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Ketogenic diet and other dietary treatments for epilepsy (Review)

Martin K, Jackson CF, Levy RG, Cooper PN

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TABLE OF CONTENTS

[Intervention Review]

Ketogenic diet and other dietary treatments for epilepsy

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ABSTRACT

Background

The ketogenic diet (KD), being high in fat and low in carbohydrates, has been suggested to reduce seizure frequency. It is currently used mainly for children who continue to have seizures despite treatment with antiepileptic drugs. Recently, there has been interest in less restrictive KDs including the modified Atkins diet (MAD) and the use of these diets has extended into adult practice.

Objectives

To review the evidence for efficacy and tolerability from randomised controlled trials regarding the effects of KD and similar diets.

Search methods

We searched the Cochrane Epilepsy Group's Specialized Register (30 March 2015), the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO, 30 March 2015), MEDLINE (Ovid, 30 March 2015), ClinicalTrials.gov (30 March 2015) and the WHO International Clinical Trials Registry Platform (ICTRP, 30 March 2015). We imposed no language restrictions. We checked the reference lists of retrieved studies for additional reports of relevant studies.

Selection criteria

Studies of KDs and similar diets for people with epilepsy.

Data collection and analysis

Two review authors independently applied pre-defined criteria to extract data and assessed study quality.

Main results

We identified seven randomised controlled trials that generated eight publications.

All trials applied an intention-to-treat analysis with varied randomisation methods. The seven studies recruited 427 children and adolescents and no adults. We could not conduct a meta-analysis due to the heterogeneity of the studies.

Reported rates of seizure freedom reached as high as 55% in a 4 : 1 KD group after three months and reported rates of seizure reduction reached as high as 85% in a 4 : 1 KD group after three months.

One trial found no significant difference between the fasting-onset and gradual-onset KD for rates of seizure freedom and reported a greater rate of seizure reduction in the gradual-onset KD group.

Studies assessing the efficacy of the MAD reported seizure freedom rates of up to 10% and seizure reduction rates of up to 60%. One study compared the MAD to a 4 : 1 KD, but did not report rates of seizure freedom or seizure reduction.

Adverse effects were fairly consistent across different dietary interventions. The most commonly reported adverse effects were gastrointestinal syndromes. It was common that adverse effects were the reason for participants dropping out of trials. Other reasons for drop-out included lack of efficacy and non-acceptance of the diet.

Although there was some evidence for greater antiepileptic efficacy for a 4 : 1 KD over lower ratios, the 4 : 1 KD was consistently associated with more adverse effects.

No studies assessed the effect of dietary interventions on quality of life, or cognitive or behavioural functioning.

Authors' conclusions

The randomised controlled trials discussed in this review show promising results for the use of KDs in epilepsy. However, the limited number of studies, small sample sizes and a sole paediatric population resulted in a poor overall quality of evidence.

There were adverse effects within all of the studies and for all KD variations, such as short-term gastrointestinal-related disturbances, to longer-term cardiovascular complications. Attrition rates remained a problem with all KDs and across all studies, reasons for this being lack of observed efficacy and dietary tolerance.

There was a lack of evidence to support the clinical use of KD in adults with epilepsy, therefore, further research would be of benefit.

Other more palatable but related diets, such as the MAD ketogenic diet, may have a similar effect on seizure control as classical KD but this assumption requires more investigation. For people who have medically intractable epilepsy or people who are not suitable for surgical intervention, a KD remains a valid option; however, further research is required.

PLAIN LANGUAGE SUMMARY

Ketogenic and other dietary treatments for epilepsy

Background

Epilepsy is a disorder where recurrent seizures (fits) are caused by abnormal electrical discharges from the brain. Most seizures can be controlled by one or more antiepileptic medicines but seizures may not be helped by these medicines after a while (called drug-resistant epilepsy). For people who have drug-resistant epilepsy a special diet (called a ketogenic diet) may be considered. Ketogenic diets are high in fat and low in carbohydrate.

This review aimed to investigate the effect of a ketogenic diet on seizure control, cognition (e.g., learning, concentration and academic performance in children; learning, concentration and memory in adults) and behaviour. We also investigated the side effects of the diet and the number of participants who dropped out of the studies and the reasons for this.

Search date

This evidence is current to March 2015.

Study characteristics

We searched medical databases for randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) of adults or children with epilepsy where a ketogenic diet was compared with other treatments. We found seven randomised controlled trials, with 427 participants. The trials were between three and six months long.

Key results

The short-term side effects of ketogenic diets included diarrhoea, constipation and vomiting. In the long term, heart heath could be affected.

All studies reported participants dropping out, due to lack of improvement in seizures and poor tolerance of the diet.

No studies reported upon the effect of ketogenic diets on cognition and behaviour.

Recently, other, more agreeable, ketogenic diets, such as the modified Atkins ketogenic diet, found similar effects on seizure control as those more restrictive ketogenic diets. However, more research is required.

Quality of the evidence

The studies included in this review were limited by small numbers of participants and they only included children; therefore, the quality of the evidence was low.

There is little research at present into the use of these diets in adults, therefore, more research is required in this area.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Ketogenic diet or other dietary treatments for peoplewith epilepsy

Patient or population: people with epilepsy
Settings:
Intervention: ketogenic diet or other dietary treatments

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Ketogenic diet or other dietary treatments				
Seizure freedom 100% Number of people	See comment	See comment	Not estimable	256 (4)	⊕⊕◯◯ **low**[1,2]	All trials included in this table assessed seizure freedom after 3 months. For more information on seizure freedom after longer periods of dietary interventions, see Effects of interventions 3 studies reported similar rates of seizure freedom. Bergqvist 2005 compared fasting-onset KD (3/24) and gradual-onset KD (5/24); Raju 2011 compared 4 : 1 KD (5/19) and 2.5 : 1 KD (4/19) and Neal 2008 compared MCT (1/49) and

						KD (1/45) Seo 2007 reported 22/40 participants became seizure free in the 4 : 1 KD group compared with 11/36 in the 3 : 1 KD group. However, it was unclear whether this difference was statistically significant
Seizure reduction > 50% Number of people	See comment	See comment	Not estimable	387 (6 studies)	⊕⊕◯◯ **low**[1,2]	2 studies found no significant difference between comparisons made; Bergqvist 2005 reported no significant difference in seizure reduction (> 50% reduction) between the fasting-onset or gradual-onset KD and Raju 2011 reported no significant difference in seizure reduction between a 4 : 1 KD and a 2.5 : 1 KD 4 studies noted significant differences in seizure reduction between diets examined; Kossoff 2007 reported fewer seizures in 10 g carbohydrate group than the 20 g carbohydrate group of MAD, Neal 2008 reported diet

						group had significantly higher seizure reduction than controls, Seo 2007 reported fewer seizures for 4 : 1 group than 3 : 1 group and Sharma 2013 reported significantly more participants in the MAD group compared with participants in the control group
Adverse effects Number of people	See comment	See comment	Not estimable	427 (7 studies)	⊕⊕◯◯ **low**[1,2]	We list a summary of all adverse effects experienced within dietary intervention groups. For further detail of adverse effects reported in each study, see Effects of interventions The most frequent adverse effects reported by participants in dietary intervention groups were: vomiting and constipation. Other adverse effects reported included diarrhoea, dysphagia, lethargy, lower respiratory tract infection, hyperammonaemic encephalopathy, weight loss, nausea, infections (pneumonia, sep-

						sis), acute pancreatitis, decrease in bone matrix density, gallstones, fatty liver, nephrocalcinosis, hypercholesterolaemia, status epilepticus, acidosis, dehydration, tachycardia, hypoglycaemia, hunger and abdominal pain
Attrition rate Number of people	See comment	See comment	Not estimable	427 (7)	⊕⊕◯◯ **low**[1,2]	We summarise the attrition rates for each dietary intervention. For reasons for drop-outs, see Effects of interventions Overall the attrition rate in all dietary interventions ranged from 4.2% to 20.8% Attrition rates in 4 : 1 KD groups ranged from 4.2% to 20.8%, in 3 : 1 KD was 16.7%, in 2.5 : 1 KD was 15.8% Attrition rates for MAD groups ranged from 8% to 50% Attrition rates for control groups ranged from 5.8% to 23.4%

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; KD: ketogenic diet; MAD: modified Atkins diet; MCT: medium-chain triglyceride

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Studies are heterogeneous with regards to interventions examined and comparisons made.
[2] Relatively low overall sample size. Confidence in results from small number of participants is low.

