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Review

Cognitive benefits of the ketogenic diet in patients with epilepsy: A systematic overview

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ABSTRACT

The ketogenic diet (KD) has been found to be effective in reducing seizures in patients with treatment-refractory epilepsy. Less attention has been paid to additional cognitive benefits of KD. The aim of the present paper was to provide a comprehensive overview of the studies reporting effects on cognition after KD treatment in adults and children with epilepsy. To address this aim, the clinical literature on cognitive effects of KD in patients with epilepsy was reviewed using a systematic approach. We conclude that using subjective assessments of the patient's experience, cognitive improvements are frequently reported during KD treatment in the domains of alertness, attention, and global cognition. Studies that used objective neuropsychological tests confirmed benefits on alertness but found no improvement in global cognition. There are indications that these improvements are caused by both seizure reduction and direct effects of KD on cognition. The improvements appear to be unrelated to medication reduction, age when KD is started, type of KD, and sleep improvement. The findings in the present overview contribute to a better understanding of the beneficial effects of KD in patients with epilepsy.

1. Introduction

1.1. Epilepsy

Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures. Cognitive deficits are often reported in patients with epilepsy [1–4]. The impairments in cognition are thought to be due to a complex interplay between seizures, brain damage, and treatment [5, 6]. The severity of cognitive problems depends on age at epilepsy onset, seizure type, medication use, and etiology. Patients with chronic, frequent seizures and high medication use are particularly affected by cognitive problems [5, 7].

In the majority of patients with epilepsy, seizures can be controlled by antiepileptic drugs (AEDs). Unfortunately, in 30% of the patients, these drugs are not efficacious, a condition called drug-resistant, intractable, or refractory epilepsy [8]. In addition, some patients experience severe undesirable side effects of the AEDs, leading to discontinuation of AED use [9–11]. In these cases, nonpharmacological treatments may be considered, such as the ketogenic diet (KD).

1.2. KD

Ketogenic diet is a high-fat, low-carbohydrate diet that induces ketosis. Ketosis is a metabolic state where the body uses ketone bodies, made from the breakdown of fatty acids in the liver, rather than carbohydrates as primary source of energy. The classical KD (cKD) has a fat to carbohydrate plus protein ratio of 3–4:1. Less restricted forms are available as well, such as the modified Atkins diet (MAD). In this diet, patients are encouraged to eat fat; however, there is no protein restriction [12]. Additionally, cKD and MAD can be supplemented with either long- or medium-chain triglycerides (LCT or MCT) to maintain the appropriate ratio and improve effectiveness [13–15]. The diets appear to be highly effective as 36–85% of the patients with epilepsy experience more than 50% seizure reduction when on KD [14, 16–19]. Multiple epileptic syndromes, such as glucose transporter 1 (GLUT1) deficiency, are especially responsive to KD [20].

1.3. Cognitive effects of KD in epilepsy

Most studies on KD focus on the impact of the diet on seizure control. Less attention has been paid to additional benefits of KD treatment, such as the effect on cognition. Cognitive improvement has

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Table 1
Overview of clinical studies reporting cognitive effects with KD treatment in patients with epilepsy.
cKD = classic ketogenic diet; MAD = modified Atkins diet; MCT = medium chain triglycerides; GLUT1 = GLUT1 deficiency syndrome; CSWS = continuous spike during slow wave sleep; MSNPE = myoclonic status in nonprogressive encephalopathy; TSC = tuberous sclerosis complex; PDC = pyruvate dehydrogenase complex deficiency.

