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Ketogenic diets for drug-resistant epilepsy (Review)

Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN

Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN.
Ketogenic diets for drug-resistant epilepsy.
Cochrane Database of Systematic Reviews 2020, Issue 6. Art. No.: CD001903.
DOI: 10.1002/14651858.CD001903.pub5.

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[Intervention Review]

Ketogenic diets for drug-resistant epilepsy

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Editorial group: Cochrane Epilepsy Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2020.

Citation: Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. *Cochrane Database of Systematic Reviews* 2020, Issue 6. Art. No.: CD001903. DOI: 10.1002/14651858.CD001903.pub5.

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ABSTRACT

Background

Ketogenic diets (KDs) are high in fat and low in carbohydrates and have been suggested to reduce seizure frequency in people with epilepsy. Such diets may be beneficial for children with drug-resistant epilepsy.

This is an update of a review first published in 2003, and last updated in 2018.

Objectives

To assess the effects of ketogenic diets for people with drug-resistant epilepsy.

Search methods

For this update, we searched the Cochrane Register of Studies (CRS Web) and MEDLINE (Ovid, 1946 to 26 April 2019) on 29 April 2019. The Cochrane Register of Studies includes the Cochrane Epilepsy Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), and randomised controlled trials (RCTs) from Embase, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). We imposed no language restrictions. We checked the reference lists of retrieved studies for additional relevant studies.

Selection criteria

RCTs or quasi-RCTs of KDs for people of any age with drug-resistant epilepsy.

Data collection and analysis

Two review authors independently applied predefined criteria to extract data and evaluated study quality. We assessed the outcomes: seizure freedom, seizure reduction (50% or greater reduction in seizure frequency), adverse effects, cognition and behaviour, quality of life, and attrition rate. We incorporated a meta-analysis. We utilised an intention-to-treat (ITT) population for all primary analyses. We presented the results as risk ratios (RRs) with 95% confidence intervals (CIs).

Main results

We identified 13 studies with 932 participants; 711 children (4 months to 18 years) and 221 adults (16 years and over).

We assessed all 13 studies to be at high risk of performance and detection bias, due to lack of blinding. Assessments varied from low to high risk of bias for all other domains. We rated the evidence for all outcomes as low to very low certainty.

Ketogenic diets versus usual care for children

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Seizure freedom (RR 3.16, 95% CI 1.20 to 8.35; P = 0.02; 4 studies, 385 participants; very low-certainty evidence) and seizure reduction (RR 5.80, 95% CI 3.48 to 9.65; P < 0.001; 4 studies, 385 participants; low-certainty evidence) favoured KDs (including: classic KD, medium-chain triglyceride (MCT) KD combined, MCT KD only, simplified modified Atkins diet (MAD) compared to usual care for children. We are not confident that these estimated effects are accurate. The most commonly reported adverse effects were vomiting, constipation and diarrhoea for both the intervention and usual care group, but the true effect could be substantially different (low-certainty evidence).

Ketogenic diet versus usual care for adults

In adults, no participants experienced seizure freedom. Seizure reduction favoured KDs (MAD only) over usual care but, again, we are not confident that the effect estimated is accurate (RR 5.03, 95% CI 0.26 to 97.68; P = 0.29; 2 studies, 141 participants; very low-certainty evidence). Adults receiving MAD most commonly reported vomiting, constipation and diarrhoea (very low-certainty evidence). One study reported a reduction in body mass index (BMI) plus increased cholesterol in the MAD group. The other reported weight loss. The true effect could be substantially different to that reported.

Ketogenic diet versus ketogenic diet for children

Up to 55% of children achieved seizure freedom with a classical 4:1 KD after three months whilst up to 85% of children achieved seizure reduction (very low-certainty evidence). One trial reported a greater incidence of seizure reduction with gradual-onset KD, as opposed to fasting-onset KD. Up to 25% of children were seizure free with MAD and up to 60% achieved seizure reduction.

Up to 25% of children became seizure free with MAD and up to 60% experienced seizure reduction. One study used a simplified MAD (sMAD) and reported that 15% of children gained seizure freedom rates and 56% achieved seizure reduction. We judged all the evidence described as very low certainty, thus we are very unsure whether the results are accurate.

The most commonly reported adverse effects were vomiting, constipation and diarrhoea (5 studies, very low-certainty evidence). Two studies reported weight loss. One stated that weight loss and gastrointestinal disturbances were more frequent, with 4:1 versus 3:1 KD, whilst one reported no difference in weight loss with 20 mg/d versus 10 mg/d carbohydrates. In one study, there was a higher incidence of hypercalcuria amongst children receiving classic KD compared to MAD. All effects described are unlikely to be accurate.

Ketogenic diet versus ketogenic diet for adults

One study randomised 80 adults (aged 18 years and over) to either MAD plus KetoCal during the first month with MAD alone for the second month, or MAD alone for the first month followed by MAD plus KetoCal for the second month. No adults achieved seizure freedom. More adults achieved seizure reduction at one month with MAD alone (42.5%) compared to MAD plus KetoCal (32.5%), however, by three months only 10% of adults in both groups maintained seizure reduction. The evidence for both outcomes was of very low certainty; we are very uncertain whether the effects are accurate.

Constipation was more frequently reported in the MAD plus KetoCal group (17.5%) compared to the MAD only group (5%) (1 study, very low-certainty evidence). Diarrhoea and increase/change in seizure pattern/semiology were also commonly reported (17.5% to 20% of participants). The true effects of the diets could be substantially different to that reported.

Authors' conclusions

The evidence suggests that KDs could demonstrate effectiveness in children with drug-resistant epilepsy, however, the evidence for the use of KDs in adults remains uncertain. We identified a limited number of studies which all had small sample sizes. Due to the associated risk of bias and imprecision caused by small study populations, the evidence for the use of KDs was of low to very low certainty.

More palatable but related diets, such as the MAD, may have a similar effect on seizure control as the classical KD, but could be associated with fewer adverse effects. This assumption requires more investigation. For people who have drug-resistant epilepsy or who are unsuitable for surgical intervention, KDs remain a valid option. Further research is required, particularly for adults with drug-resistant epilepsy.

PLAIN LANGUAGE SUMMARY

Ketogenic diets for drug-resistant epilepsy

Background

Epilepsy is a disorder where recurrent seizures are caused by abnormal electrical discharges from the brain. In most people, seizures can be controlled by one or more antiepileptic medicines. For people who continue to have seizures (drug-resistant epilepsy) a special diet, a ketogenic diet, may be considered. Ketogenic diets are high in fat and low in carbohydrate.

This review looked at the effects of ketogenic diets on seizure control, learning and memory, and behaviour. We also investigated the side effects of the diet and the number of people who withdrew from studies, plus the reasons why.

Study characteristics

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We searched medical databases for clinical trials of adults or children with epilepsy, where a ketogenic diet was compared with other treatments. We found 13 trials, with 932 participants. The trials were between two and 16 months long.

Key results

Children given ketogenic diets may be up to three times more likely to achieve seizure freedom and up to six times more likely to experience a 50% or greater reduction in seizure frequency compared to children given their usual care. Although the rates of seizure freedom reported by most of the studies were fairly modest, in one study over half of the children given a classical ketogenic diet became seizure free. This rate reduced to only 15% of children achieving seizure freedom when they were given a less restrictive modified Atkins diet. Another study reported that 85% of children given a classical ketogenic diet had a significant reduction in their number of seizures compared to only around half of children who received a modified Atkins diet. One study, however, found similar effects on seizure control with the better tolerated modified Atkins diet as with the more restrictive ketogenic diet, highlighting that more research is required.

There were no reports of seizure freedom in adults following ketogenic diets, however, adults given ketogenic diets may be up to five times more likely to experience a 50% or greater reduction in seizure frequency.