BACKGROUND

Description of the condition

Epilepsy is a common treatable neurological condition with a lifetime risk of 1% to 3% (Hauser 1990). It is characterised by recurrent involuntary brain activity that manifests in seizures (Chang 2003). Although the majority of people with epilepsy will have a good response and become seizure free by treatment with antiepileptic drugs (AED), approximately 30% of people with epilepsy will continue to have seizures even when taking multiple AEDs (Granata 2009). Uncontrolled seizures pose a significant risk to quality of life (Lawn 2004; Schmidt 2002; Villeneuve 2004). In addition, uncontrolled tonic-clonic seizures are likely to be one of the strongest risk factors of sudden death in epilepsy (Nilsson 1999). Therefore, it is important not to rely on pharmacological interventions when treating refractory epilepsy and further evidence for alternative interventions must be developed.

Description of the intervention

Diets have been used in an attempt to control epileptic seizures throughout the centuries, indeed there is a biblical reference to prayer and fasting in epilepsy (St Mark 9: 14-29). Scientific assessment of dietary manipulation reported in Guelpa 1911, and subsequently in Geyelin 1921, confirmed that seizures may cease on absolute fasting, but neither study was a randomised controlled trial (RCT). Wilder 1921 suggested that a diet high in fat and low in carbohydrates would be similar to fasting. The classical ketogenic diet (KD) uses a 4 : 1 ratio of total energy from fat to carbohydrate and protein. The KD has been described as unpalatable and difficult to tolerate, thus leading to poor compliance. Therefore, several diets have been investigated to improve palatability. The Atkins diet was initially used for weight reduction. It offers approximately a 1 : 1 ratio of energy from fat to carbohydrate and protein, through restricting carbohydrate to 10 g to 20 g per day (Atkins 1972), and is considered less restrictive.

Prior to the introduction of anticonvulsant medications (Merritt 1938), the KD was used in children (and adults) who were more representative of the current general population of people with epilepsy. However, case series published since the mid-1980s have generally included people with multiple seizure types refractory to multiple AEDs. The classic KD and other more palatable versions have a positive effect on infantile spasms, severe myoclonic epilepsy, tuberous sclerosis complex (Kossoff 2005), and children with refractory status epilepticus (O'Connor 2014).

How the intervention might work

Although the anticonvulsant effects of the KD remain unclear, numerous biochemical theories have been suggested for the possible action of the diet. One theory suggests that the anticonvulsant effect of ketone bodies (acetoacetate, beta-hydroxybutyrate), ketone reduction of alanine efflux, charge of water and electrolyte imbalance (Schwartz 1989), results in changes occurring either in nerve cell lipid membranes or neurotransmitter production (Schwartz 1989; Schwartzkroin 1999).

Why it is important to do this review

Despite the use of the KD and other dietary treatments for adults and children with refractory epilepsy within clinical settings, the number of high-quality RCTs has been limited in recent years. Therefore, the evidence base for this intervention has been unclear. This review aims to assess the effectiveness of KDs and other dietary interventions when considering RCTs.

OBJECTIVES

To review the evidence for efficacy and tolerability from randomised controlled trials regarding the effects of ketogenic and similar diets.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs or quasi-RCTs (using adequate methods of allocation concealment) of KD and other dietary interventions for people with epilepsy.

Types of participants

Adults and children with a diagnosis of epilepsy irrespective of their seizure type or epilepsy syndrome.

Types of interventions

Ketogenic diet group (related diet)

- Any diet that is designed to produce ketones. There are several KDs that have been used depending upon the proportion of the different types of lipids. The two main types of diet are classical and medium-chain triglyceride (MCT); we also considered the modified Atkins diet (MAD).

Control group

- Placebo/sham diet given as a control treatment that is thought to have no effect on epilepsy.
- Any treatment with known antiepileptic properties.

Types of outcome measures

Primary outcomes

- Seizure freedom (100% reduction in seizure frequency).
- Seizure reduction (50% or greater reduction in seizure frequency).
- Adverse effects.

Secondary outcomes

- Cognitive and behaviour outcomes as measured by validated rating scales.
- Quality of life as measured by validated rating scales.
- Attrition rate.

Search methods for identification of studies

Electronic searches

For the most recent update of this review we searched:

- the Cochrane Epilepsy Group Specialized Register (30 March 2015) using the search strategy outlined in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO, 30 March 2015) using the search strategy outlined in Appendix 2;
- MEDLINE (Ovid, 30 March 2015) using the search strategy outlined in Appendix 3;
- ClinicalTrials.gov (30 March 2015) using the search terms: epilepsy AND diet;
- the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP, 30 March 2015) using the search terms: epilepsy AND diet.

We searched EMBASE from 1980 to March 2003. We no longer have access to that database. However, RCTs and quasi-RCTs in EMBASE are included in CENTRAL. Therefore, these records are available to us via our searches of CENTRAL.

Searching other resources

We searched references from previous versions of this review (backward referencing) and newer references from more up to date studies.

We contacted experts in the area to enquire about other relevant studies.

Data collection and analysis

Two review authors independently selected all potential RCTs for eligibility according to criteria specified with data extracted from each publication. We resolved any disagreements by discussion. In addition to the main outcome measures listed above, for each study, we collected the following data using a pre-standardised data extraction form.

- Participant characteristics including age, sex, number of participants (randomised to each group).
- Diet intervention (classical, MCT, MAD or other).
- Length of follow-up.
- Epilepsy seizure type.
- Reason for commencement.
- Adverse effects.
- Reason for drop-out including compliance.

We conducted an intention-to-treat (ITT) analysis where possible, including all allocated participants in the treatment groups to which they were allocated, irrespective of the treatment they received. Where necessary, we contacted original trial authors for additional data or clarification. We stratified results according to method of allocation concealment.

We assessed clinical heterogeneity by investigating the distribution of important prognostic factors between trials and assessed statistical heterogeneity using a Chi^2 test (P value < 0.05). Provided we found no heterogeneity, we planned summary estimates across trials. Our preferred estimator was risk ratio with 95% confidence intervals (CIs) calculated using the Mantel-Haenszel method using both fixed-effect and random-effects models.

For behaviour, quality of life and cognitive outcomes, it was unlikely that individual authors would have addressed this in a uniform manner. In the first instance, we planned to summarise the results using text and tables.

Selection of studies

Two review authors (CJ, KM) independently reviewed the titles and abstract of the studies identified by the electronic searches and removed studies that did not meet the inclusion criteria. The same two authors reviewed the full-text reports to determine eligibility. We resolved any disagreements by discussion. In the event of there being multiple reports deriving from one study, we linked the reports together. We produced a final list of studies to be included in the review.

Data extraction and management

In addition to the main outcome measures listed in Primary outcomes; Secondary outcomes, two review authors (CJ, KM) completed data extraction for each study. We cross-checked results of the data extraction and resolved any disagreements by discussion.

We collected the following data using a pre-standardised data extraction form.

- Participant characteristics including age, sex and number of participants (randomised to each group).
- Diet intervention (classical or MCT or other).
- Length of follow-up.
- Epilepsy seizure type.
- Reason for commencement.
- Adverse effects.
- Reason for drop-out including compliance.

We conducted an ITT analysis where possible, including all allocated participants in the treatment groups to which they were allocated, irrespective of the treatment they received. Where necessary, we contacted original trial authors for additional data or clarification.