Study	Cognitive domain								Diet	Number of patients	Age of patients	Epilepsy subtype	Diet duration	Seizure efficacy[a]	Cognitive assessment	Cognitive outcome
	Attention	Alertness	Adaptability	Concentration	Learning & memory	Language	Global cognition	Cognitive development								
	Parent reports															
Park et al., 2017 [23]							X		cKD or MAD	12	2.9-76.5	TSC	3-44 months	83.3%	Subjective: patient experience	75% improved, 8.3% worsened
Alqhatani and Mahmoud, 2016 [24]		X							cKD	30	0.5- 15 years	Mixed	Undefined	76%	Subjective: patient experience	60% improved
Maydell et al., 2001 [25]		X							cKD	143	0.5-29 years	Mixed	1 week – 58 months	30%	Subjective: patient experience	48% improved
Farasat et al., 2006 [21]							X		cKD	100	0.5-15 years	Mixed	6 months	70%	Subjective: patient experience	62% improved
Pulsifer et al., 2001 [26]	X								cKD	34	1.5-14 years	Mixed	12 months	79%	Subjective: Child behaviour checklist	Significant improvement in total group
								X							Subjective: Developmental profile 2nd edition	Significant improvement in total group
	Retrospective studies															
Thompson et al., 2017 [27]		X							cKD	4	6-10 weeks	Mixed	10 months – 2.5 year	75%	Subjective: parental experience	100%
Caraballo et al., 2017 [28]							X		cKD	6	2.5-9 years	MSNPE	1-3.5 years	80%	Objective: undefined tests	100%
Alter et al., 2015 [29]							X		cKD	12	0.1-31 years	GLUT1	8.9-23 years	100%	Objective: PPVT-III, Raven Coloured Matrices, Beery test	No significant improvements
Fujii et al., 2016 [30]								X	MAD/ cKD	12	3-35 years	GLUT1	1-96 months	79%	Objective: Kyoto Scale of Psychological Development	No significant improvements
							X								Objective: WISC-III and TBS	No significant improvements
Laux and Blackford, 2016 [31]		X							cKD	20	1-10 years	Dravet	6 months – 5.6 years	65%	Subjective: patient experience	75% improved
Eun et al., 2006 [32]								X	cKD	34	1-14 months	Infantile spasms	1-36 months	63%	Objective: Bayley developmental test	44% improved
Nordli et al., 2001 [33]		X							cKD	34	Mean 14 months	Mixed	Undefined	55%	Subjective: patient experience	Majority of patients improved
Vaisleib et al., 2004 [34]		X							cKD	54	0-18 years	Mixed	1-58 months	65%	Subjective: patient experience	37% improved
Kinsman et al., 1992 [35]		X							cKD	58	1-20 years	Mixed	1-48 months	67%	Subjective: patient experience	28% improved
Kossoff et al., 2004 [36]		X							cKD	81	0.5-15 years	Mixed	6 months	47% >90% improvement	Subjective: patient experience	58% improved
Leen et al., 2010 [37]		X							cKD	37	5-21 years	GLUT1	Undefined	86%	Subjective: patient experience	51% improved
Nabbout et al., 2011 [38]	X								cKD	15	4-11 years	Dravet	3-12 months	66%	Subjective: Conners and Achenbach scale	86% improved
	Prospective studies															
Carrette et al., 2008 [39]				X					MAD	3	3-4 years	Mixed	6 months	33%	Subjective: patient experience	100% improved
Gumus et al., 2015 [40]		X							cKD	4	2-11 years	GLUT1	Undefined	100%	Subjective: patient experience	100% improved
				X											Subjective: patient experience	100% improved
							X								Objective: WISC-IV and SBISC-IV	No significant improvements
Nikanorova et al., 2009 [41]	X								cKD	5	8-13 years	CSWS	9-36 months	40%	Subjective: patient experience	40% improved
							X								Objective: WISC-III	No significant improvements
Ramm-Pettersen		X							cKD/MAD	6	2-64	GLUT1	6-17	100%	Subjective: patient	100% improved

et al., 2014 [42]											years		months		experience	
					X										Objective: CALVT-III	66% improved
						X									Objective: Bayley-III and WPPSI-III	86% improved
Ito et al., 2011 [43]		X							MAD	6	7-16 years	GLUT1	1-42 months	80%	Subjective: patient experience	100% improved
							X								Objective: WISC-III and TBS	Slight increase in IQ
Sirven et al., 1999 [44]				X					cKD	7	19-45 years	Mixed	8 months	86%	Subjective: patient experience	28% impaired
							X								Subjective: patient experience	63% improved
Lambrechts et al., 2013 [45]		X							cKD	11	6-18 years	Mixed	6 months	33%	Objective: Reaction time tests	Improvement in all patients, but not significant in total group
							X								Objective: PPVT-III-NL	No significant improvements
Weber et al., 2009 [46]							X		MAD	11	2-17 years	Mixed	3 months	40%	Subjective: Visual analogue scale	54% improved
Klein et al., 2010 [47]		X							cKD 3:1	12	24-65 years	Mixed	4-26 months	75%	Subjective: patient experience	No significant improvements
Sofou et al., 2017 [48]							X		cKD	15	1 week – 15 years	PDC	6 – 100 months	75%	Subjective: parental experience	93% improved
								X		12					Objective: WPPSI-III and WISC-IV (no statistics)	91% improved
Lambrechts et al., 2012 [49]		X							cKD/MCT	15	18-41 years	Mixed	4 months	20%	Subjective assessment	60% improved
							X								Objective: Raven's progressive matrices	No significant improvements
Hallböök et al., 2007 [50]	X								cKD	18	2-15 years	Mixed	3 months	66%	Subjective: Child behaviour checklist	Attentional behaviour was improved
Schoeler et al., 2014 [51]		X							cKD/MAD	23	16-65 years	Mixed	3 months	39%	Subjective: freely mentioned patient experience	65% improved
				X											Subjective: freely mentioned patient experience	30% improved
Sharma et al., 2016 [52]		X							MAD	40	Mean 6 years	Mixed	3 months	56%	Subjective: patient experience	67% improved
Zhu et al., 2016 [53]								X	cKD	42	0.5-6 years	Mixed	18 months	33.3%	Objective: Gesell developmental scale	33% improved
						X									Objective: Gesell developmental scale	No significant improvements
			X												Objective: Gesell developmental scale	Significant improvements
	Randomized controlled trial															
IJff et al., 2016 [54]		X							cKD/ MCT	28	1-18 years	Mixed	4 months	50%	Objective: Reaction time tests	Significant improvement in reaction time
							X								Objective: PPVT-III-NL	No significant improvements

[a] = Seizure efficacy is defined as the percentage of patients that reported a >50% reduction in seizure frequency with KD treatment

been reported by parents of patients with epilepsy to be one of the major motivators to start and continue KD [21, 22]. For instance, Farasat and colleagues showed that 90% of the parents reported that cognitive improvement is a critical goal of the treatment [21]. Moreover, achieving the expectations of cognitive improvement significantly correlated with a longer KD use duration, whereas goals for seizure control and anticonvulsant use reduction did not. These findings highlight the importance of understanding the effects of KD on cognition in patients with epilepsy. The first randomized controlled trial (RCT) study that examined the behavioral and cognitive impact of KD in patients with epilepsy was recently published [54]. However, a systematic overview of all clinical studies on the effects of KD on cognition in patients with epilepsy is not available.

