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REVIEW ARTICLE

# Ketogenic diet for the treatment of pediatric epilepsy: review and meta-analysis

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## Abstract

The ketogenic diet (KD), containing high levels of fat and low levels of carbohydrates, has been used to treat refractory epilepsy since the 1920s. In the past few decades, there has been more interest in less restrictive KDs such as the modified Atkins diet (MAD).

## Purpose

Our aim was to review all evidence regarding the efficacy and tolerability of the KD and MAD from randomized controlled trials (RCTs) in children and adolescents with refractory epilepsy.

## Methods

We reviewed the current literature using Cochrane, EMBASE, and MEDLINE (using PubMed). We implemented predefined criteria regarding dataextraction and study quality.

## Results

We identified five RCTs that generated seven publications and recruited 472 children and adolescents with refractory epilepsy (≤ 18 years). The primary outcome (seizure frequency reduction (SFR) ≥ 50%) was attained in 35–56.1% of the participants in the intervention group, compared with 6–18.2% in the control group. Our meta-analysis underlined the significant efficacy of the KD compared with the control group: RR = 5.1 (95% CI 3.18–8.21, $p < 0.001$). Additionally, only two studies mentioned possible biomarkers to objectively evaluate the efficacy. Secondary outcomes, such as seizure severity and quality of life, were studied in three trials, leading to indecisive generalization of these findings. Gastro-intestinal adverse effects were the most prevalent, and no severe adverse effects were reported.

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**Conclusion**
Despite the heterogeneity between all studies, the beneficial results underline that dietary interventions should be considered for children and adolescents with refractory epilepsy who are not eligible for epilepsy surgery. Future studies should be multi-center and long-term, and evaluate potential biomarkers and adverse effects.

**Keywords** Epilepsy · Drug-resistant · Ketogenic diet · Modified Atkins diet · Meta-analysis

## Introduction

Epilepsy is a neurological disorder characterized by seizures, which affects 65–70 million people worldwide [1]. Achieving complete seizure control, preserving quality of life (QoL), and avoidance of adverse events are three major goals of epilepsy treatment [2]. Nonetheless, more than 30% of the patients with epilepsy do not reach seizure control with the currently available anti-epileptic drugs (AEDs) [3]. In addition, AEDs cause significant adverse effects affecting the QoL [4]. Therefore, one should first consider surgical therapies if a patient is eligible [5, 6].

If epilepsy surgery is not an option, other therapy modalities are possible, such as non-pharmacological treatments (e.g., nervus vagus stimulation [7]) and dietary treatments like the ketogenic diet (KD) [8]. The KD, a strict diet high in fat and low in carbohydrates, increases the ketone body concentrations that could lead to an enhancement of inhibitory neurotransmission and thereby possibly reducing the seizure frequency [9].

The exact mechanism of the KD is under investigation, and ketone bodies could exert anti-oxidative, anti-inflammatory, cellular, epigenetic, and gut-microbiome alterations [10–12].

Initial studies report the classical KD that consists out of long-chain triglycerides (LCTs) in a fat:carbohydrate and protein ratio ranging from 2:1 to 5:1 [13]. A KD using medium-chain triglycerides (MCTs), such as triglycerides of octanoic and decanoic acids, yields relatively more ketones per kilocalorie of energy and leads to a more efficient absorption. As a result, the MCT has a lower need of total fat and enables a higher intake of carbohydrate and protein (less restrictive diet) [14]. The modified Atkins diet (MAD) is another variation to the KD, which mimics the effect on ketosis but is less restrictive [15]. Another liberalized alternative of the KD is the low-glycemic index treatment (LGIT), with a ratio of 1:1 fat:carbohydrate and protein. The LGIT also specifies a limit of carbohydrates (10% a day) and has shown similar efficacy in reducing the seizure frequency as other dietary interventions [16, 17]. LGIT is the most liberalized type of KD, although patients are restricted to carbohydrates with a glycemic index below 50 [18].

In a clinical setting, seizure frequency reduction (SFR) is at least 50% (≥ 50%) in half of the patients on the KD or MAD, i.e., somewhat higher compared with vagal nerve stimulation (VNS) [19]. Even as the KD and the MAD are non-invasive compared with neurostimulation, its use is limited due to bad tolerability, feasibility by caregivers (complexity of diet), and a relatively low compliance. Nonetheless, dietary treatment options remain a valid option for patients with epilepsy, and the absence of neurotoxic effects, compared with the standard AED treatment, should be taken into account [8]. Due to the limited number of studies and small sample sizes, we wanted to review all high-quality studies to generate an overview of the efficacy of dietary interventions for the treatment of pediatric epilepsy.

We reviewed the evidence from randomized controlled trials (RCTs) concerning the efficacy (SFR) of the KD and the MAD in children and adolescents with epilepsy. The primary outcome measure to evaluate efficacy of treatment in refractory epilepsy is usually an SFR ≥ 50% [19] and will therefore be the main outcome measure of this review. Other secondary outcome measures, such as QoL, adverse effects, and effects on cognition and behavior, will be included. In addition, potential biomarkers will be discussed.

The efficacy of the KD (classical or MCT) and the MAD will be compared with the standard treatment and monitoring according to the good clinical practice [20], i.e., the control group (care as usual, CAU).

## Materials and methods

### Protocol

We built up this review according to the PRISMA guidelines, which imply the statement for reporting systematic reviews of studies evaluating health care interventions [21]. No ethics board was needed since we reviewed already published trials.

