replications). The ICERs were calculated by dividing the incremental costs by the incremental QALYs. The ICER represents the cost of an additional QALY gained and was used to estimate the cost-utility of KD as opposed to CAU. The ICERs were presented on a cost-effectiveness (CE-) plane, which is divided into four quadrants. The southeast quadrant represents the instances where the intervention is more effective and less costly than the comparators (dominates), with the opposite situation in the northwest quadrant, representing interventions that are more costly and less effective than comparators (dominated). The northeast quadrant represents interventions that are more costly yet more effective, whereas the southwest quadrant represents less effective and less costly interventions.²² A treatment is deemed cost-effective when it is dominant or when the costs per QALY are below a specified ceiling ratio. In The Netherlands, an informal ceiling ratio exists between approximately €20,000 and €80,000 per QALY, depending on the burden of disease.³² The burden of disease can be expressed in disability weights, ranging from 0 (implying no loss of health) to 1 (implying a health loss equivalent to death). The disability weight of severe epilepsy is estimated to be 0.657³³; this corresponds to a threshold of approximately €50,000 per QALY,³² which was taken as a ceiling ratio in this study. To show the probability that a KD is cost-effective, given different ceiling ratios, a cost-effectiveness acceptability curve (CEAC) was constructed.²² Furthermore, the number of responding patients ($\geq 50\%$ seizure reduction) and the incremental cost per responding patient were calculated.

Univariate and multivariate sensitivity analyses were performed to explore how robust the results were to changes in the assumptions upon which they were based. First, the scenario was calculated in which the economic evaluation was performed from the health care perspective in order to comply with the guidelines of other policy bodies.³⁴ Secondly, we explored the impact on the cost-effectiveness of the KD by varying the cost of the intervention and diet, as these costs are based mainly on the specific protocol of epilepsy center Kempenhaeghe. Other centers initiate the KD during

outpatient visits and/or offer only the classical diet, possibly due to reimbursement issues. We therefore included this realistic and policy-relevant sensitivity analysis to provide the reader with information about the cost-effectiveness if another protocol, policy, or organization of care is followed.

RESULTS

Between August 2010 and September 2014, a total of 58 patients were included in the study. One patient dropped out of the study before and nine patients dropped out after randomization: six from the control group, due to dissatisfaction regarding the randomization result, and three patients from the KD group, due to spontaneous seizure reduction (one patient) and gastrointestinal side effects (two patients), leaving 48 patients in the ITT analysis.

There were no statistical differences between the KD and CAU group at baseline in utilities (both TACQOL/TAPQOL and EQ-5D) or in total health care, patient, and family and productivity losses. Therefore, baseline correction was assumed to be unnecessary. Demographic data and baseline utilities are presented in Table 2.

Outcomes

In total, 13 patients from the KD group (50%) and 4 patients from the CAU group (18.2%) were responders ($\geq 50\%$ seizure reduction). Measuring utilities with the EQ-5D-Y seemed only possible in a minority of patients in our sample. We, therefore, used the QoL scores of the TAPQOL and TACQOL (age-dependent) to calculate QALYs for the patients. The QALYs of the parents were based on utilities of the EQ-5D. No significant differences were found in patients' QALYs or in parents' QALYs between the two groups (Table 3). Total health care costs differed significantly between the two groups due to significantly higher intervention and diet costs in the KD group. No other significant cost differences were found.

ICERs

The CE plane for the cost-utility analysis from a societal perspective, representing the uncertainty surrounding the cost per QALY ratio, is shown in Figure 2A. The KD is more expensive than CAU (resp. €20,986 and €15,245) and (almost) equally effective in terms of QALYs (resp. 0.253 and 0.250). As a result, most bootstrapped ICERs lie in the northern part of the CE plane (40% northwest and 56% northeast). Based on the cost-utility analysis, the KD is not a cost-effective treatment option. Figure 2B presents the CEAC based on the cost per QALY, showing the probability that the KD is cost-effective at different ceiling ratios. At the ceiling ratio of €50,000, there is only a 5% probability of the KD being cost-effective.