1.4. Aim of the review

The aim of the current paper was to provide a comprehensive overview of what has been described on the cognitive benefits of KD in patients with epilepsy. The clinical data on cognitive effects of KD in patients with all types of epilepsy were reviewed using a systematic approach. Subsequently, variables that could have had an impact on the interpretation of the data were discussed. The findings in this paper contribute to a better understanding of the potential advantages of KD as treatment for epilepsy to inform researchers, clinicians, and patients with epilepsy and their parents and caregivers. The review of the effects of KD on behavior in patients with epilepsy is beyond the scope of this review.

2. Methods

2.1. Search string

Articles were searched in the databases Medline, M-base, and Cab-abstracts. The search term included the following categories:

+ Keto parameters: ketogenic, ketone, ketones, ketosis, ketogenesis, high fat–low carbohydrates, modified Atkins diet, medium chain, MCT, MCTS, or low glycemic.
+ Diet parameters: diet, dietary, diets, nutrition, food, or supplement.
+ Cognition parameters: cognition, IQ, memory, behavior, mental, attention, problem-solving, comprehension, language, intelligence, alertness, school performance (and synonyms), sleep, sleeping, REM, insomnia, chronobiology, or circadian rhythm.
+ Epilepsy parameters: seizure, epilepsy, antiepileptic, antiseizure, convulsion, anticonvulsant.
+ Inclusion of human studies: human, patient, man, woman, subject, baby, child, kid, pediatric, infant, people, clinical trial, or plural forms.
+ Exclusion of animal studies: rat, bovine, murine, mouse, ape, monkey, rabbit, cow, sheep, fish, cattle, poultry, chick, chicken, goat, avian, bird, dog, canine, canid, or plural forms.

The articles were not bound to a time range. Conference papers and abstracts were excluded from the results.

2.2. Search strategy

The first phase of selection was based on title relevance. Inclusion criteria were 1) epilepsy (all age groups and subtypes) and 2) English language. The exclusion criterion was any form of treatment other than dietary intervention without including KD. Next, articles were assessed based on their abstracts. Inclusion criteria were 1) KD or any form of dietary intervention, 2) epilepsy (all age groups and subtypes), and 3) primary source of clinical patient data. In cases where the abstract was ambiguous, the article was checked for the inclusion criteria. Subsequently, full papers were reviewed. Articles were excluded if they did not meet the following criteria: 1) KD or any form of dietary intervention, 2) epilepsy (all age groups and subtypes), 3) primary source of clinical patient data, and 4) cognition as outcome measure. Case reports were excluded because of bias in patient selection.

Next, the articles were categorized by cognitive domains and whether the measurements were subjective or objective. Subjective measurements assess the experience of the patient whereas objective measurements use standardized, neuropsychological tests. Seizure responder rate was defined as the percentage of patients reporting more than 50% seizure reduction with KD treatment.

3. Results

The literature search was last updated on September 15th, 2017 resulting in 746 studies. After applying the selection criteria for title relevance, 130 articles were left. Subsequently, the abstracts of the articles were checked for relevance, which resulted in 58 articles. After reviewing the full articles, another 25 articles were removed as they did not appear to meet the inclusion criteria. In the end, 33 studies were left: five parent reports, 12 retrospective studies, 15 prospective studies, and one RCT. Overall, the effects of KD were reported in eight cognitive domains.

The details of the studies are summarized in Table 1. Below, we provide an overview of the results. First, we will focus on the results based on subjective outcomes, followed by a discussion of the results based on objective outcomes.

3.1. Subjective outcomes

Twenty-nine studies reported on subjective cognitive outcomes of the KD in patients with epilepsy in four cognitive domains. These subjective outcomes have been derived from parents' opinions, patients' experiences, or clinicians' impressions. Fig. 1 shows the outcomes in percentages of patients that were cognitively improved in each study, scaled to the number of patients included in the study. It should be noted that three studies are not included in this figure because they did not specify the percentage of patients that were improved but rather provided other types of measurements [26, 33, 50].