### Eligibility criteria

We included all RCTs of the KD and the MAD for children and/or adolescents with refractory epilepsy. There have been no randomized controlled trials (RCTs) regarding the LGIT, and therefore, LGIT was not within the scope of this review.

Studies were included if they described children and/or adolescents (age 1–18 years) with refractory epilepsy irrespective of etiology and seizure type. Refractory epilepsy refers to the fact that seizure freedom was not achieved by two trials of adequately dosed AEDs (in monotherapy or combination) [3].

Dietary interventions of interest were the KD and the MAD. The classical KD consists of LCTs, though more recent studies report the use of MCTs as a fat source due to its better absorption and higher yield of ketones (ketosis) [22].

The MAD is an alternative of the KD that mimics the effects of ketosis but is less restrictive [23]. These diets result in the production of ketones, which is believed to be involved for the anti-epileptic effects [24].

The control group received a placebo diet, believed to have no impact on epilepsy, or received no dietary intervention at all, i.e., CAU. There was a continuation of the AED regime in both groups (intervention and control group).

The primary outcome was an SFR of at least 50% (SFR ≥ 50%), which is clinically relevant and defined as success [25].

Secondary outcomes were seizure severity, adverse effects, cognitive and behavior outcomes, QoL, and attrition rate. A severe adverse effect was defined as an event that led to the withdrawal of the dietary intervention and/or the need for immediate intervention. Studies were included if they incorporated the primary and/or secondary outcomes.

## Information sources

We reviewed the current literature using Cochrane, EMBASE, and MEDLINE (using PubMed) up to September 2019.

## Search

The literature search is summarized in Fig. 1. PubMed was used as primary search engine by using free and medical subject heading (MeSH) terms since the other sources did not result in any additional studies (supplementary information, online only).

## Study selection

Articles of interest were examined by two investigators (JS and MM). If the analysis of title and abstract was not sufficient to decide if the article should be included, the full text was reviewed. The following studies were excluded: (1) no RCT, (2) no mention of the KD (classical or MCT) or the MAD, (3)

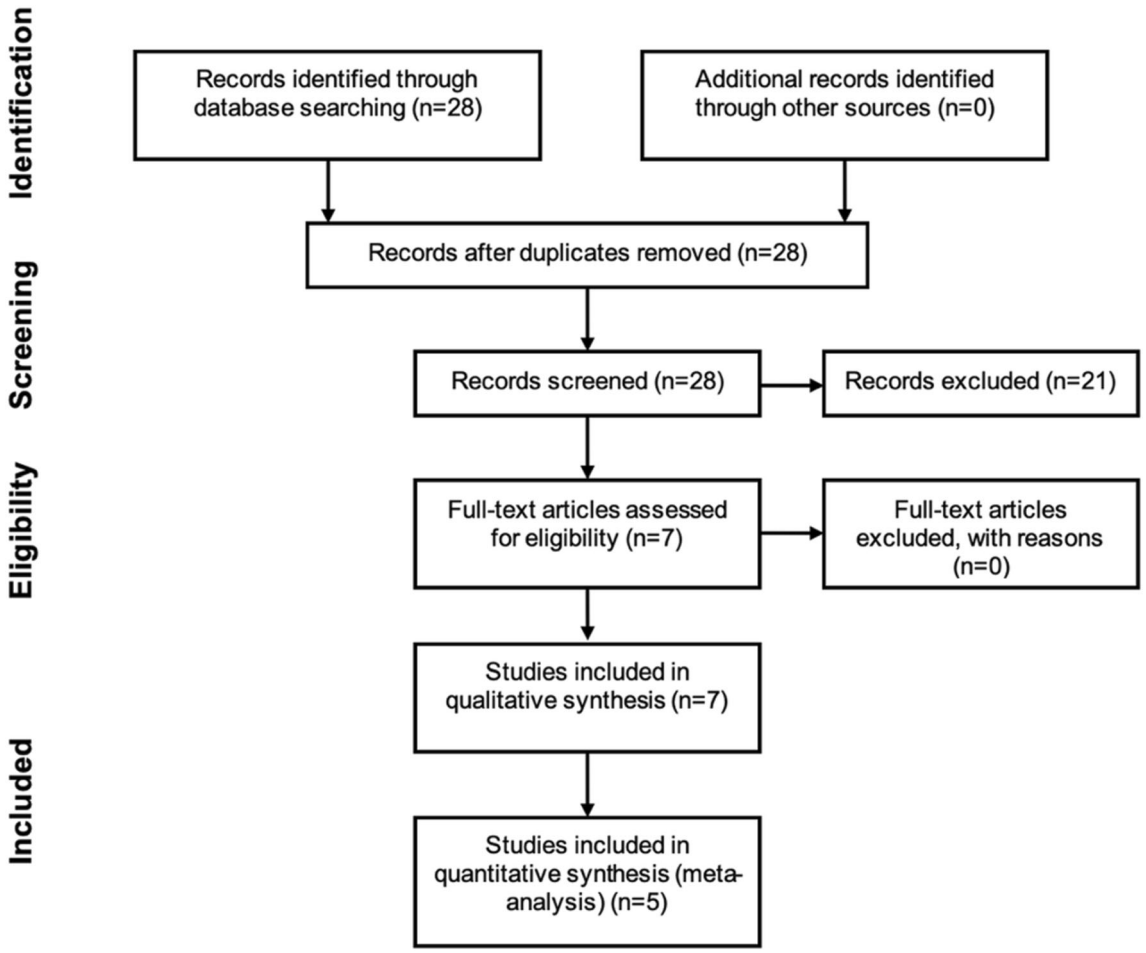


**Fig. 1** Flow chart of study identification, screening, eligibility screening, and inclusion (adjusted from the PRISMA guidelines [49])

no control group without a dietary intervention, and (4) insufficient information regarding the primary outcome (SFR) and/or secondary outcomes. Subsequently, full-text articles in English or Dutch were checked to determine eligibility. Furthermore, reference lists were checked to identify possible relevant articles, and a final list of studies was generated to be included in the review.