Assessment of risk of bias in included studies

Two review authors (CJ, KM) independently assessed the risk of bias and compared the results from these assessments to identify any inconsistencies. We resolved any disagreements by discussion. We assessed all domains of the current Cochrane tool for assessing risk of bias (Higgins 2011). We presented an overall summary judgement of risk of bias for each outcome per study and made an overall risk of bias assessment for each outcome across all studies. Where possible, we planned to incorporate the risk of bias judgement into the analysis using sensitivity analysis. This analysis of the data would have included only studies rated as low risk of bias. We created a 'Summary of findings' table for outcomes, and graded each outcome using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Guyatt 2008).

Measures of treatment effect

Where possible, we presented outcomes as RRs with 95% CI and reported secondary outcomes narratively.

Unit of analysis issues

In the event of unit of analysis issues being identified across studies (e.g. cross-over, cluster randomised or repeated measures studies), we planned to:

- determine whether the methods in such studies were conducted appropriately;
- combine extracted effect sizes from such studies through a generic inverse variance meta-analysis.

Dealing with missing data

In the event of missing data, we planned to contact study authors for the data or to determine if data were missing at random or not.

Assessment of heterogeneity

Two review authors assessed clinical and methodological heterogeneity by investigating the distribution of important prognostic factors between trials and the study design. We assessed statistical heterogeneity using a Chi^2 test (P value < 0.05) and an I^2 statistic of greater than 50% to indicate statistical heterogeneity in accordance with Cochrane guidelines (Higgins 2011).

Provided we found no heterogeneity, we planned summary estimates across trials. Our preferred estimator was RRs with 95% CIs calculated using the Mantel-Haenszel method using both fixed-effect and random-effects models.

Assessment of reporting biases

We investigated outcome reporting bias using the ORBIT matrix system (Kirkham 2010). We requested all protocols from study authors to compare outcomes of interest.

To examine publication bias, We identified any unpublished data by carrying out a comprehensive search of multiple sources and requesting unpublished data from study authors. We planned to examine funnel plots in the event of there being 10 or more studies that could be combined, in accordance with Cochrane recommendations (Higgins 2011).

Data synthesis

Ideally, we would have presented the data in a fixed-effect meta-analysis; however, as we expected some heterogeneity across the studies, we carried out a random-effects meta-analysis.

We planned to present seizure freedom, seizure reduction by 50% and adverse effects as RRs with 95% CIs.

Due to significant clinical and methodological heterogeneity, meta-analysis was not possible and, therefore, we reported the outcomes narratively.

We planned to carry out the following comparisons:

- KD compared with a control;
- KD compared with other dietary interventions;
- KD compared with other interventions;
- other dietary interventions compared with a control;
- other dietary interventions compared with other interventions.

Subgroup analysis and investigation of heterogeneity

We planned to stratify comparisons by control group, participant group, study characteristics, or a combination of these to ensure appropriate combination of study data.

Sensitivity analysis

We intended to carry out sensitivity analysis if we found peculiarities between study quality. We planned to report and compare analyses for all studies only of studies at low risk of bias.

RESULTS

Description of studies

Results of the search

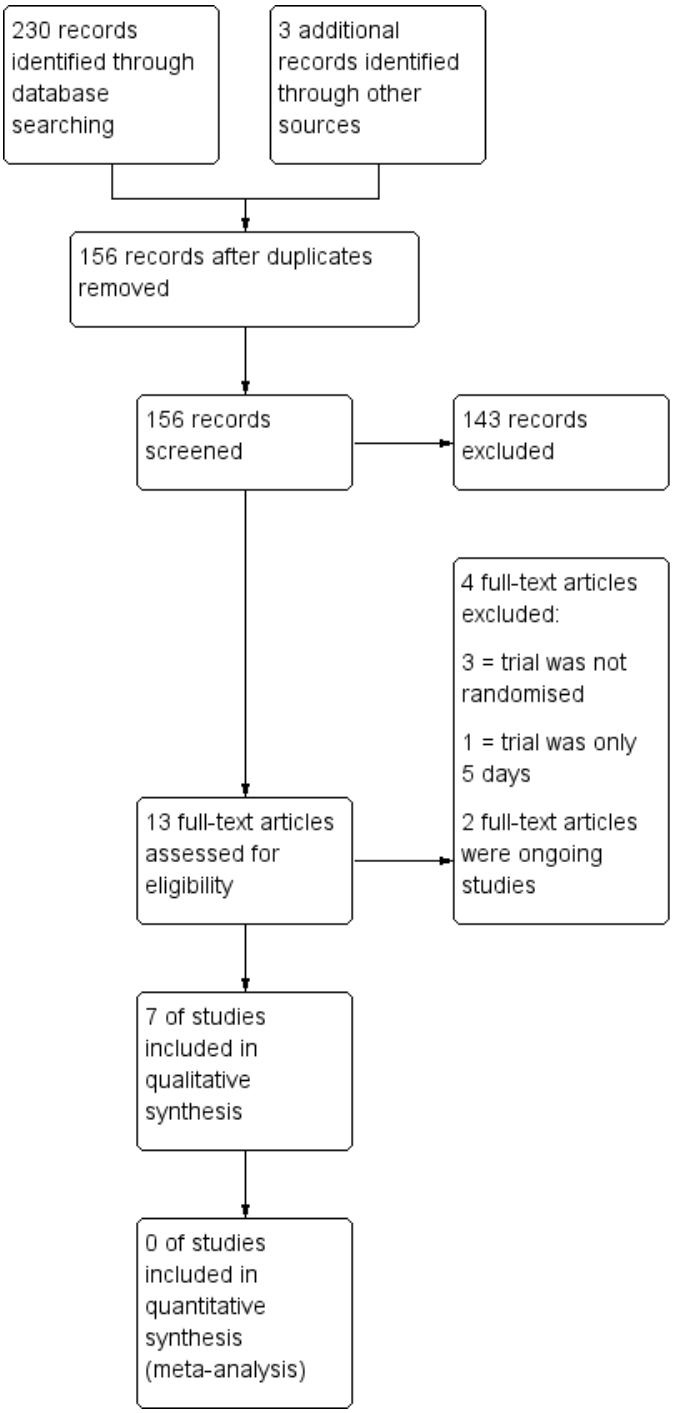
Previous versions of this review identified four RCTs (Bergqvist 2005; Kossoff 2007; Neal 2008; Seo 2007).

The search strategies were updated and, therefore, there were no date restrictions placed on the updated searches.

The updated search revealed 230 studies from the databases outlined in Electronic searches and three additional studies through other sources. After removing duplicates, 156 studies remained. Initial screening removed 143 irrelevant studies leaving 13 studies. The remaining studies underwent full-text review after which we excluded a further four studies (Freeman 1999; Freeman 2009; Hemingway 2001; Smith 2011), identified two studies as ongoing (Hulshof 2014; Yoon 2014), and deemed seven studies eligible for inclusion in the present review update. Four of the identified studies were included in previous versions of this review (Bergqvist 2005; Kossoff 2007; Neal 2008; Seo 2007), therefore we included three new RCTs in this update (El-Rashidy 2013; Raju 2011; Sharma 2013).

Figure 1 shows the search results from the present update.

Figure 1. Study flow diagram.



Included studies

Bergqvist 2005 (USA)

Bergqvist 2005 was a prospective, randomised, single-centre study of 48 participants aged one to 14 years (mean 5.3, standard deviation (SD) 2.7) comparing fasting and gradual-onset KD over a three-month period. Participants were recruited from The Children's Hospital of Philadelphia and randomised into two groups of equal numbers using permuted blocks of random size. Participants were stratified by age, one to two years and two to 14 years to aid equal allocation. Baseline data of seizure activity was collected 28 days prior to diet initiation. There was no significant difference in participant demographics between the groups. Inclusion criteria applied were children aged one to 14 years, having one or more seizures per 28 days, tried at least three antiepileptic medications and a discontinuation of steroidal medication three months previous. Exclusion criteria applied to children with metabolic disorders, genetic disorders and known or suspected neurodegenerative disorders. Forty-two percent of children included in the study had cerebral palsy. The study aimed to compare the efficacy of fasting KD to gradual initiation KD. Primary outcome was seizure reduction and secondary outcomes were ketosis and adverse effects.