All studies reported people dropping out due to lack of improved seizures and poor tolerance of diet. Adults following ketogenic diets may be up to five times more likely to drop out of studies compared with usual care. For children, dropout rates may be similar in ketogenic diet and usual care treatment groups.

One study reported the effects of ketogenic diets on quality of life, learning, memory, and behaviour in children. The study suggested no difference in the quality of life of children following a ketogenic diet and those receiving usual care. Children following ketogenic diets were suggested to be more active, more productive and less anxious, but more research is needed.

Certainty of the evidence

The trials only included a small number of people and their methods were unclear. We therefore judged the certainty of the evidence to be low to very low. This means that we are not confident that the results described are accurate of the true effect of ketogenic diets in people with epilepsy.

This evidence is current to April 2019.

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Summary of findings 1. Ketogenic diet (KD) compared to usual care for children with drug-resistant epilepsy

Ketogenic diet (KD) compared to usual care for children with drug-resistant epilepsy

Patient or population: children (aged 1 to 18 years) with drug-resistant epilepsy
Setting: outpatients
Intervention: KD (including: classic KD (4:1), classic KD and MCT KD combined, MAD, MCT KD, and sMAD)
Comparison: control intervention (usual care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with KD				
Seizure freedom (100% reduction in seizure frequency) Follow-up: 3 months to 4 months	**Study population**		**RR 3.16** (1.20 to 8.35)	**385** (4 RCTs)	⊕⊖⊖⊖ **Very low** [a,c]	
	21 per 1000	66 per 1000 (25 to 174)				
50% or greater reduction in seizure frequency Follow-up: 3 months to 4 months	**Study population**		**RR 5.80** (3.48 to 9.65)	**385** (4 RCTs)	⊕⊕⊖⊖ **Low** [a,b]	
	78 per 1000	453 per 1000 (272 to 754)				
Adverse effects Follow-up: 3 months to 4 months	The most frequent adverse effects reported by participants in dietary intervention groups were: vomiting, constipation and diarrhoea. These adverse effects were also commonly reported by participants in the usual care groups. Other less common adverse effects reported included: dysphagia, lethargy, lower respiratory tract infection, hyperammonaemic encephalopathy, weight loss, nausea, infections (pneumonia, sepsis), acute pancreatitis, decrease in bone matrix density, gallstones, fatty liver, nephrocalcinosis, hypercholesterolaemia, status epilepticus, acidosis, dehydration, tachycardia, hypoglycaemia, hunger, abdominal pain, clinically relevant reduction in height, hypercalcinaemia and renal stones.			**425** (5 RCTs)	⊕⊕⊖⊖ **Low** [a,d]	
Cognition and behaviour Follow-up: 4 months	Children randomised to KD were more active (P = 0.005), more productive (P = 0.039) and less anxious (P = 0.049) after four months, than children randomised to the usual care group.			**57** (1 RCT)	⊕⊖⊖⊖ **Very low** [a,c,d]	

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Quality of life Follow-up: 4 months	There were no significant differences in QALYs between KD and usual care treatment groups at four or 16 months.			**57** (1 RCT)	⊕⊖⊖⊖ **Very low** [a,c,d]
Treatment withdrawal Follow-up: 3 months to 6 months	**Study population**		**RR 1.08** (0.74 to 1.57)	**425** (5 RCTs)	⊕⊕⊖⊖ **Low** [a,b]
	184 per 1000	198 per 1000 (136 to 288)			

*__The risk in the intervention group__ (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; **QALY:** quality of life-adjusted year; **RCT:** randomised controlled trial **RR:** risk ratio; **sMAD**: simplified modified Atkins diet

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to risk of bias: some included studies were not blinded, had missing data or unclear methodological details reported.
[b]Downgraded once due to imprecision: low overall sample size, plus low number of events (< 200). Confidence in results from small number of participants is low.
[c]Downgraded twice due to imprecision: low overall sample size, plus low number of events (< 50). Confidence in results from small number of participants is low.
[d]Downgraded once due to imprecision: a narrative synthesis was used for this outcome.

Summary of findings 2. Ketogenic diet (KD) compared to usual care for adults with drug-resistant epilepsy

Ketogenic diet (KD) compared to usual care for adults with drug-resistant epilepsy

Patient or population: adults (aged 16 years and over) with drug-resistant epilepsy
Setting: outpatients
Intervention: KD (modified Atkins diet (MAD))
Comparison: control intervention (usual care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with KD				
Seizure freedom	No adults in either the MAD or the usual care group achieved seizure freedom, therefore we were unable to calculate an effect.			**141** (2 RCTs)	⊕⊖⊖⊖ **Very low** [a,b]	

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Follow-up: 2 months to 3 months					
50% or greater reduction in seizure frequency Follow-up: 2 months to 3 months	**Study population**		**RR 5.03** (0.26 to 97.68)	**141** (2 RCTs)	⊕⊖⊖⊖ **Very low** [a,b,d]
	29 per 1000	144 per 1000 (7 to 1000)			
Adverse effects Follow-up: 2 months to 3 months	Common adverse effects reported by participants receiving MAD were: vomiting, constipation and diarrhoea. One study reported a significant reduction in BMI, as well as an increase in cholesterol in the MAD group, whilst the other study reported significant weight loss. Other adverse effects included: anorexia, lethargy, lower respiratory tract infections and hyperammonaemic encephalopathy.			**141** (2 RCTs)	⊕⊖⊖⊖ **Very low** [a,b,c]
Cognition and behaviour	Outcome not reported				N/A
Quality of life	Outcome not reported				N/A
Treatment withdrawal Follow-up: 2 months to 3 months	**Study population**		**RR 5.38** (0.42 to 69.53)	**141** (2 RCTs)	⊕⊖⊖⊖ **Very low** [a,b,d]
	86 per 1000	461 per 1000 (36 to 1000)			

*__The risk in the intervention group__ (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).

BMI: body mass index; **CI:** confidence interval; **KD**: ketogenic diet;**MAD**: modified Atkins diet; **NA**: not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to risk of bias: some included studies were not blinded, had missing data or unclear methodological details reported.
[b]Downgraded twice due to imprecision: low overall sample size, plus low number of events (< 50). Confidence in results from small number of participants is low.
[c]Downgraded once due to imprecision: a narrative synthesis was used for this outcome.
[d]Downgraded once due to inconsistency: significant statistical heterogeneity was detected ($P < 0.10$ and $I^2 > 50\%$).

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Summary of findings 3. Ketogenic diets (KDs) compared with other KDs for children with drug-resistant epilepsy

Ketogenic diets (KDs) compared with other KDs for children with drug-resistant epilepsy

Patient or population: children (aged 4 months to 16 years) with drug-resistant epilepsy
Settings: outpatients
Intervention: KDs (fast KD, modified Atkins diet (MAD), MAD with 10 g per day carbohydrate limit, 4:1 (classic) KD)

Control: other KDs (gradual KD, classic KD, MAD with 20 g per day carbohydrate limit, 2.5:1 KD, 3:1 KD)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other KDs	KDs				
Seizure freedom (100% reduction in seizure frequency) Follow-up: 3 months to 6 months	Proportion of children achieving seizure freedom ranged from 10% to 25% on MAD. There was no information about whether the seizure freedom varied depending on the restriction of carbohydrates (10 mg/d versus 20 mg/d). 21% of children on 2:5:1 KD achieved seizure freedom compared to 26% to 55% on 4:1 KD and 35% on the 3:1 KD. 33% of children on a classic KD were seizure free at 3 months. 21% of both children randomised to fasting-onset KD and gradual-onset KD became seizure free.		Not estimable	286 (5 RCTs)	⊕⊖⊖⊖ **Very low** a,b,d,e	Due to heterogeneity of both interventions and methodology, meta-analysis could not be conducted
Seizure reduction (50% or greater reduction in seizure frequency) Follow-up: 3 months to 6 months	The proportion of children achieving seizure reduction ranged from 42% to 60% on MAD, however, the rate decreased to 10% when daily carbohydrate intake was increased to 20 mg/d, compared to 10 mg/d. 43% of children on a classic KD achieved seizure reduction with 58% to 85% on 4:1 KD, 72% on the 3:1 KD and 63% on 2.5:1 KD. 58% on the fasting-onset KD and 67% on the gradual-onset KD attained 50% or greater reduction in seizure frequency.		Not estimable	286 (5 RCTs)	⊕⊖⊖⊖ **Very low** a,b,c,e	
Adverse effects Follow-up: 3 months to 6 months	The most frequent adverse effects reported by children were: vomiting, constipation and diarrhoea. Two studies reported weight loss, with one study stating that weight loss and gastrointestinal disturbances were more frequently reported with 4:1 KD versus 3:1 KD. One study reported a significantly high incidence rate for hypercalcuria amongst children receiving classic KD compared to MAD at three months. There was no significant difference in weight loss between treatment groups given 20 mg/d versus 10 mg/d carbohydrates.		Not estimable	286 (5 RCTs)	⊕⊖⊖⊖ **Very low** a,b,c,e	