### Data extraction and management

Two investigators (JS and SK) extracted the data of the relevant articles by using a standardized Excel datasheet: study characteristics (sex, age, number of participants in each group, study design), diet intervention (KD and/or MAD), length of follow-up, seizure severity, adverse effects, reasons for drop-out, limitations of each study, and risk of bias.

### Risk of bias in individual studies

Two investigators (JS and SK) assessed the risk of bias (selection, performance, attrition, reporting, and other biases) by using the different domains of the Cochrane Collaboration tool for assessing risk of bias [26]. An overall summary of the risk of bias was made.

### Summary measures

Study characteristics were presented in detail. Overall, we presented the data as a percentage (number of patients with a certain event/condition in the intervention or control group), and computed the risk ratio (RR) for the MAD/KD group compared with the control group (CAU). In addition, the proportion of patients with an SFR of ≥ 50% for the MAD or KD group was calculated. Statistical heterogeneity between studies was quantified as the I-squared ($I^2$) statistic. The $I^2$ denotes the percentage variability in RR that is due to heterogeneity rather than sampling variance. A pooled estimate including 95% confidence interval was computed using either a random effect (RE) or fixed effect (FE) meta-analysis model. In case the $I^2$ statistic would be over 50%, a RE model was used. If not, the FE model was used. Regarding the sensitivity analysis, the pooled effect measure was computed on eligible studies. Studies were eligible if they reported the SFR during a follow-up period that was equal in the intervention and control group.

## Results

### Study selection

Our search strategy has resulted in 28 studies. Three studies were excluded due to the focus on an intervention distinct from a dietary intervention (VNS, vigabatrin, or lacosamide). Five studies did not include a control group (CAU), and five other studies were no RCT. Six studies were reviews and two articles described a study protocol. Therefore, our current review resulted in the inclusion of seven studies [15, 20, 27–31] (Fig. 1). Three studies described the KD, three studies described the MAD, and no studies evaluated the LGIT (Table 1).

### Study characteristics

All included studies are RCTs (Table 1). The number of participants ranged from 40 to 145. The follow-up duration varied between three and 16 months; in six out of seven studies, follow-up ranged between three and 6 months.

All studies included children or adolescents (age 1–18 years) who had not responded to two or more AEDs, described as refractory epilepsy [3]. Furthermore, all studies excluded patients with suspected or known metabolic disorders (e.g., diabetes, hyperinsulinism, fatty acid oxidation disorders).

Two studies excluded patients if they were not dietary-therapy-naïve [27, 29], and two studies excluded patients if there were motivational issues within the family [28, 29].

Only one RCT, resulting in three different articles [20, 30, 31], had more restrictive exclusion criteria; i.e., prolonged QT-syndrome, severe liver, kidney or pancreas disease, hypertriglyceridemia, hypercholesterolemia, malnutrition, treatment with acetazolamide or topiramate, presence of risk factors, or positive family history for kidney stones or acidosis. This RCT also excluded patients if they had a severe behavioral disorder. Nonetheless, patients with AD(H)D and autism were included in this RCT.

Even if patients with focal epilepsy were not excluded, most RCTs report a relatively low percentage of patients with focal epilepsy (< 25%), except two RCTs (42% and 50% for Neal et al. [27] and the Dutch RCT [30, 31], respectively).

### Risk of bias within studies

We assessed the risk of bias according to the Cochrane Collaboration tool for assessing risk of bias [26], which is summarized in Table S1 (online only). The risk of bias is also visualized by Fig. 2, made by RevMan (version 5.0).

There were five RCTs that generated seven publications reviewing the use of the KD and/or MAD for patients with refractory epilepsy.

### Results of individual studies

#### Primary outcome

Regarding the primary outcome, i.e., an SFR ≥ 50%, all five trials reported a statistically significant difference between the