Two studies investigated attention in a total of 17 patients. It was found that 74.5% of their patients were cognitively improved [38, 41]. In addition, one study reported an improvement in the majority of their 34 patients without giving specific numbers and is thus, not included in Fig. 1 [33]. Alertness was studied in the majority of the papers reviewed, namely, fifteen studies. Taking these studies together, 533 patients were evaluated, 51.5% of whom experienced improvements in alertness [24, 25, 27, 31, 34–37, 40, 42, 43, 45, 47, 51, 52]. Four studies examined concentration in 37 patients. Improvements were found in 86.4% of these patients [39, 40, 44, 51]. Finally, 145 patients in five studies were tested for subjective improvements in global cognition, and 65.7% of these patients experienced improvements [21, 23, 44, 46, 48]. In addition to this finding, three studies reported a significant improvement in global cognition in their patient groups of 34, 18, and 34 patients, respectively [26, 33, 50].

3.2. Objective outcomes

Thirteen studies examined cognitive effects of KD in patients with epilepsy using standardized neuropsychological tests and statistical analyses. Table 2 summarizes the outcomes of these studies. Two studies looked at improvements in alertness in patients with epilepsy who were on the KD. One study with 28 patients saw significant improvement while the second study which examined 11 patients, did not [45, 54]. The latter study did mention that they saw improvement in all patients but that the effect size was too small to reach significance. Language and adaptability (a measure of intelligence) were assessed in 42 patients by Zhu and colleagues. Adaptability, but not language, significantly improved after three, six, twelve, and eighteen months of KD

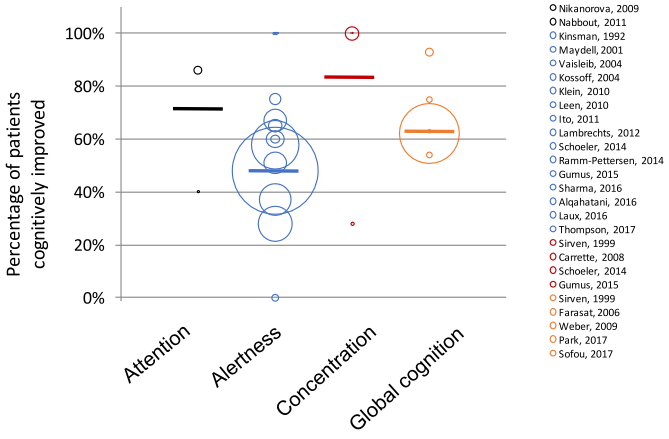

Fig. 1. Overview of the observed subjective cognitive changes after KD treatment, categorized by cognitive domain. Shown are the articles that subjectively assessed cognitive improvements in their patient cohorts. The studies are categorized according to the cognitive domain on which they reported. The figure shows the percentage of patients that experienced improvements in cognition from each individual study. Patient group size is represented by the width of the data points. The articles of Nordli et al. [33], Hallböök et al. [50] and Pulsifer et al. [26] were not included in the figure as they did not report the percentage of patients improved. Nordli and colleagues [33] found an improvement in the majority of the patient group in alertness, and Hallböök et al. and Pulsifer et al. reported that cognition was significantly improved in total group.

Table 2
Objective outcomes of studies investigating cognitive effect of KD in patients with epilepsy.

Cognitive domain	Study	Number of patients	Statistically significant improvement in total group?
Alertness	Lambrechts et al., 2013 [45]	11	No
Alertness	IJff et al., 2016 [54]	28	Yes
Adaptability	Zhu et al., 2016 [53]	42	Yes
Language	Zhu et al., 2016 [53]	42	No
Global cognition	Nikanorova et al., 2009 [41]	5	No
Global cognition	Lambrechts et al., 2012 [49]	15	No
Global cognition	Lambrechts et al., 2013 [45]	11	No
Global cognition	Alter et al., 2015 [29]	12	No
Global cognition	Gumus et al., 2015 [40]	4	No
Global cognition	Fujii et al., 2016 [30]	12	No
Global cognition	IJff et al., 2016 [54]	28	No

[53]. Global cognition was examined in seven studies. None of the studies, with a total of 87 patients, reported statistically significant improvements in their patients [29, 30, 40, 41, 45, 49, 54].

A number of studies used neuropsychological tests but did not perform statistical analysis to assess the cognitive effects of KD [28, 32, 42, 43, 53]. It is difficult to interpret these results as it is unknown which criteria the authors used to conclude when a change in outcome was a true cognitive improvement. Caraballo and colleagues used objective tests to investigate improvements in global cognition and reported improvements in all four of their patients [28]. Six patients were studied by Ito and colleagues [43]. A slight increase in intelligence quotient (IQ), determined by objective tests, was reported in all patients. Two studies reported that 44% (34 patients) and 33% (42 patients) showed improvements in cognitive development [32, 53]. Ramm-Pettersen and colleagues used objective tests to evaluate improvements in learning, memory, and language in six patients. They reported learning and memory improvements in 66% of the patients and language in 86% of the same patients [42].

3.3. Are there specific diet or patient characteristics that might drive the cognitive changes seen with KD?

The 33 clinical papers reviewed differed considerably in design. The majority of papers describe changes in cognition in a mixed patient population or a mix of diets with different treatment durations. However, there are some studies that describe the effects in a specific patient subpopulation or one specific diet and report specific intervention duration or protocols for AED use. Using these more homogeneous papers, we investigated whether there are specific diet protocols or patient characteristics that might drive the cognitive changes seen with KD.