The incremental costs (KD €20,986, CAU €15,245) divided by the incremental number of responders, taking the difference in group sizes into account (KD 13/26, CAU

Table 2. Demographic characteristics and baseline utilities

	KD N = 26 N (%)	CAU N = 22 N (%)
Female	8 (30.8)	13 (59.1)
Age mean (range)	7.8 (2.1–16.5)	8.1 (1.1–15.7)
Age seizure onset (range)	2.4 (0–8)	1.9 (0–10)
Genetic	9 (34.6)	1 (4.5)
Structural	2 (7.7)	10 (45.5)
Unknown	15 (57.7)	11 (50.0)
Full scale IQ		
<50	10 (38.5)	11 (50.0)
50–69	3 (11.5)	4 (18.2)
70–99	11 (42.3)	5 (22.7)
≥100	2 (7.7)	2 (9.1)
Behavioral/cognitive problems		
ADHD	0 (0.0)	1 (4.5)
ADD	1 (3.8)	1 (4.5)
Autism	3 (11.5)	5 (22.7)
Number of AEDs at start study		
None	0 (0.0)	1 (4.5)
One	3 (11.5)	4 (18.2)
Two	12 (46.2)	8 (36.4)
Three	9 (34.6)	5 (22.7)
Four	2 (7.7)	2 (9.1)
Five	0 (0.0)	2 (9.1)
Diet type		
MCT	18 (69.2)	–
Classical	7 (26.9)	–
Mixture	1 (3.9)	–
PGT	6 (23.1)	5 (22.7)
Mean quality of life		
TACQOL or TAPQOL	0.77	0.75
EQ-5D-youth ^a	0.53	0.64
Number AEDs tried in the past		
Three	3 (11.5)	4 (18.2)
Four	4 (15.4)	5 (22.7)
Five	9 (34.6)	3 (13.6)
Six	3 (11.5)	3 (13.6)
Seven	2 (7.7)	1 (4.5)
Eight	4 (15.4)	2 (9.1)
Nine	1 (3.8)	4 (18.2)
VNS in the past	1 (3.8)	1 (4.5)
Epilepsy surgery in the past	1 (3.8)	0 (0.0)

KD, ketogenic diet; CAU, care as usual; N, number; AEDs, antiepileptic drugs; ADHD, attention-deficit/hyperactivity disorder; ADD, attention-deficit disorder; VNS, vagus nerve stimulator; MCT, medium-chain triglycerides; PGT, percutaneous gastrostomy tube.

^aBased on N = 10 KD group and N = 11 CAU group.

4/22), resulted in an ICER of €18,044 per responder. The uncertainty analysis of this ICER is presented in the CE plane in Figure 3. Most ICERs lie in the northeast quadrant, indicating that the KD is more expensive but also more effective than CAU in children and adolescents with intractable epilepsy.

Sensitivity analyses

First, performing the analyses from a health care perspective and at a ceiling ratio of €50,000, results showed that the

KD has only 3% probability of being cost-effective when looking at the cost per QALY (CE planes and CEACs not presented). From a health care perspective, the mean costs per patient in the KD and CAU group are resp. €12,139 and €7,589 (see Table 3), resulting in an ICER of €14,300 per responder.

Second, lowering the cost of the intervention by initiating the KD without 5-day admission to the epilepsy center, ignoring the telephone meetings with dietician and/or nurse (in both groups), and simultaneously lowering the cost of the KD by offering solely the classical variant of the diet, the KD has a 32% probability of being cost-effective at a ceiling ratio of €50,000 per QALY from a societal perspective (CE planes and CEACs not presented). In this situation, the mean costs per patient in the KD group are €16,241 compared to €14,478 in the CAU group, resulting in an ICER of the costs per responder of €5,544.

DISCUSSION

To our knowledge, this is the first study reporting an economic evaluation comparing KD with CAU in children and adolescents with intractable epilepsy alongside a randomized controlled trial. The economic evaluation was conducted from the societal perspective.

The main results of this study are the following: (1) the KD is more effective than CAU in terms of seizure reduction—resp. 50% and 18.2%; (2) the mean costs per participant were €20,986 for the KD compared to €15,245 for CAU, resulting in an ICER of the costs per responder of €18,044; and (3) we did not find any benefits in terms of QALYs and, therefore, the costs per QALY rise high above any acceptable ceiling ratio. Hence, this 4-month analysis shows that the KD is not cost-effective when including the QALY as a primary outcome parameter. This apparent lack of effectiveness of the KD in terms of QoL could point toward the KD being an ineffective way of treating patients with epilepsy. This conclusion, however, is too short-sighted and needs some nuance. On the one hand, the question arises whether the QoL instruments used in our study were sufficiently sensitive to measure clinical changes (e.g., being a responder). First, it is likely that a generic instrument such as the EQ-5D-Y is not able to detect patients' clinical improvements on broadly defined (health) domains. Second, half of the patients in our study were children and adolescents with combinations of severe intellectual and physical disabilities, which makes measuring QoL a huge challenge.³⁵ It is possible that proxies have difficulties taking into account changes in mood and anxiety levels, especially in patients having trouble expressing themselves. On the other hand, being a clinical responder (i.e., seizure reduction of 50% or more) may not be sufficient to have an impact on a patient's QoL, as patients are left with disabling seizures. Total seizure freedom has, however, been reported to be one of the most important factors determining QoL in