**Table 1** Study characteristics

| Study | Methods | Participants | Intervention | Outcomes |
|---|---|---|---|---|
| Neal et al. 2008 | RCT (in the UK, at three different centers), not blinded. Comparison of KD (classical and MCT) with CAU over a 3-month period. Initial seizure baseline of 4 weeks. Data collection at 3 months. Study design described in the article. | 145 participants (age 2–16 years), with daily seizures (or > 7 seizures/week). Participants had not responded to ≥ 2 AEDs and have not been treated previously with a KD. | Participants were randomized to start a KD (classical or MCT, 73 participants) or to receive CAU (control group, 72 participants). | SFR and tolerability |
| El-Rashidy et al. 2013 | Single-center RCT (in Egypt), not blinded. Comparison of KD (classical and MAD) and a control group (AED). Data collection at 3 and 6 months. Details regarding study design were not mentioned in the article. | 40 participants (age 12–36 months) with symptomatic, refractory epilepsy. | Participants were randomized to start the classical KD (10 participants), MAD (15 participants), or CAU (control group, 15 participants). | SFR, seizure severity, adverse effects, and attrition rate |
| Sharma et al. 2013 | Single-center RCT (in India), not blinded. Comparison of MAD with CAU over a 3-month period. Initial seizure baseline of 4 weeks. Data collection at 3 months. Study design similar to Neal 2008. | 102 participants (age 2–14 years), with refractory epilepsy and daily seizures (2–14 per day). Participants had not responded to 3 AEDs. | Participants were randomized to start the MAD (50 participants) or to receive CAU (control group, 52 participants). | SFR, tolerability and adverse effects |
| Ijff et al. 2016 | Single-center RCT (in the Netherlands), not blinded. Comparison of KD (classical and MCT) with CAU over a 4-month period. Initial seizure baseline of 4 weeks. Data collection at 6 weeks and 4 months. Study design described elsewhere [25]. | 57 participants (age 1–18 years), with refractory epilepsy which are not eligible for epilepsy surgery. Participants had not responded to ≥ 2 AEDs and have not been treated previously with a KD. | Participants were randomized to start the KD (classical or MCT, 29 participants) or to receive CAU (control group, 28 participants). | Mood, behavior and cognition, seizure severity |
| Sharma et al. 2016 | Single-center RCT (in India), not blinded. Comparison of MAD with CAU over a 3-month period. Initial seizure baseline of 4 weeks. Data collection at 3 months. Study design similar to Neal 2008. | 81 participants (age 2–14 years), with daily seizures (or > 7 seizures/week). Participants had not responded to ≥ 2 AEDs and have not been treated previously with a KD. | Participants were randomized to start the MAD (41 participants) or to receive CAU (control group, 40 participants). | SFR, tolerability, and adverse effects |
| Lambrechts et al. 2017 | Same study as Ijff et al. [20]. | Same study as Ijff et al. [20]. | Same study as Ijff et al. [20]. | SFR, seizure severity and adverse effects |
| Wijnen et al. 2017 | Same study as Ijff et al. [20] with longer follow-up (data collection up to 16 months for the intervention group). | Same study as Ijff et al. [20]. | Same study as Ijff et al. [20]. | SFR, seizure severity, adverse effects, and cost effectiveness |

*RCT*, randomized controlled trial; *KD*, ketogenic diet; *MCT*, medium-chain triglycerides; *CAU*, care as usual; *AED*, anti-epileptic drug

intervention group (group I, KD and/or MAD) and the control group (group II, CAU), except at 16-month follow-up (Table 2).

The meta-analysis of studies focusing on the KD [15, 27, 31] showed that the proportion of patients with ≥ 50% SFR is 0.52 (95% CI 0.29–0.74; RE model) (Fig. 3). Studies regarding the MAD [15, 28, 29] showed that the proportion of patients with ≥ 50% SFR is 0.52 (95% CI 0.42–0.61; FE model) (Fig. 4).

For the KD and MAD combined, more than 35% of the participants of the intervention group (KD and MAD) showed an SFR of ≥ 50%, compared with 6–18.2% in the control group. Our overall meta-analysis underlined the significant efficacy (SFR in the dietary intervention vs. control group; RR = 5.1 (95% CI 3.18–8.21), $p < 0.001$; Fig. 5).

## Secondary outcomes

**Adverse effects** All studies reported adverse effects due to the dietary interventions. The RCTs investigating the KD reported mainly gastro-intestinal (GI) adverse effects in 30% of the participants, such as vomiting, diarrhea, and constipation [15, 27, 30, 31]. Three trials, investigating the MAD, also reported GI adverse effects to be the most common; e.g.,

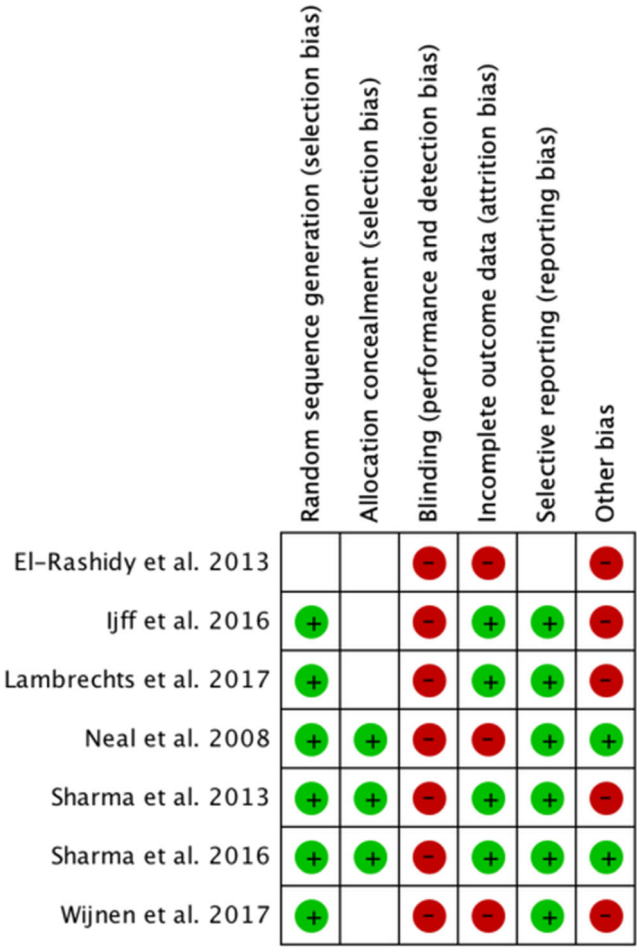


**Fig. 2** Risk of bias summary. Review author's judgments about each risk of bias item for each included study. The green color refers to a low risk of bias, the red color refers to a high risk of bias, and an unclear risk of bias is left blank

15–46% of the participants experienced constipation [15, 28, 29].