El-Rashidy 2013 (Egypt)

El-Rashidy 2013 was a single-centre RCT of 40 participants aged 12 to 36 months (mean 27.13, SD 6.63) to compare two different dietary interventions and a control group. Participants were recruited from the Paediatric Neurology Outpatient Clinic at Children's Hospital Ain Shams University and were randomised into one of three groups; MAD (15 children), classic ketogenic (4 : 1) liquid diet (10 children) and a control (polytherapy) (15 children). There was no significant difference in age or gender across the groups. The trial excluded children under the age of one year diagnosed with idiopathic epilepsy or with other systemic chronic conditions. Two children in the classic group had infantile spasms and one child in the classic group had myoclonic encephalopathy. Aims of the study were to assess efficacy and tolerability. Outcomes reported were changes in seizure frequency at three and six months, adverse effects and attrition rates.

Kossoff 2007 (USA)

Kossoff 2007 was a prospective, randomised, cross-over controlled trial of 20 participants aged three to 18 years comparing daily carbohydrate limits of 10 g and 20 g, using MAD. Participants were recruited from the John Hopkins Hospital outpatient paediatric epilepsy clinic and randomised into two groups, 10 g carbohydrate MAD (10 children) or 20 g carbohydrate MAD (10 children), which was followed for a three-month period. After this time, participants were crossed over into the other group and followed for a further three months. A return to the previous carbohydrate amount was permitted after two weeks if parents deemed seizure control to be worse. There was no significant difference in participant demographics between the groups. Inclusion criteria were aged three to 18 years, prior use of at least two anticonvulsants and daily seizures. Epilepsy syndromes included were idiopathic (15 children), Rett syndrome (two children), cortical dysplasia (two children) and tuberous sclerosis complex (one child). Exclusion criteria included children with prior experience of the diet for more than seven days, hypercholesterolaemia, kidney dysfunction, body mass index less than 3% for age and children with heart disease. The study aimed to investigate the ideal starting value of carbohydrate in the MAD. Primary outcome was seizure control and secondary outcomes were ketosis and tolerability.

Neal 2008 (UK)

Neal 2008 was a prospective, randomised, non-blinded, controlled trial of 145 participants aged two to 16 years comparing KD (classic and MCT combined) to controls over a three-month period, with a follow-on study that compared classic KD versus MCT KD over a 12-month period. Most participants were recruited from Great Ormond Street Hospital for Children, with a few participants seen in Central Middlesex Hospital and a residential centre (National Centre for Young People with Epilepsy). Participants were randomised, using a computer package, to commence a diet (classic or MCT) after a four-week baseline or after baseline and a further three months of seizure recording, with the latter group acting as the control. The study used three defined age groups to aid the randomisation between groups (two to six years, seven to 11 years and 12 to 16 years). Participant demographics were well matched between the groups. Inclusion criteria were children aged two to 16 years, with daily seizures and more than seven seizures per week, who had not responded to two or more AEDs who had not previously been treated with a KD. Exclusion criteria included hyperlipidaemia, renal stones or organic acid deficiency syndromes. Fourteen participants had Lennox-Gastaut syndrome and 11 had West syndrome. The study aimed to investigate the efficacy of the KD in comparison to a control and to compare classic KD versus MCT KD for efficacy and tolerability at three, six and 12 months. The primary outcome was efficacy, with the secondary outcome of tolerability (assessed via a questionnaire at three, six and 12 months).

Raju 2011 (India)

Raju 2011 was a randomised, non-blinded, open-label, parallel controlled trial of children aged six months to five years, with refractory epilepsy comparing a 4 : 1 and a 2.5 : 1 ratio KD. Participants were recruited from a single centre, paediatric department of a tertiary care hospital in India. Participants were randomised using a computer-generated random number table and concealment was undertaken using opaque envelopes. Thirty-eight participants were recruited, 19 received a 4 : 1 ratio KD and 19 received a 2.5 : 1 KD, with outcomes being assessed three months after dietary initiation. There were no significant differences between participant demographics at baseline. Epilepsy syndromes included were West syndrome (nine participants in 4 : 1 KD group and seven participants in 2.5 : 1 KD group), Lennox-Gastaut syndrome (eight participants in 4 : 1 KD group and nine participants in 2.5 : 1 KD group), Doose (no participants in 4 : 1 KD group and two participants in 2.5 : 1 KD group) and unclassified syndromes (two participants in 4 : 1 KD group and one participant in 2.5 : 1 KD group). Trial included participants with cerebral palsy (15 participants in 4 : 1 KD group and nine participants in 2.5 : 1 KD group). Inclusion criteria were children aged six months to five years, at least two seizures per months, despite appropriate use of at least two AED and at least one newer AED. Exclusion criteria were known or suspected inborn errors of metabolism, systemic illness or surgical remediable causes of epilepsy. Aims of the study were to compare the efficacy and tolerability of 2.5 : 1 KD versus 4 : 1 KD. Primary outcome was the proportion of participants with more than 50% reduction in seizure frequency in both groups and secondary outcome was adverse effects.

Seo 2007 (Korea)

Seo 2007 was a single-centre RCT of 76 children with intractable childhood epilepsy aged four months to 16 years comparing 3 : 1 KD and 4 : 1 KD. Participants were recruited from a paediatric epilepsy clinic in Severance Children's Hospital and were randomised into two groups, 4 : 1 KD group (40 participants) and 3 : 1 KD group (36 participants) and the diet was followed for three months. A baseline seizure frequency monitoring period was completed two months prior to commencement of KD. After a three-month period of the diet, children who were seizure free in the 4 : 1 group were recommended to change to a 3 : 1 ratio, and children who were not seizure free in the 3 : 1 group were recommended to change to a 4 : 1 ratio and re-evaluated after a further three months. There were no significant differences in participant demographics between the groups. Epilepsy syndromes included Lennox-Gastaut syndrome and study also included participants with infantile spasm. Inclusion criteria were more than four seizures per months and seizures were not controlled by at least three AEDs. Exclusion criteria were children with metabolic disorders or known or suspected neurological degenerative disorders (or both). The study aimed to compare the antiepileptic efficacy and diet tolerability of 3 : 1 and 4 : 1 KDs. Primary outcome was a reduction in seizure activity from baseline and secondary outcome was to assess tolerability.

Sharma 2013 (India)

Sharma 2013 was an open-label, parallel-group, RCT of children aged two to 14 years with refractory epilepsy comparing the MAD to a control group. This was conducted in a single, tertiary care centre. Authors noted the study design to be similar to that of Neal 2008. Participants were randomised into an intervention (MAD) or a control (normal diet) arm using computer-generated random number tables. Concealment was carried out using opaque sealed envelopes. There were 102 participants, 50 received MAD and 52 received a normal diet for a period of three months. There were no significant differences in participant demographics across the two groups. Epilepsy syndromes included Lennox-Gastaut syndrome (25 participants in MAD group and 22 participants in control group), West syndrome (nine participants in MAD group and 10 participants in control group) and myoclonic astatic epilepsy (two participants in MAD group and three participants in control group). Other inclusion criteria were two to 14 daily seizures and previous tried three AEDs. Exclusion criteria were known or suspected inborn errors of metabolism, systemic illness or motivational issues of the family that would prelude compliance. Seizure frequency was recorded for a four-week baseline period and repeated at the end of the three-month study period. Aim of the study was to evaluate the efficacy of the MAD. Outcomes reported were seizure frequency, tolerability and adverse effects.

Excluded studies

The present update excluded four studies at full-text review. Three studies were not RCTs (Freeman 1999; Hemingway 2001; Smith 2011), and one study was successfully blinded after fasting (by administration of saccharin or glucose) (Freeman 2009); however, Freeman 2009 was only for 12 days and ketosis was not completely eliminated in the glucose arm).