Table 3. Number of responders, QALYs and bootstrapped mean (CI) costs (€) per patient during 4-month study period

	Ketogenic diet n = 26		Care as usual n = 22		Difference	
	Mean	CI	Mean	CI	Mean	CI
Outcomes						
Number responders	13	–	4	–	9	–
Patients' QALYs	0.25	0.241–0.265	0.25	0.232–0.265	0.003	–0.016 to 0.024
Parents' QALYs	0.29	0.265–0.311	0.27	0.238–0.303	0.014	–0.023 to 0.055
Health care costs						
Intervention costs	4,311.81	–	1,548.60	–	2,763.21 ^a	–
Hospitalization	1,769.77	–	–	–	1,769.77	–
Dietician	411.53	–	–	–	411.53	–
Epilepsy nurse	1,096.57	–	986.92	–	109.65	–
Neurologist	421.26	–	280.84	–	140.42	–
Pediatrician	421.26	–	280.84	–	140.42	–
Ketosis check	86.08	–	–	–	86.08	–
ECG	105.34	–	–	–	105.34	–
Diet costs	1,972.06	1,587.35–2,396.38	–	–	1,972.06	1,587.35 to 2396.38
MCT diet	2,491.20	–	–	–	2,491.20	–
Classical	0	–	–	–	0	–
Mixture	1,245.60	–	–	–	1,245.60	–
PGT diet	3,476.40	–	–	–	3,476.40	–
Ketosis check	67.12	47.51–85.61	–	–	67.12 ^a	47.51 to 85.61
GP visits	31.70	15.15–49.57	25.92	5.72–54.08	5.78	–24.38 to 33.36
Specialist visits	481.81	294.32–694.75	429.89	234.75–645.61	51.93	–233.86 to 334.43
Paramedic visits	586.58	295.31–905.61	695.46	338.66–1106.40	–108.89	–621.25 to 337.69
Psychologist visits	13.93	0.00–31.34	8.29	0.00–21.77	5.10	–14.21 to 24.95
General hospital	861.15	206.23–1733.67	293.12	0.00–875.93	568.03	–296.42 to 1605.21
Academic hospital	65.34	0.00–168.08	59.61	0.00–192.58	5.73	–148.44 to 136.43
Epilepsy center	1,466.90	51.17–3,860.79	878.33	0.00–2,926.22	588.57	–2158.24 to 3,344.54
Other inpatient stay	974.88	0.00–2723.55	0.00	0.00–0.00	974.88	–564.53 to 2592.29
Day care	903.69	0.00–2124.44	3065.13	883.92–5,717.45	–2161.44	–4771.99 to 103.59
Social services	43.66	10.89–80.42	25.99	3.19–57.27	17.67	–27.09 to 61.92
Prescribed medication	435.11	322.44–552.24	504.32	245.05–836.28	–69.21	–420.12 to 209.23
Total health care costs	12,138.99	9,162.98–15,807.64	7,589.02	4,602.69–10,824.91	4,549.97 ^a	475.66 to 9,259.31
Patient and family costs						
Informal care	6,711.72	4,148.67–9,852.93	4,984.69	2,874.20–7319.12	1,727.03	–1,947.42 to 5,756.65
Child care	60.05	11.87–133.93	565.65	60.14–1,294.58	–505.60	–1,294.71 to 7.37
Home care	954.36	184.41–2,276.94	521.57	5.36–1,544.28	432.80	–875.50 to 1,814.92
Medication (OTC)	13.02	2.17–30.50	19.04	0.00–62.78	–6.02	–50.77 to 23.58
Activities	52.90	19.29–91.06	163.63	52.44–337.73	–110.74	–291.94 to 6.26
Transport	170.45	115.54–224.96	249.94	51.48–541.71	–79.50	–367.98 to 129.26
Total patient and family costs	7,962.49	5,178.51–11,222.17	6,504.52	3,988.27–8,899.74	1,457.97	–2,192.30 to 5,494.42
Production losses	884.87	141.74–1,849.97	1,151.58	211.07–2,316.99	–266.71	–1676.35 to 1,025.13
Total costs	20,986.35	16,445.37–25,744.34	15,245.12	104,64.85–20,407.78	5,741.24	–1555.69 to 12,667.06

CI, confidence intervals based on the 2.5th percentile and the 97.5th percentile; QALYs, quality adjusted life years; GP, general practitioner; OTC, over the counter.