Overall, most of the adverse effects could be treated by dietary adjustments and/or drugs (anti-emetics and H2-blockers), and thereby did not lead to discontinuation of treatment in all RCTs [15, 27–29, 31]. However, persistence of adverse effects but also the lack of efficacy were the main reasons for participants to drop out of trials.

Interestingly, the only trial that lasted longer than 12 months [30] did not show a statistically significant increase of GI adverse effects due to the KD, even though this was the case at 4-month follow-up [31]. Moreover, they reported significantly fewer adverse effects regarding behavior/irritability, cosmetic/dermatological, and motor problems [30].

Severe adverse effects such as kidney stones, gallstones, fatty liver, nephrocalcinosis, acute pancreatitis, and QTc-prolongation were not reported. In contrast, biochemical parameter alterations were documented but were interpreted as clinically irrelevant [15, 29].

Other adverse effects documented by the trials in lower numbers were lower respiratory tract infections, abdominal pain, anorexia, lethargy, and hyperammonemic encephalopathy.

**Cognitive and behavior outcomes** One RCT evaluated the effects of the KD on psychosocial impact [20]. Higher productivity, reduced tension/anxiety/hostility, and better cognitive functioning were reported at 4-month follow-up. These improvements were irrespective of seizure control, in contrast to the improvement of activation. In addition, Sharma et al. reported improvements in alertness, behavior, social interaction, and sleep [29].

**Quality of life** Only a minimal difference was reported regarding the QoL by one RCT [30]. Utilities were measured by validated instruments, TAPQOL and TACQOL, to determine the quality-adjusted life years (QALYs) for the participants. Due to the relatively higher costs in the KD group, inconclusive cost per QALY ratios was reported [30]. Moreover, the authors did not investigate a relationship between the level of functioning and the QoL.

**Attrition rate** All the RCTs experienced dropouts for various reasons, ranging from 10 to 26% for the trials with the KD during a follow-up period of 3–6 months [15, 27, 31]. The trial in the Netherlands documented a higher dropout (42%) when the follow-up extended to 16 months [30]. This dropout was due to various reasons (Table S2, online only). Overall, reasons for dropout were mostly intolerance of the diet or adverse effects (mostly GI tract related), change of seizures (increase or decrease), and change of mind. In the trials regarding the MAD, dropout rates ranged from 2 to 14% [15, 28, 29]. Reasons for dropping out were intolerance of the diet, weight loss, parental unhappiness, and adverse effects (hyperammonemic encephalopathy and lower respiratory tract infections).

**Seizure severity** Three out of seven studies did not report changes in seizure severity. Two out three RCTs reported a statistically significant decrease in seizure severity. El-Rashidy et al. reported a mean decrease of seizure severity of 37.63% (MAD) and 35.89% (KD), compared with 1.79% (CAU) at 6-month follow-up ($p < 0.0001$ for both dietary interventions compared with the CAU) by using the Chalfont Seizure Severity Scale (CSSS) [15]. In line with these findings, Lambrechts et al. reported a mean decrease of seizure severity of 65.2% (KD), compared with 36.8% (CAU) at 4-month follow-up ($p = 0.007$ for the KD compared with the CAU) by using the National Hospital Seizure Severity Scale (NHS3) [31]. Consistently, Ijff et al. reported a significant reduction in seizure severity in the KD group, compared with

**Table 2** Primary outcome (seizure frequency reduction at follow-up)

| Study | Participant intervention group (group I) | Percentage of participants with ≥ 50% SFR (group I) | Participant control group, CAU (group II) | Percentage of participants with ≥ 50% SFR (group II) | Follow-up (m) | Statistical significance of intervention vs. CAU (group I vs. II)[b] |
|---|---|---|---|---|---|---|
| Neal et al. 2008 | 54 | 38.00 | 49 | 6.00 | 3 | *p < 0.0001* |
| El-Rashidy et al. 2013 | 25 | 49.41[a] | 15 | 8.31[a] | 6 | *p < 0.005* |
| Sharma 2013 [28]<sup>28</sup> | 50 | 52.00 | 52 | 11.50 | 3 | *p < 0.001* |
| Ijff et al. 2016 [20]<sup>20</sup> | 28 | NA | 22 | NA | 4 | NA |
| Sharma et al. 2016 | 41 | 56.10 | 40 | 7.50 | 3 | *p < 0.0001* |
| Lambrechts et al. 2017 | 26 | 50.00 | 22 | 18.20 | 4 | *p = 0.022* |
| Wijnen et al. 2017 | 26 | 35.00 | 22 | 18.00 | 16 | *p* = 0.171 (NS) |

*SFR*, seizure frequency reduction; *CAU*, care as usual; *m*, months; *NA*, not applicable; *NS*, no statistically significant difference

[a] Calculation based on the average of the two intervention groups (modified Atkins diet and classical ketogenic diet group)

[b] Statistical significance is defined as a *p* value < 0.05 and marked in italics

the CAU ($p = 0.038$) by using a different scoring scale (Hague Restrictions in Childhood Epilepsy Scale, HARCES) [20]. Caution is warranted since the aforementioned studies used different seizure severity scales, i.e., the CSSS [15], NHS3, and HARCES [20, 30, 31]. Moreover, seizure severity was assessed by an experienced clinician at 6 weeks and 4 months in the study of Lambrechts et al. [31] and Ijff et al. [20], while El-Rashidy et al. [15] did not provide any details regarding the assessment of the seizure severity.