3.3.1. Both cKD and MAD result in cognitive improvements

The patients in our search were either treated with cKD or a less restricted diet, such as MAD. While the efficacy in reducing seizures is higher with cKD compared with MAD, compliance is higher in MAD [14, 18, 19, 55]. It is therefore of interest to determine whether the observed changes in cognition are comparable between the two types of diet. To look at this, we focused on alertness. When taking the studies on the cognitive domain of attention and alertness together, there are two studies using MAD. When excluding the studies reporting results from mixed KD/MAD or KD with MCT populations, there are 16 studies using KD (Fig. 2). Comparing these two categories of articles indicates that the diets generate comparable improvements in cognition. This conclusion has to be taken with some caution as there is only a limited number of studies available for the MAD. Given the increased usage of this diet, additional research is needed to further explore the cognitive benefits seen with MAD.

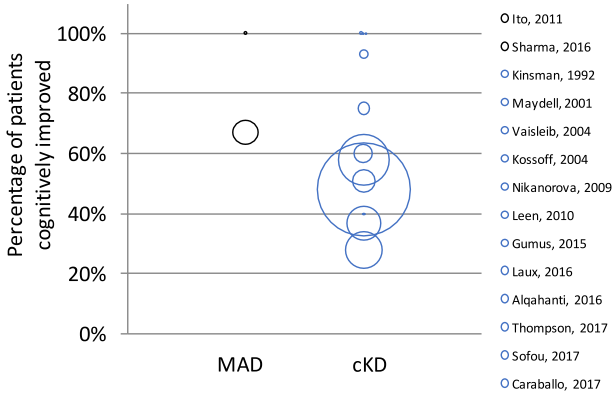

Fig. 2. MAD, a less restrictive form of KD, generates comparable improvements in cognition as with the more stringent cKD. Articles were categorized according to the type of diet they treated their patients with; MAD or cKD. Shown are the percentages of patients with improved cognition in the individual articles, the width of the circle indicates the total number of patients included in the studies. Please note that the studies that used nonnumerical outcomes were not included in this figure.

3.3.2. Prolonged KD might result in more cognitive benefits

The efficacy of the KD in terms of seizure reduction is, in most cases, already apparent within two to three months on the diet [56] while in many instances, patients are weaned off the diet after 2 years. A wide variation in KD durations was found in our systematic overview. When taking the studies on the cognitive domain of attention and alertness together and comparing those that have short durations of intervention, e.g., up to three months of treatment [36, 46, 57], with those that had longer interventions [26, 36, 45, 49, 54], comparable results were found.[1] Interestingly, one article assessed cognitive improvements at multiple time points during KD [53]. They found that the longer the patients was on KD the more improvement they had in adaptability (a measure of intelligence).

It would be highly informative to determine whether the observed cognitive changes continue after the KD discontinuation. Unfortunately, patients in the included studies were usually not followed up after KD discontinuation and, as a consequence, long-term effects of KD on cognition were not evaluated. In our search, one single study was found that examined long-term side effects after KD treatment was discontinued [58]. Although this study did not specifically focus on cognition, the authors reported that the majority of patients were in good health, without apparent adverse outcomes. Further clinical research is warranted to specifically examine whether cognitive benefits of KD remain after diet discontinuation.

3.3.3. Impact of duration of epilepsy and age at seizure onset requires more investigations

It has been reported that the duration of epilepsy and age at seizure onset positively correlate with the severity of cognitive impairments [7] although contradictory evidence can be found as well [59]. Unfortunately, none of the included studies discussed whether the duration of epilepsy and age at seizure onset might have had an influence in their data nor do the reviewed studies provide enough details on these parameters to make a comparison.

3.3.4. Cognitive benefits of KD are found in infants, children, and adults

In our analysis, studies on patients of all ages were included. Given the difficulties of adult patients in adhering to this diet, the KD is less often prescribed to this group of patients. However, efficacy rates are similar to those observed in children [60]. It is therefore of interest to investigate whether cognitive benefits are comparable as well. Interestingly, two studies reported that the youngest patients improved the

[1] Studies were only considered when they described a single treatment duration for all patients.

most in global cognitive functioning compared with older subjects [43, 61]. In our search, we also uncovered several studies that examined a specific age range. For instance, three studies investigated KD in infants (zero–two years old) [27, 32, 33], and 13 studies included children between one and 18 years of age [21, 24, 28, 34–38, 41, 43, 46, 53, 54]. Additionally, our search retrieved four studies investigating cognitive improvements in adult patients with epilepsy [44, 47, 49, 51]. When comparing the studies reporting on the percentage of patients that cognitively improved (regardless of cognitive domain) for a specific age range, it appears that children and adults have comparable cognitive benefits. For infants, this effect seems to be less (Fig. 3) although evidence is limited to two studies.