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	Other adverse effects reported included: dysphagia, lethargy, lower respiratory tract infection, hyperammonaemic encephalopathy, nausea, infections (pneumonia, sepsis), acute pancreatitis, decrease in bone matrix density, gallstones, fatty liver, nephrocalcinosis, hypercholesterolaemia, status epilepticus, acidosis, dehydration, tachycardia, hypoglycaemia, hunger,abdominal pain, clinically relevant reduction in height, hypercalcinaemia and renal stones.			
Cognition and behaviour Follow-up: NA	Outcome not reported			NA
Quality of life Follow-up: NA	Outcome not reported			NA
Attrition rate Follow-up: 3 months to 6 months	Proportion of individuals withdrawing from KD groups were: 8% gradual-onset KD; 16% on 2:5:1 KD and 4:1 KD; 17% on fasting-onset KD and on the 3:1 KD; 32% on MAD; and 33% on the classic KD.	Not estimable	286 (5 RCTs)	⊕⊝⊝⊝ **Very low** [a,b,c,e]

*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; **NA**: not applicable; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to risk of bias: some included studies were not blinded, had missing data or unclear methodological details reported.
[b]Downgraded once due to inconsistency: studies are heterogeneous with regards to interventions examined and comparisons made.
[c]Downgraded once due to imprecision: low overall sample size, plus low number of events (< 200). Confidence in results from small number of participants is low.
[d]Downgraded twice due to imprecision: very low overall sample size, plus low number of events (< 50). Confidence in results from small number of participants is low.
[e]Downgraded once due to imprecision: a narrative synthesis was used for this outcome.

Summary of findings 4. Ketogenic diets (KDs) compared with other KDs for adults with drug-resistant epilepsy

Ketogenic diets (KDs) compared with other KDs for adults with drug-resistant epilepsy

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Patient or population: adults (aged 18 years and over) with drug-resistant epilepsy
Settings: outpatients
Intervention: KDs (modified Atkins diet (MAD) plus KetoCal during first month, followed by MAD alone in second month)

Control: other KDs (MAD alone in the first month, followed by MAD plus KetoCal during second month)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other KDs	KDs				
Seizure freedom (100% reduction in seizure frequency) Follow-up: 6 months	No adult participants achieved seizure freedom with either MAD plus KetoCal in month one (intervention) or MAD plus KetoCal in month two (control).		Not estimable	80 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b,c]	No adults in either the MAD or the control group achieved seizure freedom; therefore we were unable to calculate an effect.
Seizure reduction (50% or greater reduction in seizure frequency) Follow-up: 6 months	The proportion of adults achieving 50% or greater reduction in seizure frequency at one month was 32.5% for the intervention group (MAD plus KetoCal month one) and 42.5% for the control (MAD plus KetoCal month two). This decreased to 25% versus 32.5%, respectively at two months. At three months, 10% of adults in both groups maintained a 50% or greater reduction in seizure frequency.		Not estimable	80 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b,c]	
Adverse effects Follow-up: 6 months	Constipation was reported more frequently by adults in the MAD plus KetoCal group (17.5%) compared to MAD only treatment group (5%). Diarrhoea and increase/change in seizure pattern/semiology were also commonly reported (17.5% to 20% of participants). Other less commonly reported adverse effects included: abdominal pain, headache, irregular menses, halitosis, somnolence, nephrolithiasis, kidney infection, nausea, easy bruising, vaginal odour and brittle hair/nails.		Not estimable	80 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b,c]	
Cognition and behaviour	Outcome not reported				NA	
Quality of life	Outcome not reported				NA	

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Attrition rate Follow-up: 6 months	12.5% of adults withdrew from the intervention group (MAD plus KetoCal month one) compared to 32.5% from the control group (MAD plus KetoCal month two).	Not estimable	80 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b,c]

*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; **NA:** not applicable; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to risk of bias: the study did not appear to be blinded, it was not clear whether there was missing data. Unclear methodological details were reported.
[b]Downgraded twice due to imprecision: low overall sample size, plus low number of events (< 50). Confidence in results from small number of participants is low. Unable to conduct a meta-analysis.
[c]Downgraded once due to imprecision: a narrative synthesis was used for this outcome.

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BACKGROUND

This is an update of a review first published in 2003 (Levy 2003), and last updated in 2018 (Martin-McGill 2018).

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 (AEDs), approximately 30% of people with epilepsy will continue to have seizures, even when taking multiple AEDs; a condition referred to as drug-resistant epilepsy (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 drug-resistant epilepsy, and further evidence for alternative interventions is needed.

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 combined. KDs have been described as unpalatable and difficult to tolerate, thus leading to poor compliance. Therefore, several diets have been developed to improve palatability, including those of lower ratios (such as 3:1), the medium-chain triglyceride (MCT) KD (Huttenlocher 1971), and the modified Atkins diet (MAD). The MCT KD allows for an increase in carbohydrate and protein due to the potential to increase ketone levels through the inclusion of MCT fats. The MAD, adapted from the Aktins diet initially used for weight reduction (Atkins 1972), restricts carbohydrate to 10 g to 20 g per day, and is considered less restrictive than classical KDs.

Prior to the introduction of anticonvulsant medications (Merritt 1938), KDs were 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 drug-resistant to multiple AEDs. The classical KD and other more palatable versions have a positive effect on infantile spasms, severe myoclonic epilepsy, tuberous sclerosis complex (Kossoff 2005), and children with drug-resistant status epilepticus (O'Connor 2014).

How the intervention might work

Although the anticonvulsant effects of KDs remain unclear, numerous biochemical theories have been suggested for the possible action of the diet. These include the anticonvulsant effects of elevated ketone bodies, elevated fatty acids and reduced glucose levels (Bough 2007), with further research ongoing in this field.

Why it is important to do this review

Despite the use of KDs for adults and children with drug-resistant epilepsy within clinical settings, the number of high-quality RCTs has been limited. Therefore, the evidence base for this intervention has been unclear. This review aims to assess the effectiveness of KDs when considering evidence from RCTs, across all healthcare settings, for both adults and children with drug-resistant epilepsy. In this review we will include RCTs which compare KDs to usual care and one KD to another KD.

OBJECTIVES

To assess the effects of ketogenic diets for people with drug-resistant epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) or quasi-RCTs of ketogenic diet (KD) interventions for people with drug-resistant epilepsy, with a minimum study period of one month.

Types of participants

Adults and children with a diagnosis of drug-resistant epilepsy, irrespective of their seizure type or epilepsy syndrome. We did not predefine what we considered to be adult or paediatric trial populations. Instead, we followed the classification set by each individual trial author team. Reflective of clinical services, in some cases adults were defined as aged 16 years and over, whilst all paediatric studies only included participants aged 18 years and under.

For the first time, we also attempted to report on epilepsy populations with intellectual disabilities.