In addition, we were unable to determine if the long-term data, i.e., 16-month follow-up of the RCT published by Lambrechts et al. [30], also revealed a statistically significant difference. They only reported a decrease in seizure severity of 46.2% in the KD group, compared with 32.0% in the CAU group.

### Biomarkers for efficacy of individual studies

Lambrechts et al. correlated seizure control to ketosis (beta-hydroxybutyrate (BHB) concentrations in the blood) at 3 months [31]. This significant difference disappeared at six and 12 months [30]. Moreover, the other RCTs did not investigate possible biomarkers to objectively evaluate the KD.

## Discussion

### Summary of main results

Miranda and colleagues described the KD, the MAD, and the LGIT as dietary interventions for the treatment of pediatric epilepsy [18]. There have been several reviews regarding observational studies on the efficacy of these dietary interventions [32, 33]. In addition, four Cochrane systematic reviews of dietary interventions for epilepsy are published [8, 34–36], of which some quite recently. However, we complement these studies by focusing on RCTs and applying statistical methods in an attempt to quantify the efficacy of dietary interventions. We also concentrated on those RCTs that included a true placebo group, i.e., care as usual (CAU) to evaluate the effect of a dietary intervention compared with no intervention at all.

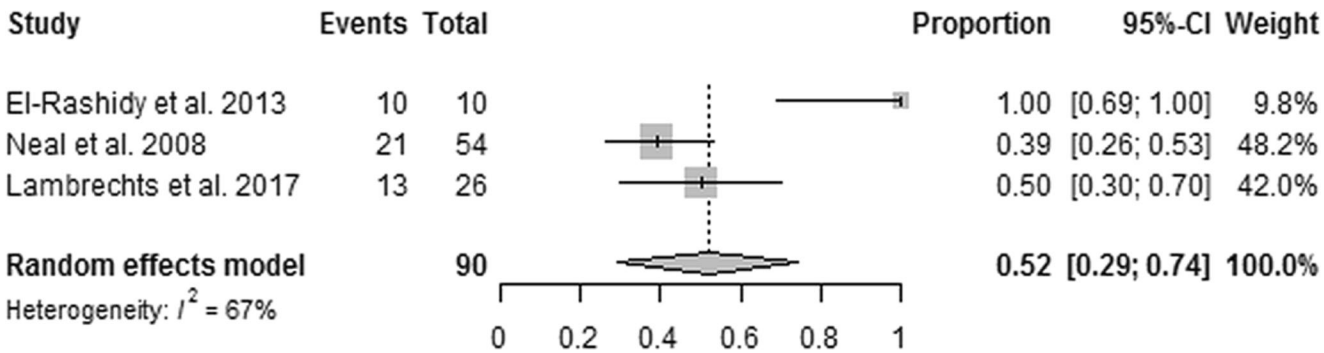


**Fig. 3** Forest plot of the proportion of patients with a seizure frequency reduction (SFR) of at least 50% treated with the KD. The proportion of patients with ≥ 50% SFR is 0.52 (95% CI 0.29–0.74; RE model). 95%-CI, 95% confidence interval; $I^2$, statistical heterogeneity

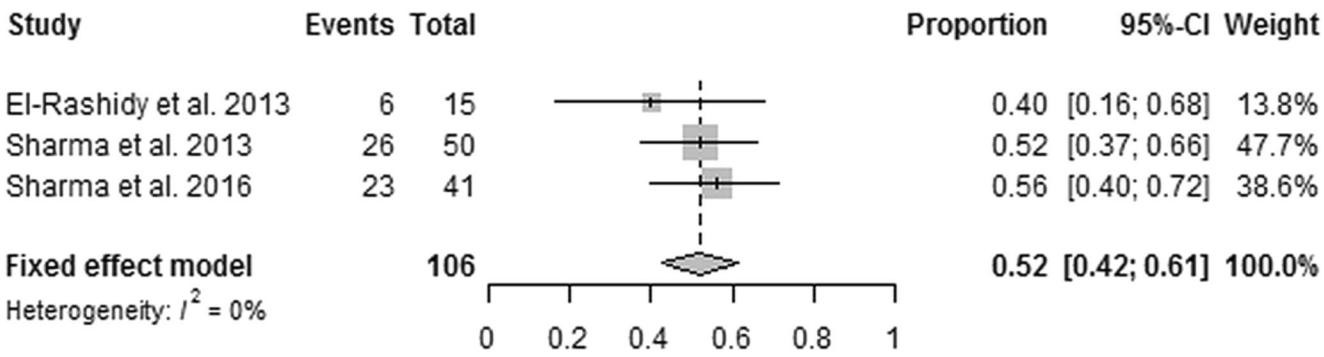


**Fig. 4** Forest plot of the proportion of patients with a seizure frequency reduction (SFR) of at least 50% treated with the MAD. The proportion of patients with ≥ 50% SFR is 0.52 (95% CI 0.42–0.61; FE model). 95%-CI, 95% confidence interval; $I^2$, statistical heterogeneity

Hence, studies comparing two types of KDs (classical vs. MCT) [37] or glucose supplements to the MAD [38] were beyond the scope of this review.