3.3.5. Cognitive effects of KD in specific syndromes

In our systematic literature search, the papers found cover a range of epilepsy syndromes. In addition to refractory epilepsy, seven specific epileptic syndromes were described, namely GLUT1 deficiency syndrome, Dravet syndrome, infantile spasms, continuous slow waves during sleep (CSWS), tuberous sclerosis complex (TSC), pyruvate dehydrogenase (PDC), and myoclonic status in nonprogressive encephalopathy (MSNPE). It is of interest to understand whether KD affects cognition in specific populations differently as the underlying brain pathology is distinct between epileptic subtypes. Of special interest is GLUT1 deficiency syndrome as the symptoms are directly related to the impaired glucose handling in the brain. When comparing the cognitive outcomes of patients with GLUT1 deficiency syndrome on KD versus the population with mixed epilepsies on KD, it seems that KD is more favorable for patients with GLUT1 deficiency syndrome in terms of cognitive improvements (Fig. 4). However, the data on patients with GLUT1 deficiency syndrome are skewed by many small (i.e., five patients or less) studies. The cognitive outcomes of the single study with a larger sample size, namely, the study of Leen et al. [37] with 37 patients with GLUT1 deficiency syndrome, show similar cognitive results compared with the patient groups with mixed pathologies. The cognitive results from patients with infantile spasms and CSWS are comparable with the results in the patient group with mixed epilepsy; however, results in both subtypes are limited to a single study. The studies investigating Dravet syndrome, TSC, PDC, and MSNPE showed more cognitive improvements compared with the patient group with mixed epilepsy; however, these results are also skewed by small studies [23, 28, 31, 38, 48]. Clearly, given the small number of dedicated studies, additional investigations are needed to confirm these findings. Moreover, we would suggest that studies examining patient groups with mixed epileptic syndromes should make data available on the specific syndromes studied.

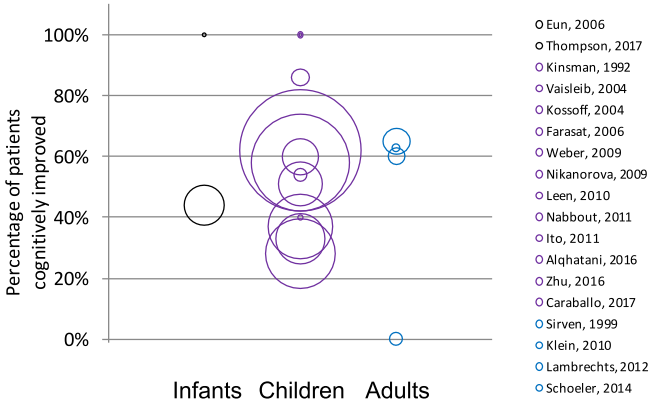

Fig. 3. KD treatment has a slight, increased, advantageous impact on cognition in adults compared with infants and children. Shown are the percentages of patients that are cognitively improved for the articles that investigated cognitive benefits of the KD in a specific age group. The age ranges are specified as follows: infant, zero–two years old; child, two–18 years old; and adult, 18 + years. The width of the circle indicates the number of patients included in the article. Please note that the studies that used nonnumerical outcomes were not included in this figure.

It should be noted that even within epileptic syndromes, patient characteristics are extremely heterogeneous. This complicates pinpointing the effects of KD on cognition in patients with epilepsy. In addition to epilepsy, many of the patients are diagnosed with a variety of cognitive and neurodevelopmental comorbidities, such as autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) [2, 62]. A recent study reported that 43% of the patients with epilepsy have a psychiatric or neurodevelopmental comorbidity, compared with 6% of the population without epilepsy [63]. These comorbidities are often not adequately recognized. For instance, Reilly and colleagues showed that only one-third of the patients having a comorbidity had been diagnosed before the study [64]. In our search, none of the articles specified whether neuropsychiatric comorbidities affected the impact of KD on cognitive improvements in their patient group. Recently, human and animal studies on KD in patients with ASD showed positive effects in terms of symptom reduction [65, 66]. It would be worthwhile to further explore whether KD could be particularly suited for those children who have epilepsy with neuropsychiatric comorbidities such as autism.

3.3.6. Effects of KD on cognition are independent of AED use

Except for treatment of GLUT1 deficiency, KD is not considered a first-line treatment for epilepsy. Thus, when patients start a KD, they generally have used or are using one or multiple AEDs. Cognitive side effects of AEDs have been described especially for older AED generations, including slowing of central information processing and disturbances in working memory [1, 67, 68]. These cognitive problems often decrease when AED treatment is reduced or stopped [69]. Many patients that respond to KD generally wish to quit AEDs [36]. In these cases, medication reduction might cause the observed improvements in cognition. Interestingly, multiple studies in our search reported cognitive improvements while medication was continued during KD treatment [38, 39, 41, 43–46, 50, 52–54]. On average, these studies show that the outcome in cognitive improvements is comparable with two studies that reduced medication in all patients [28, 36] (Fig. 5). Furthermore, Pulsifer and colleagues found no correlation between medication reduction and improvements in cognitive development in 34 patients [26]. Taking these results together, it appears that the cognitive benefits of KD treatment are independent of AED reduction and that patients will benefit from the cognitive improvements seen with KD even when they stay on AED.

3.4. Are changes in cognition related to the response to KD?

Next to investigating whether diet or patient characteristics affect cognitive outcomes, there might be particular features of the response to KD that contribute to the changes seen in cognition. In our review of the literature, we came across clinical studies addressing this question.