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 main types of diet are:
  - classical KD;
  - medium-chain triglyceride (MCT) KD;
  - modified Atkins diet (MAD); and
  - low glycaemic index treatment (LGIT).
- We also included studies which compared different types of KDs or different KD regimes (fasting versus gradual initiation).

Usual care group

- Placebo/usual/sham diet given as a standard 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);

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- 50% or greater reduction in seizure frequency (seizure reduction);
- Adverse effects.

Secondary outcomes

- Cognition and behaviour, 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

We ran searches for the original review in March 2005 and subsequent searches in July 2007, January 2010, June 2011, March 2015, April 2017, and April 2019. For the most recent update of this review we searched:

- the Cochrane Register of Studies (CRS Web, 29 April 2019) using the search strategy outlined in Appendix 1;
- MEDLINE (Ovid, 1946 to April 26, 2019) using the search strategy outlined in Appendix 2.

The Cochrane Register of Studies (CRS Web) includes the Cochrane Epilepsy Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), and randomised controlled trials from Embase, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).

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 field to enquire about other relevant studies.

Data collection and analysis

Selection of studies

Two review authors (KMM, RB) independently reviewed the titles and abstract of the studies identified by the electronic searches and removed studies that did not meet the inclusion criteria. Two review authors (KMM, RB) 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.

Data extraction and management

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

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

- Participant characteristics including known learning disability, age, sex and number of participants (randomised to each group);
- Diet intervention (type of KD);
- Length of follow-up;
- Epilepsy seizure type;
- Reason for commencement;
- Adverse effects;
- Reason for drop out, including compliance.

Assessment of risk of bias in included studies

Two review authors (KMM, RB) independently assessed the risk of bias and compared the results from these assessments to identify any inconsistencies. We resolved any disagreements by discussion.

We judged whether each study was at high, low or unclear risk of bias in each of the following domains.

- Random sequence generation;
- Allocation concealment;
- Blinding of participants and personnel;
- Blinding of outcome assessment;
- Incomplete outcome data;
- Selective outcome reporting;
- Other potential risks of bias.

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 at low risk of bias.

Measures of treatment effect

We presented the dichotomous outcomes, namely seizure freedom, 50% or greater reduction in seizure frequency, and attrition, as risk ratios (RRs) with 95% confidence intervals (CIs). We reported all other outcomes narratively.

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.

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; and
- 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 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.

Assessment of heterogeneity

Two review authors (KMM, RB) assessed clinical and methodological heterogeneity by investigating the distribution of important prognostic factors between trials and their study design. We assessed statistical heterogeneity using a Chi^2 test (P <

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0.10) and an I^2 statistic of greater than 50% to indicate statistical heterogeneity in accordance with Cochrane guidelines (Higgins 2011).

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

In datasets which lacked heterogeneity ($P \geq 0.10$), we conducted a meta-analysis using a fixed-effect model. Where we detected significant heterogeneity ($P < 0.10$), we used a random-effects model. All meta-analyses, regardless of model used, utilised the Mantel-Haenszel method.

We planned to carry out the following comparisons.

- KD compared with a usual care (standard of care and usual diet)
- KD compared with other dietary interventions
- KD compared with other interventions
- One KD compared with another KD intervention.

Meta-analysis was possible for KDs compared with a usual care (standard of care and usual diet). We were unable to conduct meta-analyses for the other comparisons due to the clinical heterogeneity and limited data available.

Subgroup analysis and investigation of heterogeneity

We recognised clinical heterogeneity within the studies included in the meta-analysis with regard to the age of the study population used. For this reason, we completed a subgroup analysis according to age, separating studies into those which investigated the use of KDs in children and those that investigated the use of KDs in adults.

Sensitivity analysis

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

Summary of findings and assessment of the certainty of the evidence

We graded the evidence for each outcome using the GRADE approach (Schünemann 2013), which is a formal process used to rate the certainty of evidence for outcomes in systematic reviews. We used the GRADEpro GDT software to import data from Review Manager 5 software (GRADEpro 2015) and used it to create four 'Summary of findings' tables for all outcomes and comparisons: KD compared to usual care for children with drug-resistant epilepsy (Summary of findings 1); KD compared to usual care for adults with drug-resistant epilepsy (Summary of findings 2); KDs compared with other KDs for children with drug-resistant epilepsy (Summary of findings 3); and KDs compared with other KDs for adults with drug-resistant epilepsy (Summary of findings 4).

RESULTS

Description of studies

Results of the search

Previous versions of this review identified 11 randomised controlled trials (RCTs) (Bergqvist 2005; El-Rashidy 2013; Kim 2016; Kossoff 2007; Lambrechts 2017; Neal 2008; Raju 2011; Seo 2007; Sharma 2013; Sharma 2016; Zare 2017), and one ongoing study that remains ongoing (CTRI/2015/07/006048).

The updated search from April 2019 revealed 139 studies from the databases outlined in Electronic searches. After removing duplicates, 111 studies remained. Initial screening removed 99 irrelevant studies, leaving 12 studies. The remaining studies underwent full-text review; we identified seven of these as ongoing studies (CTRI/2017/12/010898; Hulshof 2017; NCT02708030; NCT03764956; NCT03464487; NCT03807141; Titre-Johnson 2017; see Characteristics of ongoing studies), and we recognised that one publication was not a RCT (NCT03183076). We therefore excluded the latter publication (see Characteristics of excluded studies). We deemed two studies eligible for inclusion in the present review update (Kverneland 2018; McDonald 2018; see Characteristics of included studies). After the addition of the two most recent trials, the review contains 13 studies from a total of 17 publications.

See Figure 1 for a PRISMA study flow diagram (Moher 2009).

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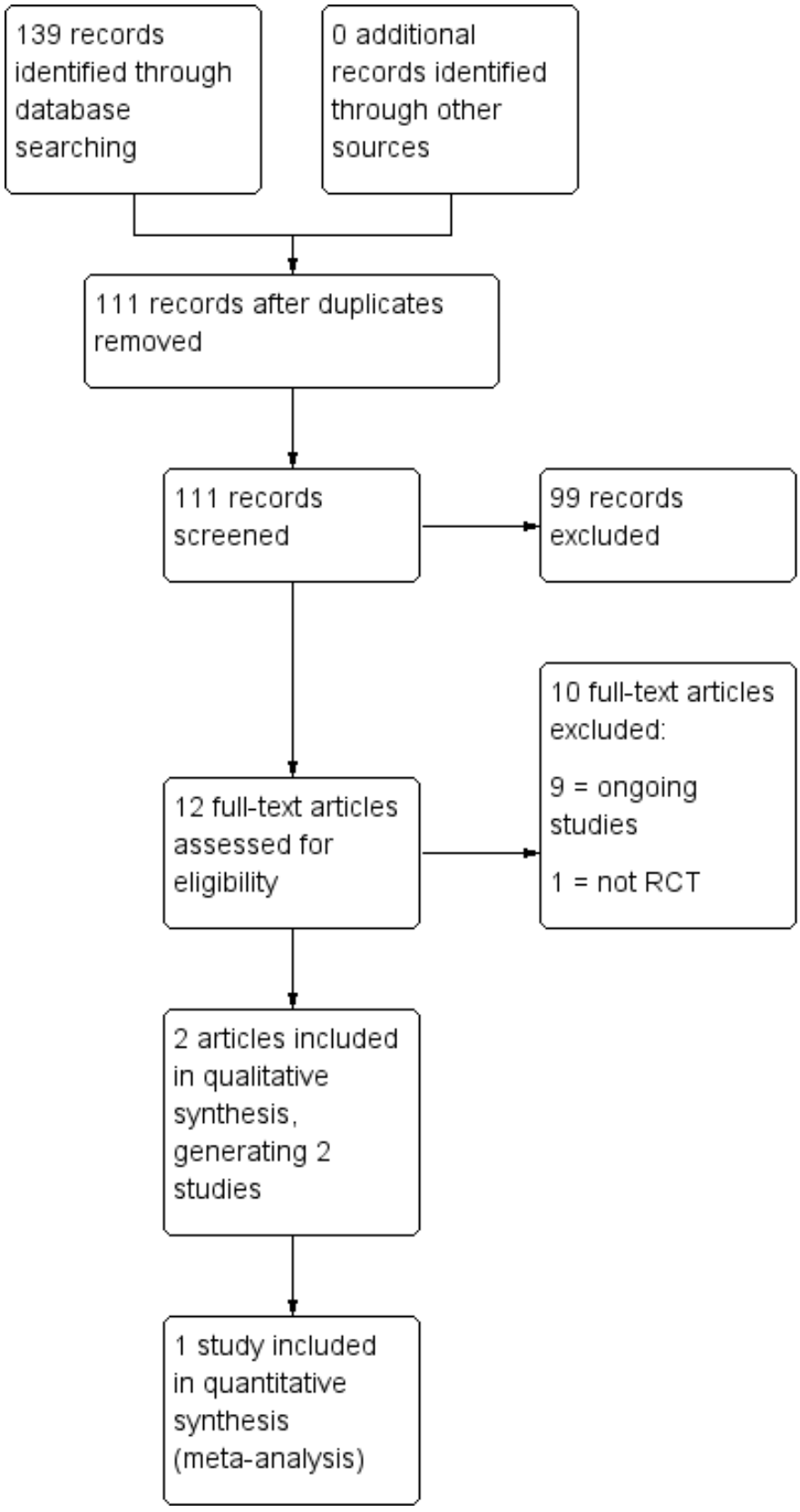
Figure 1. Study flow diagram (results illustrate the latest update).