Risk of bias in included studies

There were seven RCTs that generated eight publications reviewing the use of ketogenic and other diets appropriate for analysis of bias. For further details please refer to Characteristics of included studies table.

Allocation

Three studies used a computer-generated method of sequence generation and allocation concealment (Neal 2008; Raju 2011; Sharma 2013), and one study used a permuted block randomisation method (Bergqvist 2005). We rated these studies at low risk of allocation bias.

The method of sequence generation and allocation concealment was unclear in three studies (El-Rashidy 2013; Kossoff 2007; Seo 2007).

Blinding

We rated all studies at high risk of performance bias and detection bias. This may be due to the design of such studies, in that blinding participants and study personnel did not occur.

Incomplete outcome data

Two studies reported comparable drop-out rates across the groups but did not complete an ITT analysis (Bergqvist 2005; Kossoff 2007). Three studies also reported comparable drop-out rates across the groups and completed an ITT analysis (Raju 2011; Seo 2007; Sharma 2013). We rated these studies at low risk of attrition bias.

One study reported a high level of participants in the control group being lost to follow-up (Neal 2008), and one study reported uneven drop-out rates across the groups and did not complete an ITT analysis (El-Rashidy 2013). We rated these studies at high risk of attrition bias.

Selective reporting

We contacted the authors of all included studies to request protocols. Two study authors provided the protocol for the included studies and on reviewing the outcomes, there was no evidence to suggest selective reporting for either study (Kossoff 2007; Neal 2008). Therefore, we rated these studies at low risk of bias. Protocols for the remaining five studies were unavailable and we rated these studies at unclear risk of selection bias (Bergqvist 2005; El-Rashidy 2013; Raju 2011; Seo 2007; Sharma 2013).

Other potential sources of bias

One study reported that three participants in one of the intervention group had other conditions; two had been diagnosed with infantile spasms and one with myoclonic encephalopathy (El-Rashidy 2013). One study reported a high level of co-morbidity among all groups and although they were comparable within this study, this may introduce bias when evaluating in a meta-analysis (Raju 2011). One study excluded children where motivational issues within the family that may impact on compliance had been identified (Sharma 2013). We rated these studies at high risk of bias.

There were no other sources of bias identified in four studies (Bergqvist 2005; Kossoff 2007; Neal 2008; Seo 2007).

Effects of interventions

See: **Summary of findings for the main comparison** Ketogenic diet or other dietary treatments for people with epilepsy

All outcomes are presented in Summary of findings for the main comparison and are described in more detail below.

Seizure freedom (100% reduction in seizure frequency)

Raju 2011 reported 26% (5/19) of participants following a 4 : 1 KD and 21% (4/19) of participants following a 2.5 : 1 KD to be seizure free at three months. Seo 2007 found a greater response rate to both ratios of the KD, reporting 55% (22/40) of participants to be seizure free after following a 4 : 1 KD for three months compared to 35% (11/36) of participants following a 3 : 1 KD. Neal 2008 reported one participant to be seizure free after three months of following a KD (classic and MCT). When comparing a fasting-onset and a gradual-onset KD, Bergqvist 2005 stated 21% (5/24) of participants of both fasting-onset and gradual-onset KD groups were seizure free at three months. For the MAD, Kossoff 2007 reported 10% (2/20) of participants to be seizure free by six months. However, the intervention group (10 g or 20 g carbohydrate per day via MAD) was not stated.

Seizure reduction (50% or greater reduction in seizure frequency)

Raju 2011 found the number of participants with greater than 50% seizure reduction after three months to be 58% (11/19) in the 4 : 1 KD group and 63% (12/19) in the 2.5 : 1 KD group; however, there was no significant difference. Seo 2007 stated 85% (34/40) of participants following a 4 : 1 KD and 72.2% (26/36) of participants following a 3 : 1 KD to have greater than 50% seizure reduction after three months. Neal 2008 reported 38% (28/73) of participants had greater than 50% seizure reduction after three months in the KD (classic and MCT) group compared to 6% (4/72) of participants in the control group (P value < 0.0001). When comparing fasting-onset and gradual-onset KD, Bergqvist 2005 found 58% (14/24) of participants in the fasting-onset KD and 67% (16/24) of participants in the gradual-onset KD group to have greater than 50% seizure reduction at three months.

When investigating the effects of MAD on seizure reduction, Sharma 2013 reported significantly higher results in the MAD group (52%) to the control (11.5%, P value = 0.001), when comparing greater than 50% seizure reduction at three months. Kossoff 2007 reported a significant difference (P value = 0.03) in seizure reduction after three months, between 10 g carbohydrate MAD and 20 g carbohydrate MAD, with 60% (6/10) of participants in the 10 g carbohydrate/day group having greater than 50% seizure reduction compared to 10% (1/10) of participants in the 20 g carbohydrate/day group.

Seo 2007 reported that antiepileptic efficacy was significantly

greater in the 4 : 1 KD group than the 3 : 1 KD group (P value = 0.041), but it was unclear as to whether this referred to seizure reduction, seizure freedom or both.

Adverse effects

All studies reported adverse effects of the dietary interventions. For those studies investigating the classical KD , the main adverse effects were gastrointestinal symptoms, including vomiting, constipation and diarrhoea (Bergqvist 2005; El-Rashidy 2013; Neal 2008; Raju 2011; Seo 2007). Seo 2007 found gastrointestinal symptoms to be significantly worse in the 4 : 1 ratio compared with the 3 : 1 ratio KD (P value = 0.038), while Neal 2008 reported vomiting to significantly affect more participants in the classical KD (45%) compared with the MCT KD group (13%, P value < 0.05). Weight loss was reported upon by two KD studies (Bergqvist 2005; Raju 2011). Raju 2011 found weight loss to affect more participants (3/19) in the 4 : 1 ratio KD group than in the 2.5 : 1 (1/19) ratio KD group. Bergqvist 2005 found gradual-onset KD participants lost significantly less weight than the fasting-onset KD group; -0.95 kg (95% CI -2.9 to 0.6) with fasting-onset KD compared to -0.3 kg (95% CI -2.1 to 1.5) with gradual-onset KD; P value = 0.006. Neal 2008 also reported statistical significance with regards to a lack of energy at three months, affecting 36% of participants in the classical KD group compared to 14% of participants in the MCT group (P value < 0.05). Other adverse effects reported by the studies in lower numbers were respiratory tract infection, infectious disease (pneumonia and sepsis), acute pancreatitis, decreased bone matrix density, gallstones, fatty liver, nephrocalcinosis, hypercholesterolaemia, status epilepticus, acidosis, dehydration, tachycardia, extended hospital stay, hunger and abdominal pain.

Adverse effects were also reported in the MAD trials (El-Rashidy 2013; Kossoff 2007; Sharma 2013). All three studies reported constipation to affect the dietary intervention groups, with 20% to 46% of participants affected. El-Rashidy 2013 reported constipation to affect 15.4% of participants in the MAD group and 25% of participants in the classic group, but no significance was reported. Sharma 2013 and El-Rashidy 2013 reported vomiting to affect 10% of participants in the MAD group and 30% of participants in the classic group. El-Rashidy 2013 also reported diarrhoea to affect more of the MAD participants than the classic KD participants (15.4% in the MAD group, 12.5% in the classic group). Kossoff 2007 found no significant difference between median weight change in the 10 g and 20 g carbohydrate MAD groups in the first three months (P value = 0.44). Other adverse effects were anorexia, lethargy, lower respiratory tract infections and hyperammonaemic encephalopathy.

Cognitive and behaviour outcomes

We found no RCTs into the effects of a KD or similar diets on psychosocial impact.

Quality of life

We found no RCTs into the effects of a KD or similar diets on quality of life.

Attrition rate

All trials experienced drop-outs.

In the studies investigating classic KD, drop-outs ranged from 10% to 20% (Bergqvist 2005; El-Rashidy 2013; Neal 2008; Raju 2011; Seo 2007). Reasons for drop-out included lack of efficacy, refusal to eat, non-acceptance of diet by other family members, along with medical conditions including acute pancreatitis, viral gastrointestinal illness, respiratory distress and increased seizure activity.