Our review identified five RCTs, resulting in seven publications that assessed the efficacy of dietary interventions (KD and MAD) for children and adolescents with refractory epilepsy. To date, there have been no RCTs regarding the LGIT. We show promising, though limited, evidence since the primary outcome (SFR ≥ 50%) was attained in the 35–56.1% of the participants in the intervention group, compared with 6–18.2% in the control group. Our meta-analysis underlined this significant difference (SFR ≥ 50% in the intervention vs. control group; RR = 5.1 (95% CI 3.18–8.21), $p < 0.001$). In addition, we evaluated the primary outcome in the KD and MAD group separately. Our calculations show that the proportion of patients with ≥ 50% SFR is equal for both groups (KD 0.52 (95% CI 0.29–0.74) and MAD 0.52 (95% CI 0.42–0.61)). These findings are in line with a recent review that elaborated on pro- and retrospective studies regarding the KD and the MAD [39]. Herein, the authors directly compared the responder rate (SFR ≥ 50%) between the KD and MAD, which did not differ substantially after 3 months of treatment.

Adverse effects were monitored by all RCTs. Overall, the KD and MAD were well tolerated, although the only long-term study failed to agree on this statement. Therefore, the major reason of dropout during the study was an intolerance to the diet, and GI adverse effects were common in at least 15% of the participants. However, fine-tuning of the diet was often sufficient to reduce the GI adverse effects.

Four out of seven trials [15, 20, 30, 31] adequately assessed seizure severity and reported statistically significant decreases within the intervention group, although different scales were used and differences were not apparent at longer follow-up (16 months) [30]. Two studies reported changes in cognition and behavior. First, the trial in the Netherlands focused on the cognitive and behavioral functioning, as well as on the QoL. They reported higher productivity, reduced tension/anxiety/hostility, and better cognitive functioning at 40-month follow-up [20] and a lack of QoL improvements [30]. This latter finding could be explained by the fact that the generic instruments for

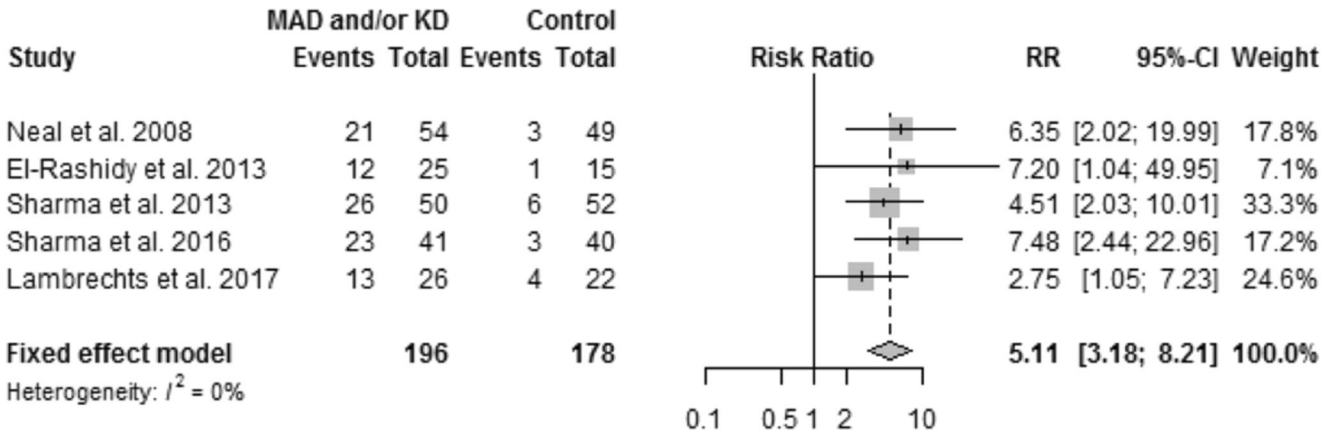


**Fig. 5** Forest plot of the RR of dietary interventions (KD and/or MAD) regarding seizure frequency reduction (SFR) of at least 50%. RR, relative risk; 95%-CI, 95% confidence interval; $I^2$, statistical heterogeneity. Pooled analysis of the individual studies of patients with an SFR of at least 50% leading to a RR = 5.1 (95% CI 3.18–8.21), $p < 0.001$. This finding indicates that the chance to obtain an SFR of at least 50% is about 5.1 times higher in the dietary intervention group compared with the care as usual (CAU). Since Ijff et al. 2016 did not report an SFR and Wijnen et al. 2017 did not state an equal follow-up duration in intervention compared with control group, we excluded these two studies in our meta-analysis

measuring the QoL were not sensitive enough or that being a responder is not sufficient to have an improvement in the QoL. Second, Sharma et al. reported improvements in (social) behavior [29]. Interestingly, these positive effects on cognition and behavior are in line with other studies [40–42].

Overall, the validity of each study can be questioned since various biases were present in the different trials (internal validity), and all trials involved a single-center study (not clear if extrapolation to other settings is plausible; external validity). Therefore, future trials should be multi-center, with a sufficiently long follow-up (preferably of at least 1 year) and should aim to keep the performance bias as low as possible (blinding of the personnel and analysts, whenever possible).

## Limitations

The follow-up duration was relatively short (three to 6 months) for most trials, which made long-term results difficult to predict. The only long-term RCT is the study by Wijnen et al.; however, the control group (CAU) was only followed for 4 months, and data were extrapolated to 16 months (last observation carried forward) [30]. From an ethical point of view, participants of the CAU group were offered to receive the KD after the first period of 4 months, but no data were available to determine the exact number of participants who agreed on this offer. In addition, there was a relatively low retention rate in the long-term trial (15/26 completed the FU at 16 months, i.e., 58%). Overall, dropouts vary between 2 and 26%, which could be the result of the experienced adverse effects by the patient (e.g., GI effects) and/or the time-intensive nature of dietary interventions, experienced by the caregiver(s). Although, the exact reasons for low retention rates during longer FU were not specified.