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Included studies

We included 13 studies in this review (n = 932). These studies were conducted across various healthcare systems worldwide. Seven studies compared a ketogenic diet (KD) to a usual care group (El-Rashidy 2013; Kverneland 2018; Lambrechts 2017; Neal 2008; Sharma 2013; Sharma 2016; Zare 2017), and six studies compared one KD intervention to another type of KD intervention (Bergqvist 2005; Kim 2016; Kossoff 2007; McDonald 2018; Raju 2011; Seo 2007). A summary of studies included can also be found in the Characteristics of included studies tables.

Methods

All 13 studies in this review were randomised controlled trials. Twelve of the included studies were single-centre studies (Bergqvist 2005; El-Rashidy 2013; Kim 2016; Kossoff 2007; Kverneland 2018; Lambrechts 2017; McDonald 2018; Raju 2011; Seo 2007; Sharma 2013; Sharma 2016; Zare 2017) while one was a multi-centre study (Neal 2008). Notably, however, the majority of participants were recruited from a single, main centre. The included studies were conducted in range of countries, namely: Egypt (El-Rashidy 2013); India (Raju 2011; Sharma 2013; Sharma 2016); Iran (Zare 2017); Korea (Kim 2016; Seo 2007); Netherlands (Lambrechts 2017); Norway (Kverneland 2018); United Kingdom (Neal 2008); and United States of America (Bergqvist 2005; Kossoff 2007; McDonald 2018). All of the studies used a parallel group design, with the exception of one study (Kossoff 2007) that utilised a cross-over design.

Participants

A total of 932 participants were enrolled across the 13 included studies. Ten of the studies investigated ketogenic diets for children, aged 4 months to 18 years (Bergqvist 2005; El-Rashidy 2013; Kim 2016; Kossoff 2007; Lambrechts 2017; Neal 2008; Raju 2011; Seo 2007; Sharma 2013; Sharma 2016), while three studies investigated ketogenic diets for adults (Kverneland 2018; McDonald 2018; Zare 2017). Notably, one of the adult studies included participants as young as 16 years old (Kverneland 2018). Despite this, we continued to recognise the study as an adult only study. We considered this to be reflective of the complexities and discrepancies in clinical services, with regard to the treatment of young adults.

No study exclusively investigated the use of KDs for epilepsy populations with intellectual learning difficulties. One study (Sharma 2016) did, however, modify the traditional educational techniques used to implement the diet, to promote the inclusion of children with parents who have low levels of literacy and who are of poor socioeconomic status.

All participants had drug-resistant epilepsy. Eight of the studies (Kim 2016; Kossoff 2007; Lambrechts 2017; McDonald 2018; Neal 2008; Raju 2011; Sharma 2016; Zare 2017) requested that participants had trialled two or more antiepileptic drugs while four studies (Bergqvist 2005; Kverneland 2018; Seo 2007; Sharma 2013 requested that participants had trialled three or more antiepileptic drugs. One study (El-Rashidy 2013) did not provide information on how many antiepileptic drugs participants were required to have previously trialled.

Interventions

There were many variants of KDs used across the 13 included studies. The interventions used by each study are listed below:

- Bergqvist 2005 compared fasting and gradual-onset 4:1 ketogenic diets (KDs);
- El-Rashidy 2013 compared modified Atkins diet (MAD) (macronutrients represented as a percentage of total daily energy – 10% carbohydrate, 60% fat, 30% protein), classic ketogenic liquid diet (4:1) and usual care (polytherapy);
- Kim 2016 compared MAD (10 g carbohydrate per day for first month followed by increase to maximum of 10% total energy requirements, with additional calorie restriction to 75% recommended daily intake) and classic KD (4:1 ratio);
- Kossoff 2007 compared 10 g daily carbohydrate limit MAD and 20 g daily carbohydrate limit MAD;
- Kverneland 2018 compared MAD (up to 16 g carbohydrate per day, excluding fibre) and usual care;
- Lambrechts 2017 compared KD (classic KD and medium-chain triglyceride (MCT) KD combined to usual care;
- McDonald 2018 compared MAD (20g net carbohydrates per day) plus KetoCal (one 8 ounce tetra pack per day) during first month, followed by MAD alone in second month (intervention) to MAD alone in the first month, followed by MAD plus KetoCal during second month (control);
- Neal 2008 compared classic KD (4:1) versus MCT KD (macronutrients as approximate percentage of total energy requirements; 15% carbohydrate, 10% protein, 30% long-chain fatty acids, 45% medium-chain triglycerides);
- Raju 2011 compared a 4:1 and a 2.5:1 ratio KD;
- Seo 2007 compared a 4:1 KD and a 3:1 ratio KD;
- Sharma 2013 compared MAD (10 g carbohydrate per day) to a usual care group;
- Sharma 2016 compared a simplified MAD (sMAD, 10 g carbohydrate per day) to usual care;
- Zare 2017 compared MAD (15 g carbohydrate; total energy derived from 4% to 6% carbohydrate, 20% to 30% protein, 60% to 70% fat) to usual care.

Outcomes

Twelve of the included studies (Bergqvist 2005; Kim 2016; Kossoff 2007; Kverneland 2018; Lambrechts 2017; McDonald 2018; Neal 2008; Raju 2011; Seo 2007; Sharma 2013; Sharma 2016; Zare 2017) reported 50% or greater reduction in seizure frequency. El-Rashidy 2013 instead reported rate change in seizure frequency at three and six months. All thirteen studies reported data regarding attrition and adverse effects. Additional outcomes included: level of ketosis (Bergqvist 2005; Kossoff 2007); quality of life, cost-effectiveness, cognitive and behavioural change (Lambrechts 2017), and dietary adherence (McDonald 2018).