3.4.1. Improvements in cognition seem to be independent of improvements in sleep

A factor that might contribute to the changes in cognition is improved sleep with KD. As mentioned earlier, the most prominent improvements after KD treatment were found in the cognitive domain of alertness. Patients with epilepsy often suffer from sleep disorders and poor sleep, which worsens alertness and concentration [70]. To this end, Hallböök and colleagues performed a prospective study where they evaluated sleep during KD treatment in 18 children. After three months, KD induced a significant increase in sleep quality (i.e., increased rapid eye movement (REM) sleep). Although attention was improved as well, the improvement in attention was not directly related to sleep quality in individual patients [71]. However, three additional studies in our search examined sleep after KD treatment and found limited

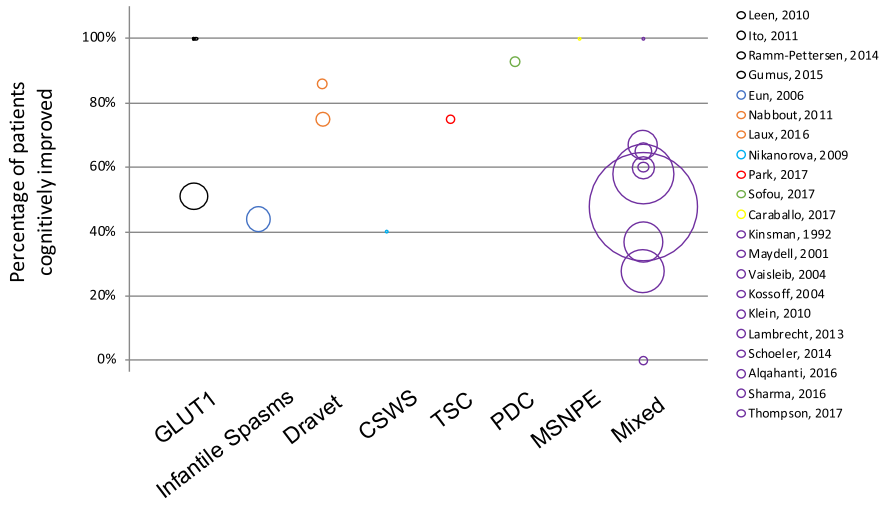

Fig. 4. Overall cognitive improvement after KD does not seem to differ between GLUT1 deficiency syndrome, infantile spasms, CSWS, and patient groups with mixed epilepsy, but increased improvement is observed in patients with Dravet syndrome. The outcomes in percentage of patients that were cognitively improved after KD treatment were compared between studies that included patients with GLUT1 deficiency syndrome, infantile spasms, Dravet syndrome, continuous slow waves during sleep (CSWS), tuberous sclerosis complex (TSC), pyruvate dehydrogenase (PDC), and myoclonic status in nonprogressive encephalopathy (MSNPE) versus studies that included a mixed population of epileptic syndromes. The width of the circles indicates the number of patients included in that particular study. Please note that the studies that used non-numerical outcomes were not included in this figure.

improvement in sleep, especially when comparing with the improvement in cognition [24, 25, 33]. Together, these findings indicate that improved sleep does not seem to underlie the observed cognitive improvements after KD treatment.

3.4.2. Both seizure reduction and direct effects of KD contribute to the effects on cognition

One of the drivers of cognitive deficits in patients with epilepsy are the epileptic seizures. It is therefore of interest to unravel whether the observed cognitive improvements are directly related to seizure reduction or whether the observed changes are independent of seizure control. In our search, two articles mentioned a positive relation between seizure control and improvement in cognition in their patients [32, 53]. In addition, Wu and colleagues looked at the relation between cognitive improvements during KD and seizure reduction efficacy in 87 patients and found a significant positive correlation [72]. On the contrary, two studies, including the RCT, found no statistical correlation between cognitive improvements and seizure reduction efficacy after KD treatment [26, 54]. The underlying differences that may explain these contradictory results are not apparent.

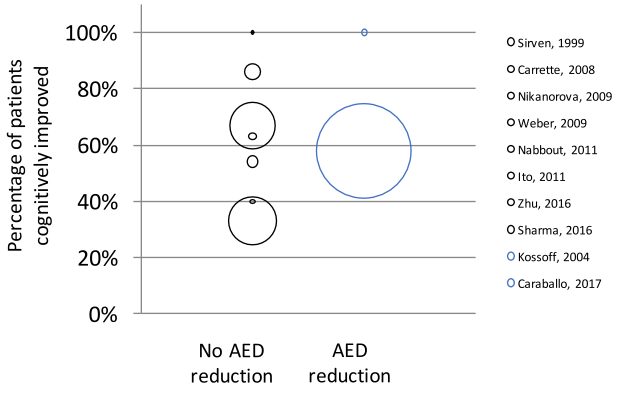

Fig. 5. Use of AED does not affect improvements in cognition of patients on KD. Shown are studies that either reduced medication in none of their patients (left) or in all of their patients (right). The studies are plotted to the outcomes in terms of percentage of patients that cognitively improved. The width of the circles indicates number of patients included in the studies. Please note that the studies that used nonnumerical outcomes were not taken into account.