In the studies investigating the MAD, drop-out rates were between 8% and 50% (El-Rashidy 2013; Kossoff 2007; Sharma 2013). Reasons for drop-out reported by El-Rashidy 2013 and Sharma 2013 were non-acceptance of the diet and weight loss, along with medical conditions including lower respiratory tract infections and hyperammonaemic encephalopathy. Kossoff 2007 did not report reasons for drop-outs; however, they found no significant difference between 10 g and 20 g carbohydrate MAD drop-out rates (P value = 0.33).

For further details, refer to Summary of findings for the main comparison.

DISCUSSION

Summary of main results

The present update identified three additional RCTs and, therefore, this review includes seven RCTs. All of the studies assessed the efficacy of various dietary interventions for children with epilepsy. The review presented some promising, although limited, evidence for the use of KDs in epilepsy. Reported rates of seizure freedom reached 55% in a 4 : 1 KD group after three months and reported rates of seizure reduction reached 85% in a 4 : 1 KD group after three months (Seo 2007).

Interestingly, Bergqvist 2005 found no significant difference between the fasting-onset and gradual-onset KD for rates of seizure freedom and reported a greater rate of seizure reduction in the gradual-onset KD group.

Studies assessing the efficacy of the MAD reported seizure freedom rates of up to 10% and seizure reduction rates of up to 60%. One study compared the MAD to a 4 : 1 KD, but did not report rates of seizure freedom or seizure reduction (El-Rashidy 2013).

Adverse effects were fairly consistent across different dietary interventions. The most commonly reported adverse effects were gastrointestinal syndromes. It was common that adverse effects were

the reason for participants dropping out of trials. Other reasons for drop-out included lack of efficacy and non-acceptance of the diet.

Although there was some evidence for greater antiepileptic efficacy for a 4 : 1 KD over lower ratios, the 4 : 1 LD was consistently associated with more adverse effects.

No studies assessed the effect of dietary interventions of quality of life, cognitive or behavioural functioning.

Overall completeness and applicability of evidence

The present review identified only seven RCTs with a total sample size of 427 children with epilepsy. Due to the clinical, methodological heterogeneity, meta-analysis was not possible for this review. This demonstrates the limitations of the evidence for dietary interventions in people with epilepsy. Furthermore, there is a lack of consensus regarding which dietary intervention is most effective and appropriate. This highlights the need for further research in this area to address these issues.

All of the included studies assessed the efficacy of dietary interventions in children. However, the evidence for the use of dietary interventions in adults with epilepsy appears to be anecdotal. Therefore, further research is required to provide high-quality evidence for the use of dietary interventions in adults, in addition to expanding on evidence in paediatric populations.

Quality of the evidence

The quality of the evidence was low. This is due to the relatively small sample size and high risk of bias in the included studies. In addition, two of the included studies reported a high incidence of co-morbidity (Bergqvist 2005; El-Rashidy 2013).

There was considerable heterogeneity across the included studies in terms of the clinical populations, interventions and methodologies. Therefore, combined data from included studies was problematic and meta-analysis was not possible in this review. This is a limitation of this study and impacts on the quality of evidence presented.

For further details please refer to Summary of findings for the main comparison.

Potential biases in the review process

Despite the thorough search strategies, we cannot be certain that we identified and included all relevant data in this review. Should further data be identified following publication of this review, it will be incorporated into subsequent updates.

There was limited information about the included studies, in particular study protocols were unavailable for the majority of included studies, therefore decisions within the risk of bias assessment were often based on insufficient information, resulting in a number of unclear risk of bias judgements.

Agreements and disagreements with other studies or reviews

We found two prospective studies investigating the effect of KD on epilepsy in an adult population (Kossoff 2008; Moesk 2009). Kossoff 2008 investigated the effects of a MAD (30 participants), while Moesk 2009 used a classic 4 : 1 KD (nine participants). Drop-out rates varied between 30% and 77%, reportedly due feeling of hunger, dietary restrictions and lack of efficacy. Moesk 2009 reported that both of the participants who completed the study had greater than 50% seizure reduction by three months, while Kossoff 2008 reported that 47% of participants had experienced this level of seizure reduction. Both studies reported an increase in cholesterol levels. The findings of Kossoff 2008 were similar to those of the included RCTs discussed above, which may demonstrate the ability for adults to achieve a similar level of seizure reduction as that of children. However, attrition rates experienced by Moesk 2009 were considerably higher than the RCTs conducted on children, which may suggest tolerability of a 4 : 1 KD or lack of efficacy to be problematic in the adult population.

Further prospective studies with children reported similar levels of seizure reduction to those of the included RCTs (Coppola 2002; Hosain 2005). Hosain 2005 administered a KD via gastrostomy tubes and reported compliance rates of 100% (12 children), likely due to the method of delivery.

Retrospective studies found 58% (Kang 2005) and 35% (DiMario 2002) of children to have greater than 50% seizure reduction following six months of KD. However, given the time scale, direct comparison of results are difficult. Adverse effects in both studies were mild and self limited. Kang 2005 reported a 32% drop-out rate, which is slightly greater than the included RCTs, reportedly due to complications and dietary intolerances. However, four participants were also reported to had died during the study, three due to lipoid pneumonia and infectious illnesses that occurred within three months of starting a KD.

AUTHORS' CONCLUSIONS

Implications for practice

The randomised controlled trials (RCTs) discussed in this review show promising results for the use of ketogenic diets (KD) in epilepsy. However, the limited number of studies, small sample sizes and a sole paediatric population result in a poor overall quality of evidence.

All studies comparing all KD variations reported adverse effects, from short-term gastrointestinal-related disturbances, to longer-

term cardiovascular complications. The adverse effects associated with the modified Atkins KDs may initially appear lower than the classic KD, but we found no significant results.

Attrition rates remained a problem in all KDs and across all studies, reasons for this being lack of observed efficacy and dietary tolerance.

One study found no significant difference in seizure reduction between gradual-onset and fasting-onset KD, which could prove cost effective and time saving. However, further large-scale studies are required.

There was a lack of evidence to support the clinical use of KD in adults with epilepsy, therefore, further research would be of benefit.

Other more palatable but related diets, such as the modified Atkins KD, may have a similar effect on seizure control as classical KD but this assumption requires more investigation.

For people who have medically intractable epilepsy or people who are not suitable for surgical intervention, a KD remains a valid option; however, further research is required.

Implications for research

Key areas for research identified by this review are as follows:

- studies should address quality of life issues and cognitive changes using a validated scale;
- consistency in outcomes across RCTs would be beneficial to research as a limitation of the present review was that meta-analysis was not possible. It may be beneficial for future RCTs to assess seizure frequency by means of seizure reduction (greater than 50% reduction in seizures) and seizure freedom (100% reduction in seizures);
- although shorter studies (e.g. six months) provide useful evidence for the efficacy of dietary interventions, it may be useful to assess the tolerability and adverse effects of such interventions in long-term studies that follow participants for over 12 months or preferably several years;
- studies of the mechanisms of action could help determine which specific seizure types or syndromes respond better to the diets;
- further studies should address other diets, particularly those that are less restrictive (such as the modified Atkins);
- the present review highlighted a paucity of evidence for the use of the KD in adults. Therefore, future studies should investigate the use and potential adverse effects of KDs, in adults with epilepsy;
- large-scale RCTs would be of benefit.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[author-defined order]*