Funding sources

Ten of the included studies confirmed their source of financial funding support:

- Bergqvist 2005 was supported in part by RRK-23 16074 and General Clinical Research Center (MO1RR00240), the Nutrition Center of the Children's Hospital of Philadelphia, P30 HD26979, and the Catharine Brown Foundation;
- El-Rashidy 2013 received no external funding support beyond the treating hospital (Children's hospital, Faculty of Medicine, Ain Shams University);

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- Kim 2016 was supported financially by the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology;
- Lambrechts 2017 was supported financially by the Netherlands Organisation for Health Research and Development;
- McDonald 2018 was supported financially by Nutricia North America;
- Neal 2008 was supported financially by HSA, Smiths Charity, Scientific Hospital Supplies, and the Milk Development Council. University College London Institute of Child Health received funding as a National Institute for Health and Research Specialist Biomedical Research Centre;
- Seo 2007 was financially supported by Yonsei University Research Fund of 2003;
- In the study by Sharma 2013, the lead author (Sharma) was financially supported as a Senior Research Associate in the "Scientists pool scheme" of the Council for Scientific and Industrial Research (CSIR), Government. of India, for this study;
- Sharma 2016 was supported financially by the Indian Council of Medical Research (ICMR);
- Zare 2017 was supported by the Plastic Surgery Research Centre, Isfahan University of Medical Sciences, Isfahan.

Two studies (Kverneland 2018; Raju 2011) confirmed that they received no financial support, while one study did not state any information regarding funding (Kossoff 2007).

Excluded studies

We excluded one additional study at full-text review in the current update as we suspected that the study was not randomised (NCT03183076).

Previous editions of this review excluded seven studies; three were not RCTs (Freeman 1999; Hemingway 2001; Smith 2011), one study was successfully blinded after fasting (by administration of glucose or saccharin), however, was only for 12 days and ketosis was not completely eliminated in the glucose arm (Freeman 2009), one study solely included infantile spasms (Dressler 2015), one study was available as an abstract only, we were unable to obtain any further data (Singh 2015), and one study was successfully blinded after fasting (by administration of saccharin or glucose) (Freeman 2009). A summary can be found in Characteristics of excluded studies table.

Ongoing studies

We identified eight ongoing studies (CTRI/2015/07/006048; CTRI/2017/12/010898; NCT03764956; NCT03464487; NCT03807141; Hulshof 2017; NCT02708030; Titre-Johnson 2017 (3 publications from one study). We will revisit these studies in future review updates (see Characteristics of ongoing studies).

Risk of bias in included studies

There were 13 RCTs that generated 17 publications reviewing the use of KDs, all of which were appropriate for analysis of bias. For further details please refer to Characteristics of included studies table and Figure 2; Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

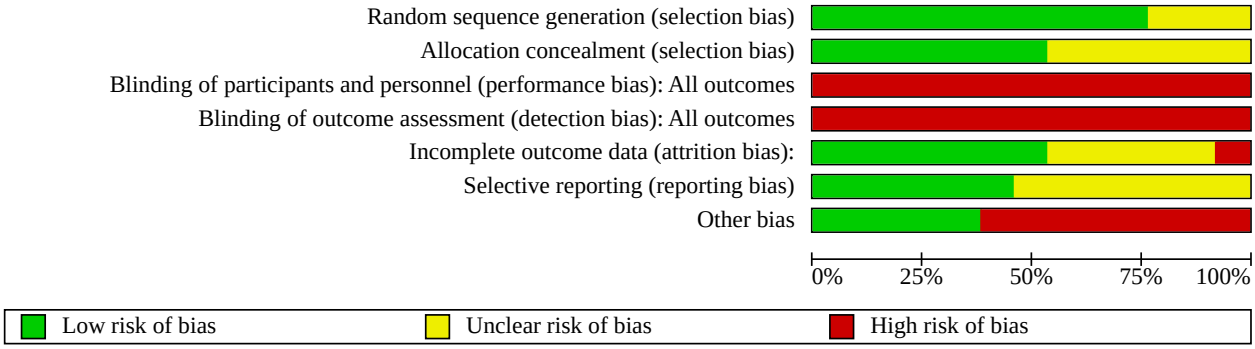

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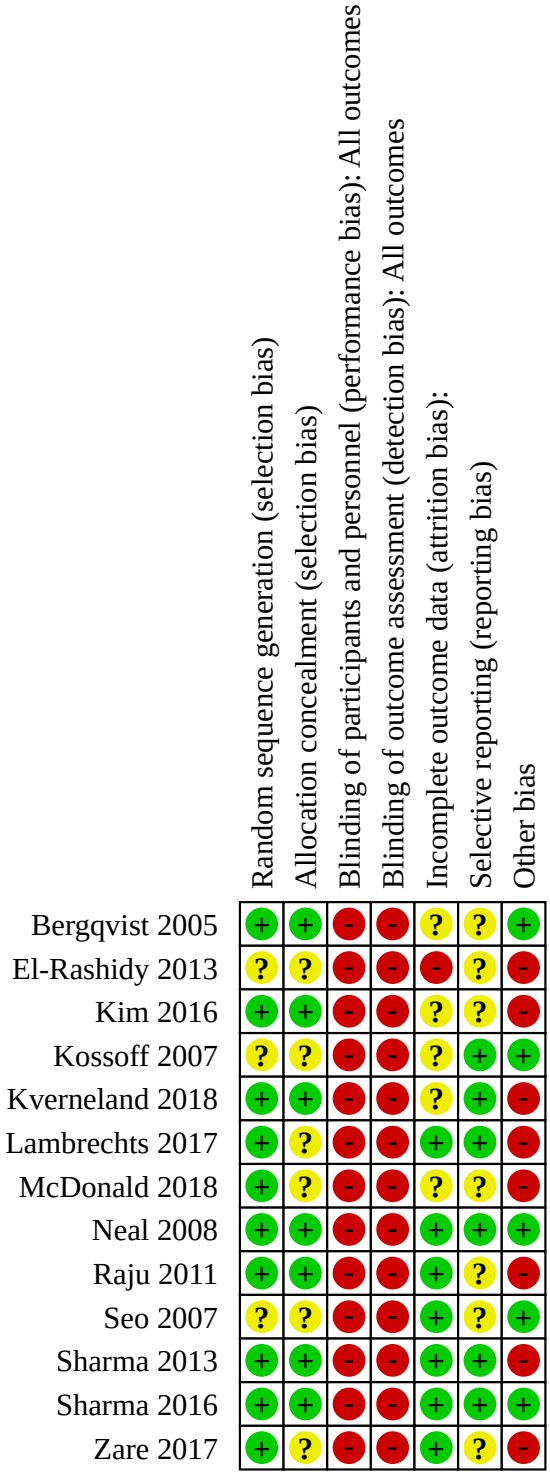
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Five studies used a computer-generated method of random sequence generation (Kim 2016; McDonald 2018; Neal 2008; Raju 2011; Sharma 2013). We therefore awarded the five studies low risk of selection bias with regard to random sequence generation. One of these studies used a computer programme to allocate participants to treatment groups (Neal 2008), whilst another three studies used opaque sealed envelopes (Raju 2011; Sharma 2013; Sharma 2016). Kim 2016 meanwhile used independent medical personnel who were blinded to participants' identity to allocate participants to treatment groups. We hence judged that all five studies were at low risk of bias for both random sequence generation and allocation concealment (Kim 2016; Neal 2008; Raju 2011; Sharma 2013; Sharma 2016). In contrast, McDonald 2018 did not provide details regarding allocation concealment. We therefore judged that this study was at unclear risk of selection bias due to allocation concealment.

One study used a permuted block randomisation method (Bergqvist 2005), whereby the size of blocks was also randomised. This method ensured that the pattern of randomisation could not be predicted, thereby adequately concealing treatment allocation. Another study also used a permuted block randomisation method but with opaque sealed envelopes for allocation concealment (Sharma 2016). One study used a manual random allocation sequence which was undertaken by personnel exclusive of the study team (Kverneland 2018). We thus deemed all three of these studies to be at low risk of selection bias for both random sequence generation and allocation concealment (Bergqvist 2005; Kverneland 2018; Sharma 2016).