The primary and some of the secondary outcomes (e.g., seizure severity) were measured by instruments that are prone to subjectivity, i.e., by seizure diaries. This method is accepted in general clinical research since no alternative is available. Nevertheless, some important limitations should be considered regarding this method: (1) self-recording may affect the observation by causing the subject(s) to be more vigilant regarding the occurrence of seizures; (2) reports could be false positive (events which are not seizures) or no compliance regarding the diary maintenance; (3) subtle (e.g., absence epilepsy), nocturnal, or high-frequent seizures could be missed by the parent/caregiver.

The other secondary outcomes (e.g., QoL, cognition, and behavior) were analyzed by two trials [20, 29] of which Sharma et al. used subjective, parent-proxy reports (dichotomous, poorly defined, and not standardized) [29]. These reports are prone to more positive results than objective measurements [43] and are partially dependent on the reactions and emotions of the parents [44]. This latter finding underlines the need to assess the patients directly, instead of their parents. In contrast, Ijff et al. used objective assessments (well-defined, standardized) [20], which allow a better interpretation and generalization [43]. However, most objective psychometric scales do not report the timing of behavior disturbances, which could be a peri-ictal phenomenon rather than an underlying disorder. In addition, there is a significant tendency of comorbidities before and after epilepsy diagnosis, even though none of the RCTs elaborated on behavioral and psychiatric comorbidities [44].

Therefore, future RCTs should use objective measurement tools, include the assessment of comorbidities, and use self-reports whenever possible.

In general, our review underlines the promising effects of the KD and MAD in the treatment of refractory epilepsy (age 1–18 years). However, the small sample sizes and the limited amount of studies resulted in a relatively low quality of evidence.

## Implications for research

The anti-epileptic mechanism of the KD and other dietary interventions is currently unknown, and evidence exists regarding the anti-epileptic and neuroprotective characteristics of ketone bodies [10]. Consistently, Lambrechts et al. were able to correlate seizure control to ketosis (by the ketones in blood, rather than urinary ketones) at 3-month follow-up [31], but not at six and 12 months [30]. The available animal studies underline the cellular and biochemical alterations by ketones (such as BHB, acetone, and acetoacetate) and its role in seizure reduction. These alterations could increase inhibitory neurotransmission (e.g., by enhancing GABAergic or ATP-sensitive potassium channels), decrease excitatory neurotransmission (e.g., by affecting vesicular glutamate transporters), or affect mitochondrial processes.

Novel pathways are reviewed elsewhere [12], and current data indicate the aforementioned plausible role of the ketones; however, most of them are not directly linked to epileptogenesis or seizure reduction. Of interest, recent preclinical data underline the possible role of the gut microbiome since in two different mouse models of different epilepsy types, anti-seizure effects of the KD were mediated by enrichment of *Akkermansia muciniphila* and *Parabacteroides* populations in the gut microbiome [45]. In addition, clinical data show that *Bacteroidetes* [11, 46] and proteobacteria [47] are more prominent after KD, which could be related to the anti-seizure effect.

Thus, research should further elucidate the complex neurobiology of the KD to discover novel targets for therapeutics, to create clinical formulations of the KD, and to determine if certain types of fat and/or ketogenic ratios relate to the clinical efficacy [48]. In addition, future trials should validate the aforementioned potential biomarkers, including the assessment of serum parameters (adenosine, ketones) and/or the gut microbiome. Moreover, these clinical trials should be adequately powered RCTs with

large number of patients and well-defined outcomes (SFR, QoL, and neurocognitive improvement).

## Conclusions

Our review identified seven studies (five RCTs) with a total sample size of 472 participants with refractory epilepsy (age 1–18 years). The primary outcome (SFR ≥ 50%) was attained in 35–56.1% of the participants in the intervention group, compared with 6–18.2% in the control group. Our meta-analysis underlined this significant difference (SFR ≥ 50% in the intervention vs. control group; RR = 5.1 (95% CI 3.18–8.21), $p < 0.001$). Objective evaluation of the efficacy, by biomarkers, has not yet been clinically validated, although two studies mention the possible correlation between the concentration BHB (ketones in the blood) and the responder rate.

Only a limited number of participants on the KD and/or MAD experienced severe adverse effects. In addition, the most prominent adverse effects were affecting the GI tract and were reversible by small adjustments of the dietary treatment. Therefore, the KD or MAD has a major benefit compared with standard epilepsy treatment with AEDs, which is related to long-term adverse effects. However, there was a significant methodological and clinical heterogeneity between all studies, and more research is needed regarding the long-term effects of dietary interventions. In addition, future trials should investigate objective methods to evaluate the efficacy, e.g. by biomarkers such as the concentration of ketones (BHB) in the blood and/or by analyzing the gut microbiome.

Nevertheless, given the beneficial clinical results regarding efficacy and safety, the KD and variations of this diet (e.g., MAD) should be considered as a treatment option for children and adolescents with refractory epilepsy who are not eligible for epilepsy surgery.

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## Compliance with ethical standards

**Conflict of interest** JS, MM, HB, SK, SvK, and DL declare no conflict of interest

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