Multiple articles mentioned cognitive improvements in patients that did not respond to KD in terms of seizure reduction, the so-called non-responders [27, 28, 35, 38, 39, 44, 45, 51]. These studies suggest that KD can improve cognition even in patients who experience no reduction in seizures, thereby implying that the cognitive benefits are beyond seizure control.

Taking these findings together, it is most likely that the effects of KD on cognition are mediated by a combination of both direct effects of the diet and seizure reduction.

4. Discussion

The present paper aimed to provide a systematic overview of clinical studies on the effects of KD treatment on cognition in epilepsy. The main conclusion from these studies is that the subjective cognitive improvements are frequently observed in patients with epilepsy after KD treatment, primarily in the domains of alertness, attention, concentration, and global cognition. Objective tests confirmed the improvements in alertness but not in global cognition. Subjective assessments and the low power of statistical testing may have introduced a bias in some of the reported results. Furthermore, we found that the duration of KD treatment appears to have a positive effect on the degree of cognitive improvement although direct evidence for this comes from only one study. The cognitive benefits may be achieved by a combination of direct effects of KD on cognition and through seizure reduction. Importantly, we found no indication that the improvement in cognition after KD treatment in patients with epilepsy is influenced by AED reduction or improved sleep. The KD seems to be especially beneficial for patients with the Dravet syndrome, TSC, PDC, or MSNPE in terms of cognitive improvement. Unfortunately, based on the current set of articles, we could not draw firm conclusions on cognitive improvements after KD treatment, neither on the impact of the age when KD is initiated nor age at seizure onset or duration of epilepsy.

The review of the clinical literature could have been influenced by confounding variables and highlighted some limitations in the literature. First of all, except for the RCT study, no control treatment groups were included. Furthermore, most studies did not follow up on participants who left the study prematurely. As patient compliance to KD is generally low [73], this may lead to a bias in the outcome. A further

limitation to the interpretation of the reviewed papers is that the majority of the studies were characterized by a large variation in patient characteristics and KD duration. In our study, we made the distinction between subjective and objective studies. The described subjective assessments were often dichotomous, poorly defined and not standardized. On the contrary, the objective assessments were well-defined, standardized tests, though most of them included a limited number of patients. In addition, the majority of the objective assessments were statistically tested, but most of them included a limited number of patients. As a consequence, the tests had low statistical power, which may lead to a high rate of false negative data. This could result in an underestimation of positive effects of KD on cognition. Nevertheless, these tests use continuous variables and are therefore more sensitive in describing interpatient variation. While subjective measures are of importance to understand the patients, objective measures may help more with understanding the effects of the KD on cognition. Together, these limitations complicate the interpretation and generalization of the results. A first attempt to deal with such issues is made by IJff and colleagues [54] using a randomized controlled clinical study design. Their study indicates that the KD improves cognition in patients on the KD and warrants confirmation with similarly rigorously designed studies.

The studies in our systematic overview covered effects of KD in eight cognitive domains.[2] Different effect sizes were observed among these domains. Most improvements in cognition were found in the attention and alertness domains. Various explanations may underlie this dominant effect. First, the majority of studies focused on attention/alertness rather than other domains. It remains undetermined whether the studies that exclusively investigated attention/alertness might also have found improvements in other cognitive domains. Second, attention/alertness was more often tested subjectively compared with the other domains. Subjective assessments generally yield more positive results than objective measurements. Nonetheless, these two reasons are unlikely to be exclusively responsible for the dominant effect in attention/alertness. The RCT of IJff et al. objectively examined multiple domains and found only improvements in alertness [54]. Third, attention deficits are one of the most frequently reported deficits in patients with epilepsy [74]. It has been shown that the deficits in attention are disproportionately strong compared with IQ impairments [75]. One of the reasons for this is that attention/alertness are particularly vulnerable to seizure activity [74]. As a consequence, when epilepsy is successfully treated, attention deficits might recover more strongly than other cognitive domains. Lastly, KD treatment might specifically improve attention/alertness. Research suggests that ketone bodies improve visual attention [76]. Taken together, the dominant effect on attention/alertness is most probably explained by both methodological issues and underlying characteristics of epilepsy and KD. Additional research is needed to confirm the specific effect of KD on attention.

5. Conclusion

The present review increases our understanding of the beneficial effects of KD in addition to seizure control in patients with epilepsy. The positive impact of KD on cognition and the motivational effect on patients of these benefits should be communicated to patients with epilepsy and their caregivers. Importantly, additional research is needed to confirm our findings and to further understand the cognitive benefits of KD. Specifically, more RCTs, including a wide range of objective measurements and appropriate controls, would provide more definitive evidence. Furthermore, continued effort is needed to establish whether the observed cognitive effects are intrinsic to KD or an indirect consequence of other improvements in the patient (e.g., through the action of seizure reduction).

[2] Although school performance was included in our search string, we did not find any article that investigated this outcome.

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Disclosure of conflict of interest

Author Annemiek A. van Berkel has served as a paid consultant for Nutricia Research. Author J. Martin Verkuyl is an employee of Nutricia Research.

Ethical statement

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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