The method of sequence generation and allocation concealment was unclear in three studies (El-Rashidy 2013; Kossoff 2007; Seo 2007). No clear details regarding methods for either random sequence generation or allocation concealment were provided for any of the three studies. Conversely, Lambrechts 2017 and Zare 2017 both provided methods for random sequence generation (ALEA clinical online randomisation and a random number table, respectively) but did not provide any details for allocation concealment. As a result, we judged that the two studies were at low risk of selection bias from random sequence generation but unclear risk of selection bias due to allocation concealment.

Blinding

We rated all 13 studies to be at high risk of performance bias and detection bias (Bergqvist 2005; El-Rashidy 2013; Kim 2016; Kossoff 2007; Kverneland 2018; Lambrechts 2017; McDonald 2018; Neal 2008; Raju 2011; Seo 2007; Sharma 2013; Sharma 2016; Zare 2017). Six studies stated they were open-label studies and therefore featured no blinding (Kossoff 2007; Neal 2008; Raju 2011; Sharma 2013; Sharma 2016; Zare 2017), whereas the other seven studies provided no information regarding blinding of either participants or outcome assessment (Bergqvist 2005; El-Rashidy 2013; Kim 2016; Kverneland 2018; Lambrechts 2017; McDonald 2018; Seo 2007). Due to the design of such studies, we judged that blinding of participants and study personnel was very unlikely to have occurred. We thus assessed these studies to be at high risk of bias for both blinding domains. Kim 2016 specified that blinded independent study personnel were responsible for participant randomisation and allocation, however, it was unclear if outcome assessors and participants were blinded. We therefore again assumed that the study was unblinded and awarded high risk for both performance and detection bias.

Incomplete outcome data

Two studies reported comparable withdrawal rates across the groups but did not complete an intention-to-treat (ITT) analysis (Bergqvist 2005; Kossoff 2007). Three studies reported comparable withdrawal rates across the groups but it was unclear if an ITT analysis was completed (Kim 2016; Kverneland 2018; McDonald 2018). We hence judged that the five studies were at unclear risk of attrition bias.

Five separate studies also reported comparable withdrawal rates across the groups and completed an ITT analysis (Lambrechts 2017; Raju 2011; Seo 2007; Sharma 2013; Sharma 2016). Two studies reported greater withdrawal from one group, but carried out an ITT analysis (Neal 2008; Zare 2017). We rated these seven studies to be at low risk of attrition bias.

One study reported uneven dropout rates across the groups and did not complete an ITT analysis (El-Rashidy 2013). We rated this study at high risk of attrition bias.

Selective reporting

Two study protocols had been published and were available for review (Lambrechts 2017; Sharma 2013). We contacted the remaining authors of all included studies to request protocols. Four study authors provided the protocol for the included studies (Kossoff 2007; Kverneland 2018; Neal 2008; Sharma 2016). On reviewing the outcomes, there was no evidence to suggest selective reporting for any of these six studies. Therefore, we rated these studies at low risk of reporting bias. Protocols for the remaining seven studies were unavailable and we rated these studies at unclear risk of selection bias (Bergqvist 2005; El-Rashidy 2013; Kim 2016; McDonald 2018; Raju 2011; Seo 2007; Zare 2017).

Other potential sources of bias

One study reported three participants in one intervention group to have other conditions; two had been diagnosed with infantile spasms and one with myoclonic encephalopathy (El-Rashidy 2013).

A high level of comorbidity among all groups was reported in one study, and although the groups were comparable within this study, bias may be introduced when evaluating in a meta-analysis (Raju 2011).

One study excluded children where motivational issues within the family had been identified, due to possible impacts upon compliance rates (Sharma 2013). Similarly, another study included only those who were motivated and capable of adhering to the diet (Kverneland 2018).

An energy restriction of 75% of recommended daily intake was introduced to the MAD group and not to the classical KD group in another study (Kim 2016). This could potentially enhance ketosis in the MAD group to the disadvantage of the classical KD group. In the same study, the significant difference noted in seizure reduction in the children under two years of age in favour of the classical KD, was likely to be underpowered due to subanalysis.

One study contributed several potential sources of bias (Lambrechts 2017). Participants with severe motivational and

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behavioural difficulties were excluded, despite the study assessing the effects of KD on these outcomes. Differences were noted in baseline mood and behaviour scores, gender balance and baseline seizure frequency, however significance values were not presented by the authors to fully assess this. The study was underpowered to assess quality of life; quality of life was assessed were assessed at four months by calculating quality-adjusted life years (QALYs) which may be too premature to assess changes in quality of life, and at the start of the study no suitable quality of life instrument was available for utility measures in children aged 0 to 18 years, resulting in some extrapolation from adult tariffs. As the control group received KD after four months, control data were extrapolated from four months to 16 months outcomes; although this may have been due to ethical rationale. The KD group also report significantly greater gastrointestinal side effects at baseline compared to the control group (P < 0.05), which could negatively impact the dietary intervention.

One study reported numerical errors within the text of the article in comparison to the tables and did not report a power calculation (Zare 2017). Low levels of urinary ketosis were reported (1.75 +/- 0.28 mmol/L) which could affect seizure outcomes.

One study was underpowered as recruitment was discontinued after six years due to poor uptake, recruiting 75 participants from a target of 92 (Kverneland 2018). The intervention group in this study was also dominated by female participants compared to the usual care group and baseline imbalances regarding types of epilepsy were present.

One study reported significant differences in baseline weight, body mass index (BMI) and habitually lower energy intake between usual care and KD groups (McDonald 2018).

We rated these studies at high risk of bias.

A subjective, non-validated tool was used to assess alertness, speech, sleeping, social and behavioural changes in one study (Sharma 2016). However, as these measures were assessed using non-validated tools, we did not include them in this review, and they therefore had low impact upon bias.

We did not identify any other sources of bias in four studies (Bergqvist 2005; Kossoff 2007; Neal 2008; Seo 2007).

Effects of interventions

See: **Summary of findings 1** Ketogenic diet (KD) compared to usual care for children with drug-resistant epilepsy; **Summary of findings 2** Ketogenic diet (KD) compared to usual care for adults with drug-resistant epilepsy; **Summary of findings 3** Ketogenic diets (KDs) compared with other KDs for children with drug-resistant epilepsy; **Summary of findings 4** Ketogenic diets (KDs) compared with other KDs for adults with drug-resistant epilepsy

All outcomes are presented in: Summary of findings 1, Summary of findings 2, Summary of findings 3, and Summary of findings 4. The results for all outcomes are described in more detail below.

Ketogenic diet (KD) versus usual care for children

Seizure freedom (100% reduction in seizure frequency)

In children, four studies (n = 385) reported results for a KD intervention compared to a usual care group.

- Neal 2008 reported one participant out of 73 (1%) to be seizure free after three months of following a KD (classic KD and medium-chain triglyceride (MCT)).
- Lambrechts 2017 reported 10% (3/29) of participants in the KD group to be seizure free at four months, compared to 7% (2/28) of the usual care group. These values remain unchanged when reported at 16 months.
- Sharma 2013 reported 10% (5/50) of participants in the modified Atkins diet (MAD) group to be seizure free at three months, compared to none in the usual care group.
- Following a simplified MAD (sMAD), Sharma 2016 reported 15% (6/41) of participants became seizure free, compared to 5% (2/40) in the usual care group; this result was not significant (P = 0.26).

Meta-analysis of the above studies favoured the use of KDs compared to usual care (risk ratio (RR) 3.16, 95% confidence interval (CI) 1.20 to 8.35; P = 0.02; very low-certainty evidence; Analysis 1.1). Specifically, the RR calculated indicates that children randomised to KDs were three times more likely to attain seizure freedom compared to children randomised to usual care.

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

In children, four studies (n = 385) compared KD intervention to a usual care group.