^aSignificant based on a 5% level.

patients with epilepsy.³⁶ Although the KD is effective in reducing seizure frequency, in our patient population with severe intractable epilepsy, it is unlikely to produce seizure freedom in many patients and hence to produce a major change in QoL. Seizure reduction may not lead directly to improved QoL; however, it is an important outcome measure for comparability purposes, as it is required by European and other health authorities and it has been used as a primary outcome measure in many other trials including KD and VNS. Furthermore, QoL is a comprehensive concept consisting of multiple dimensions. Other factors will

influence QoL in patients with intractable epilepsy such as stigma, anxiety, depression, and the unpredictability of seizures. This complexity might be one of the reasons that it is so hard to reach a QoL improvement. For future studies, one should keep in mind that perhaps other preference-based QoL instruments are more suitable and/or sensitive in children with epilepsy. For example, the Child Health Utility-9D (CHU-9D)³⁷ or Assessment of Quality Of Life-6D (AQOL-6D),³⁸ which both became available after the start of our trial, might be a welcome addition in studying QoL in children with epilepsy.

Figure 2.

(A) Cost-effectiveness plane, cost per QALY. (B) Cost-effectiveness acceptability curve, cost per QALY. *Epilepsia* © ILAE

Figure 3.

Cost-effectiveness plane, cost per responder. *Epilepsia* © ILAE

Our results are sensitive to change, as can be seen in the sensitivity analyses, where we hypothetically decreased the intervention costs, and simultaneously increased the

classical diet users from 27% to 100%. This resulted in an increased probability (32%) for the KD to be cost-effective at a ceiling ratio of €50,000 per QALY.

This study has some limitations. The first limitation concerns the utility measurement. We were aiming at calculating the cost per QALY, as this is essential information for policy makers. However, at the start of the study, there was no suitable preference-based generic QoL instrument available for utility measurements in children that covered the full developmental range between 0 and 18 years. To calculate QALYs, a QoL score between 0 and 1 was used, which we adapted from the scores of the age-dependent TAPQOL and TACQOL. The QoL scores we used to calculate QALYs, are, therefore, not preference-based utilities and subsequently not comparable with other “real” utilities. In addition, because the TAPQOL and TACQOL are age-dependent measures, our QoL scores consist of a combination of both measures, limiting the comparability of utility measurement among different age groups. Furthermore, the utilities derived from the EQ-5D-Y measurement are calculated with an adult valuation tariff,²⁷ which is not recommended by the EuroQol Group.

The second limitation is the small sample size. As is often the case when conducting trial-based economic evaluations, the sample size for this study was based on a clinical outcome measure (i.e., seizure frequency) and not on QoL or costs as the primary outcome. Hence, there is a probability that the sample size was too small to detect changes in patients’ QoL between both study arms.

The third limitation is the short time horizon of the study, which can be the reason for our inability to measure change in QALYs or costs. This analysis compares the KD group with the CAU group over a period of 4 months. Although a longer comparative period would be preferable, this was not possible due to ethical considerations. The significant differences in costs were fully related to the intervention and diet costs in the KD group. We did not find any reduction in health care costs, patient, and family costs or in productivity losses. Other intersectoral costs, such as educational costs, were not taken into account, as the Dutch guidelines do not include guidance regarding this relevant issue.³¹ Furthermore, in practice, clinicians are frequently faced with the decision of offering KD or another (new) AED. The effectiveness of a new AED is often similar to the effectiveness of KD and is (most often) established at lower treatment costs. In that case, it is very unlikely that positive cost-effectiveness results for KD will be reached. However, previous studies have shown that the efficacy of a new AED decreases rapidly after the failure of two to six other AEDs. Future research should focus on identifying patients (age, type, and duration epilepsy, etc.) who benefit the most from KD. Such information is crucial in allocating scarce resources in the most efficient way.

The final limitation relates to potential transferability problems of our results to other centers within and outside The Netherlands, as volumes and costs reported are (partly) related to the protocol of the tertiary epilepsy center Kemphaeghe.

Until now, two other published RCTs compared the KD with CAU.^{22,23} We found a higher percentage of responders (50%) in the KD group compared to Neal et al.²⁰ (38%) and a slightly lower percentage than Sharma et al.²¹ (52%). We had more responders in the CAU group (18.2%) than Neal et al. (6%) and Sharma et al. (11.5%). Our cost–utility results are in line with a recently published model-based economic evaluation that compared the KD to vagus nerve stimulation (VNS) and CAU.³⁹ The model showed that neither KD nor VNS is a cost-effective option compared to CAU (€346,899 and €641,068 per QALY, respectively). Furthermore, Mackay et al.⁴⁰ estimated the costs of 3 and 12 months of KD to be AUS\$3,879 and AUS\$7,275, respectively.

Despite a number of limitations, this study presents evidence of an economic evaluation executed alongside an RCT. We have shown that the KD is effective in terms of the number of responders. The study failed, however, to show improvements in QoL and, therefore, unfavorable cost–utility ratios resulted.

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DISCLOSURE

None of the 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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