Bergqvist 2005

Methods	Prospective, randomised, single-centre study comparing Fast KD and Grad KD over a 3-month period. Baseline data of seizure activity was collected 28 days prior to diet initiation
Participants	48 children, 24 in each of the 2 arms, aged 1-14 years (mean 5.3, SD 2.7 years), having ≥ 1 seizures per 28 days, tried at least 3 AEDs and a discontinuation of steroidal medication 3 months previous. Study done in Philadelphia, USA. All generalised and partial seizures included
Interventions	Speed of introduction of KD: Fast KD or Grad KD
Outcomes	• Proportion of participants with > 50% seizure reduction in target seizure type • Level of ketosis • Adverse effects
Notes	In the first 6 days of the KD trial, 2 participants dropped out, 1 with pancreatitis (Fast KD) and 1 due to viral gastrointestinal illness (Grad KD). 3 further drop-outs occurred in the Fast KD prior to 3 months' follow-up, 1 due to respiratory distress and 2 due to lack of efficacy. In the Grad KD group, 1 participant withdrew due to lack of efficacy Exclusion criteria: children with metabolic disorders, genetic disorders and known or suspected neurodegenerative disorders. 42% of children included in the study had cerebral palsy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by age (1-2 years and 2-14 years); randomisation in permuted blocks of random size (2-4)
Allocation concealment (selection bias)	Low risk	Randomisation through permuted blocks of random size of groups of 2 or 4 participants in order to prevent any ability to guess the next assignment
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias)	Low risk	Similar attrition rate in both groups, numbers too small for statistical analysis 1 participant dropped out in each group

Bergqvist 2005 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Other bias	Low risk	All participants admitted received same care No other bias identified

Kossoff 2007

Methods	Prospective, randomised, cross-over controlled trial to compare daily carbohydrate limits of 10 g and 20 g, using the MAD over a 6-month period
Participants	20 children, aged 3-18 years with intractable epilepsy, with a prior use of at least 2 AEDs and experiencing daily seizures. All seizure types included. Study conducted in Baltimore USA
Interventions	MAD with randomisation either to 10 g (10 children) or 20 g (10 children) of carbohydrate and cross-over at 3 months
Outcomes	• Seizure reduction • Level of ketosis • Tolerability
Notes	3 (30%) participants dropped out in the 10 g carbohydrate/day group and 5 (50%) participants in the 20 g carbohydrate/day group by 6 months, no significance was found between the groups (P value = 0.33). Reasons for drop-out were not stated Exclusion criteria: children with prior experience of the diet for > 7 days, hypercholesterolaemia, kidney dysfunction, body mass index < 3% for age and children with heart disease

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Non-blinded
Incomplete outcome data (attrition bias)	Low risk	Greater attrition rate in 20 g carbohydrate group but not significant. 3/10 in 10 g carbohydrate and 5/10 in 20 g carbohydrate group did not complete the study. P value of 0.33

Kossoff 2007 (*Continued*)

Selective reporting (reporting bias)	Low risk	Protocol received. No evidence to suggest selective reporting
Other bias	Low risk	Same care to both groups

Neal 2008

Methods	Prospective, randomised, non-blinded, controlled trial comparing KD (classic and MCT combined) to controls over a 3-month period, with a follow-on study then compared classic KD versus MCT KD over a 12-month period. 4-week seizure baseline completed
Participants	145 children (aged 2-16 years), with daily seizures and > 7 seizures/week, who had not responded to ≥ 2 AEDs who had not previously been treated with a KD. Study conducted in the UK. All seizure types included
Interventions	Participants were randomised to commence a KD (either classic or MCT) immediately (73 participants) or after a further 3 months of seizure recording (control group, 72 participants)
Outcomes	• Reduction in seizure frequency • Tolerability
Notes	Of the 65 who commenced the diet, 10 dropped out. Of these, 6 had poor dietary tolerance, 3 withdrew due to parental unhappiness, 1 increased seizures and 1 excluded due to inadequate data. In the control group, 15 participants were excluded due to inadequate data Exclusion criteria: hyperlipidaemia, renal stones or organic acid deficiency syndromes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Minimisation method with stratification
Allocation concealment (selection bias)	Low risk	Computer program
Blinding (performance bias and detection bias) All outcomes	High risk	Non-blinded
Incomplete outcome data (attrition bias)	High risk	High level of missing data in control group
Selective reporting (reporting bias)	Low risk	Initial application protocol received
Other bias	Low risk	Same care to both groups

Seo 2007

Methods	Single-centre randomised controlled trial, to compare 3 : 1 and 4 : 1 KD. Baseline period lasted 2 months. After a 3-month period of the diet, participants who were seizure free in the 4 : 1 group were recommended to change to a 3 : 1 ratio, and participants who were not seizure free in the 3 : 1 group were recommended to change to a 4 : 1 ratio and were re-evaluated after a further 3 months
Participants	76 children (aged 4 months to 16 years), with > 4 seizures/months and seizures were not controlled by at least 3 AEDs. Study done in Korea. All seizure types included
Interventions	Participants were randomised into 2 groups, 4 : 1 KD group (40 participants) and 3 : 1 KD group (36 participants) and the diet was followed for 3 months
Outcomes	• Seizure reduction rate • Tolerability
Notes	6 participants dropped out in both of the original groups. 2 of participants in the 3 : 1 group dropped out due to diet intolerance and 1 participant in the 4 : 1 KD group. 1 participant in the 3 : 1 group dropped out due to acute pancreatitis. Other reasons for drop-out of participants were not stated Exclusion criteria: children with metabolic disorders, known or suspected neurological degenerative disorders, or both

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although study stated that participants were randomly assigned to each group, there was no information regarding how randomisation was achieved
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	High risk	Study did not report whether blinding was undertaken although it seems from the design of the study that blinding would not be possible
Incomplete outcome data (attrition bias)	Low risk	Number of drop-outs and reasons for drop-outs were reported and an intention-to-treat analysis was completed
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Other bias	Low risk	No other sources of bias identified

El-Rashidy 2013

Methods	Single-centre randomised controlled trial to compare the 2 different dietary interventions (MAD and classic KD in form of 4 : 1 liquid diet) and a control group (AED)
Participants	40 children aged 12-36 months (mean 27.13, SD 6.63) with symptomatic intractable epilepsy. Study done in Egypt
Interventions	Participants were randomised into 1 of 3 groups; MAD (15 participants), KD (10 participants) and control (15 participants). Data were collected at 3 and 6 months
Outcomes	• Seizure reduction rate • Adverse effects • Attrition rate
Notes	2 participants in the MAD group dropped out of the trial as they could not accept the diet and experienced weight loss. From the results, it could be inferred that these participants dropped out between the 3- and 6-month reviews. 2 participants from the classic KD group dropped out due to intolerance; however, it was unclear when these participants dropped out Exclusion criteria: children < 1 year, diagnosed with idiopathic epilepsy or with other systemic chronic conditions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although the paper stated that participants were 'randomly assigned', there was no information regarding how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	There was no information suggesting whether allocation was concealed or not
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not discussed in this paper but considering the design of the study, binding of participants and study personnel does not seem possible
Incomplete outcome data (attrition bias)	High risk	Study attrition was reported but intention-to-treat analysis was not carried out. Reasons for drop-outs were likely to be related to interventions
Selective reporting (reporting bias)	Unclear risk	Emailed author regarding protocol, awaiting response from co-authors. Protocol currently unavailable

Other bias	High risk	No measure of seizure frequency reported at baseline. 20% of participants in the classic KD group had infantile spasms

Raju 2011

Methods	Randomised, non-blinded, open-label, parallel controlled trial, to compare a 4 : 1 and a 2.5 : 1 ratio KD over a 3-month period
Participants	38 children aged 6 months to 5 years, with refractory epilepsy, at least 2 seizures/month, despite appropriate use of at least 2 AED and at least 1 newer AED. Study done in India
Interventions	Participants were randomised into 1 of 2 groups; a 4 : 1 ratio KD (19 participants) and 2.5 : 1 KD (19 participants) and followed for 3 months
Outcomes	• > 50% reduction in seizure frequency • Adverse effects
Notes	3 participants in each group dropped out of the study. Reasons for drop-out in 4 : 1 KD group were refusal to eat, unsatisfactory seizure control and non-acceptance by other family members. In 2.5 : 1 KD group, 2 participants dropped out due to unsatisfactory seizure control and 1 due to refusal to eat Exclusion criteria: known or suspected inborn errors of metabolism, systemic illness or surgical remediable causes of epilepsy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was computer generated
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes were used to conceal allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Study was unblinded
Incomplete outcome data (attrition bias)	Low risk	Attrition was reported and was fairly equal across the groups. Intention-to-treat analysis carried out
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Other bias	High risk	Participants were all < 18 years of age and there was a high rate of co-morbidity

Sharma 2013

Methods	Open-label, single-centre, parallel-group, randomised, controlled trial, to compare the MAD to a control group over a 3-month period. Authors noted the study design to be similar to that of Neal 2008. There was a 4-week baseline of seizure frequency
Participants	102 children aged 2-14 years with refractory epilepsy and 2-14 daily seizures, having previously tried 3 AEDs. Study conducted in India
Interventions	Randomised into 1 of 2 groups; MAD (50 participants) or a normal diet (52 participants) for a period of 3 months
Outcomes	• Seizure frequency • Tolerability • Adverse effects
Notes	4 children reported to have dropped out of the trial. 2 secondary to lower respiratory tract infections, 1 secondary to hyperammonaemic encephalopathy and 1 as the child and family found the diet too restrictive. In the control group, 3 participants were lost to follow-up Exclusion criteria: known or suspected inborn errors of metabolism, systemic illness or motivational issues the family that would prelude compliance

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation sequence was computer generated
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes were used to conceal allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias)	Low risk	Study attrition reported and intention-to-treat analysis carried out
Selective reporting (reporting bias)	Low risk	Protocol available 15 August 2015 (clinicaltrials.gov/ct2/show/NCT00836836)
Other bias	High risk	Excluded participants where motivational issues within the family

AED: antiepileptic drug; Fast FD: fasting-onset ketogenic diet; Grad KD: gradual-onset ketogenic diet; KD: ketogenic diet; MAD: modified Atkins diet; MCT: medium-chain triglyceride; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Freeman 1999	Outcome measures did not match inclusion criterion as duration of study was 12 days
Freeman 2009	Study was very brief and lasted only 12 days - duration of the study did not fit entry criteria
Hemingway 2001	Not a randomised controlled trial
Kang 2011	Refractory infantile spasm population, outcome measures did not match inclusion criteria
Smith 2011	Not a randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Hulshof 2014

Trial name or title	The |Modified Atkins Diet for Epilepsy: an RCT
Methods	A single-centre, parallel, unblinded randomised controlled trial
Participants	Aimed to recruit 54 people, aged > 18 years, adults with refractory epilepsy that was controlled by 2 AEDs. Included participants must have had ≥ 2 seizures/month and have moderate-to-severe intellectual disability. Potential participants were excluded if they had undergone epilepsy surgery in the last 6 months or were awaiting surgery; underwent implantation of vagal nerve stimulation in the last 6 months; have used the MAD or KD for > 7 days in the last year
Interventions	Intervention group treated with the MAD for at least 4 months, with a total follow-up of at least 6 months Control group comprised a waiting list in which participants can begin the MAD diet after the 4-month trial period, the control group can be started on the MAD as well, in which efficacy, tolerability and safety will also be evaluated
Outcomes	Primary outcomes: • Number of responders 4 months after randomisation, compared between the intervention and the control group. Responder is defined by > 50% reduction in seizure frequency Secondary outcomes: • Retention of the diet; change in daily functioning; feasibility of the MAD in this population and setting; adverse events attributable to the MAD; predictive factors of efficacy of the diet
Starting date	8 January 2014
Contact information	H.M.Hulshof-3@umcutrecht.nl
Notes	On the 28 July 2015, the study authors reported that this trial was ongoing and was now recruiting from an additional site. They expect to end recruitment at the end of July 2016

Yoon 2014

Trial name or title	Comparison of Ketogenic Diet and Modified Atkins Diet in Children with Epilepsy: a Randomized Controlled Trial
Methods	Open-label, randomised controlled trial
Participants	108 children aged 2-16 years who had at least 1 seizure/week or > 4 seizures/month, had failed to respond to at least 2 AEDs and had not been treated previously with the diet therapy
Interventions	KD vs. MAD assessed at 1, 3 and 6 months
Outcomes	Primary endpoint was a reduction in seizures at 6 months on diet
Starting date	
Contact information	HIPO0207@yuhs.ac
Notes	On 24 July 2015, study authors reported that the full-text paper reporting the results of this study was under review with *Epilepsia*

AED: antiepileptic drug; KD: ketogenic diet; MAD: modified Atkins diet.

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialized Register search strategy

#1 MeSH DESCRIPTOR Diet Therapy Explode All
#2 MeSH DESCRIPTOR Fasting Explode All
#3 ketogenic* or diet? or dieting
#4 #1 OR #2 OR #3

Appendix 2. CENTRAL via CRSO search strategy

#1 MESH DESCRIPTOR Epilepsy EXPLODE ALL TREES WITH QUALIFIERS DH
#2 MESH DESCRIPTOR Seizures EXPLODE ALL TREES WITH QUALIFIERS DH
#3 #1 OR #2
#4 MESH DESCRIPTOR Diet Therapy EXPLODE ALL TREES
#5 MESH DESCRIPTOR Fasting EXPLODE ALL TREES
#6 (ketogenic* or diet? or dieting):TI,AB,KY
#7 #4 OR #5 OR #6
#8 (epilep* OR seizure* OR convuls*):TI,AB,KY
#9 MESH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#10 MESH DESCRIPTOR Seizures EXPLODE ALL TREES
#11 #8 OR #9 OR #10
#12 #7 AND #11
#13 #3 OR #12

Appendix 3. MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).
1. exp Epilepsy/dh [Diet Therapy]
2. exp Seizures/dh [Diet Therapy]
3. 1 or 2
4. exp Diet Therapy/
5. exp Fasting/
6. (ketogenic$ or diet? or dieting).tw.
7. 4 or 5 or 6
8. exp Epilepsy/
9. exp Seizures/
10. (epilep$ or seizure$ or convuls$).tw.
11. 8 or 9 or 10
12. exp *Pre-Eclampsia/ or exp *Eclampsia/
13. 11 not 12
14. 7 and 13
15. 3 or 14

16. (randomized controlled trial or controlled clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
17. clinical trials as topic.sh.
18. trial.ti.
19. 16 or 17 or 18
20. exp animals/ not humans.sh.
21. 19 not 20
22. 15 and 21

WHAT'S NEW

Last assessed as up-to-date: 30 March 2015.

Date	Event	Description
30 March 2015	New citation required but conclusions have not changed	Three new studies (El-Rashidy 2013; Raju 2011; Sharma 2013) have been included. Conclusions are unchanged
30 March 2015	New search has been performed	Searches updated 30 March 2015

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 3, 2003

Date	Event	Description
28 May 2012	Amended	New Summary of Findings table added.
28 January 2012	New citation required but conclusions have not changed	Review updated.
28 January 2012	New search has been performed	This review has been updated. Four new RCTs have been included. Seven prospective studies and four retrospective studies were also identified

CONTRIBUTIONS OF AUTHORS

Kirsty Martin was responsible for the update of this review.

Cerian F Jackson provided support for the update of this review.

Robert Levy provided expert opinion and feedback.

Paul Cooper provided expert opinion and feedback.

Pratima Giri contributed to previous versions.

Jennifer Weston contributed to previous versions.

DECLARATIONS OF INTEREST

KM: none known

CJ: none known

RL: none known

PC: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The background and method sections have been updated in accordance with changes to Cochrane requirements.

Searching other results now states that forward and backward referencing will be completed on included studies and experts in the area will be contacted.

INDEX TERMS

Medical Subject Headings (MeSH)

Diet, Carbohydrate-Restricted [methods]; Dietary Carbohydrates [*administration & dosage]; Dietary Fats [*administration & dosage]; Epilepsy [*diet therapy]; Intention to Treat Analysis; Ketogenic Diet [*methods]; Prospective Studies; Randomized Controlled Trials as Topic; Retrospective Studies

MeSH check words

Adolescent; Child; Humans