- 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 usual care group (P < 0.001).
- Lambrechts 2017 stated 34% (10/29) in the KD group compared to 7% (2/28) in the usual care group experienced greater than 50% seizure reduction at four months. After 16 months, seizure reduction (of greater than 50%) had reduced from 39% to 21% (6/29) in the KD group and 7% (2/28) of the usual care group. Lambrechts 2017 presented significance values as overall responders (seizure reduction and seizure freedom combined). For the KD group 50% (13/26) of participants responded to KD and 18% (4/22) in the usual care group, illustrating significant response at four months for the KD group compared to usual care (P < 0.05).
- When comparing MAD to a usual care group, Sharma 2013 reported significantly higher results in the MAD group (52%) to usual care (11.5%, P = 0.001), when comparing greater than 50% seizure reduction at three months.
- Using a sMAD, Sharma 2016 later supported these results, reporting 56% (23/41) of participants in the sMAD group experienced greater than 50% seizure reduction compared with 8% (3/40) in the usual care group (P < 0.001).

Meta-analysis of the above studies favoured the use of KDs compared to usual care for seizure reduction greater than or equal to 50% (RR 5.80, 95% CI 3.48 to 9.65; P < 0.001; low-certainty evidence; Analysis 1.3; Figure 4). The RR predicts that children who receive KDs are nearly six times more likely to attain a 50% or greater reduction in seizure frequency than children who receive usual care.

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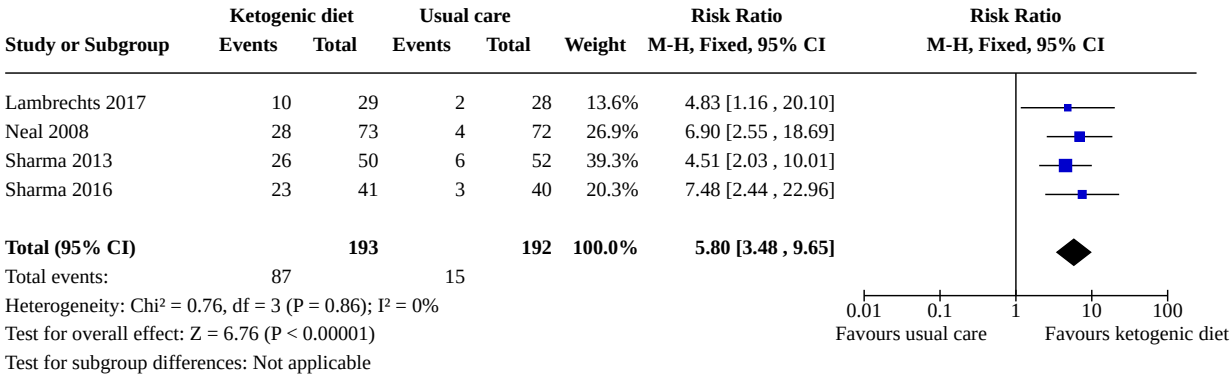
Figure 4. Forest plot of comparison: 1 Ketogenic diet versus usual care, outcome: 1.3 50% or greater reduction in seizure frequency: children.



Adverse effects

In children, five studies (n = 425) reported adverse effects for the comparison KD versus usual care.

The most frequent adverse effects reported by participants in dietary intervention groups were: vomiting, constipation and diarrhoea. These adverse effects were also commonly reported by participants in the usual care groups.

Other less common adverse effects reported included: dysphagia, lethargy, lower respiratory tract infection, hyperammonaemic encephalopathy, weight loss, nausea, infections (pneumonia, sepsis), acute pancreatitis, decrease in bone matrix density, gallstones, fatty liver, nephrocalcinosis, hypercholesterolaemia, status epilepticus, acidosis, dehydration, tachycardia, hypoglycaemia, hunger, abdominal pain, clinically relevant reduction in height, hypercalcinaemia and renal stones.

Cognition and behaviour

In children, Lambrechts 2017 (n = 57) was the only study to investigate the effect of KDs upon cognition and behaviour, reporting participants in the KD group to be more active (P = 0.005), more productive (P = 0.039) and less anxious (P = 0.049) after four months, compared to the usual care group (very low-certainty evidence).

Quality of life

Similarly, Lambrechts 2017 (n = 57) was the only study to investigate the effect of KDs on quality of life. The authors reported no significant difference in quality-adjusted life years (QALYs) between the KD group and the usual care group at four or 16 months (P value not reported; very low-certainty evidence).

Attrition rate

In children, five studies (n = 425) reported results for a KD intervention compared to a usual care group.

The proportion of children withdrawing from treatment in the KD group ranged from 8% to 38% compared to 2.5% to 32% in the usual care groups. Meta-analysis data indicated study retention to favour neither KD or usual care groups in children (RR 1.08, 95% CI 0.74 to 1.57; P = 0.71; low-certainty evidence; Analysis 1.5).

Ketogenic diet versus usual care for adults

Seizure freedom (100% reduction in seizure frequency)

In adults, two studies (n = 141) reported results for a KD intervention compared to a usual care group.

- Kverneland 2018 reported 0% seizure freedom in both MAD and the usual care group.
- Zare 2017 reported 0% seizure freedom in both the MAD and the usual care group.

The meta-analysis for seizure freedom in adults was unable to estimate an effect size due to no events being reported (very low-certainty evidence; Analysis 1.2).

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

In adults, two studies (n = 141) compared KD intervention to a usual care group.

- Kverneland 2018 reported 8% (3/37) in the MAD group and 5% (2/38) in the usual care group to experience a greater than 50% reduction in seizures at three months (P = 0.65).
- Zare 2017 reported 35% (12/34) in the MAD group and 0% (0/32) in the usual care group had greater than 50% reduction in seizures at two months (P = 0.001).

In adults, meta-analysis data illustrated the effect of KDs in reducing seizure frequency to be unclear. Although a very large effect size was calculated (RR 5.03, 95% CI 0.26 to 97.68; very low-certainty evidence; Analysis 1.4; Figure 5), the difference between treatment groups (KD versus usual care) was not statistically significant (P = 0.29). Notably, the two studies each predicted very different effect sizes and this is reflected by the I^2 value (I^2 = 70%) which indicates heterogeneity.

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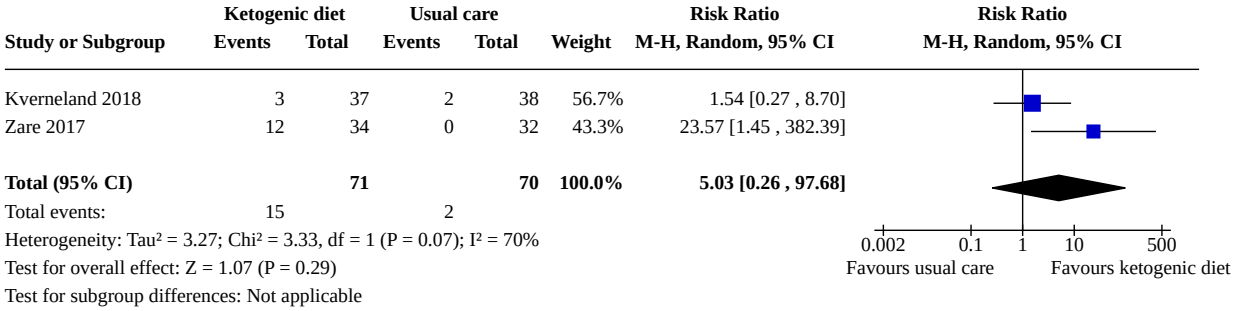
Figure 5. Forest plot of comparison: 1 Ketogenic diet versus usual care, outcome: 1.4 50% or greater reduction in seizure frequency: adults.



Adverse effects

In adults, two studies (n = 141) compared KD intervention to a usual care group.

Adults receiving KD most commonly reported: vomiting, constipation and diarrhoea. One study reported a significant reduction in body mass index (BMI), as well as an increase in cholesterol in the MAD group, whilst the other study reported significant weight loss. Other adverse effects included: anorexia, lethargy, lower respiratory tract infections and hyperammonaemic encephalopathy.

Cognition and behaviour

In adults, no studies reported this outcome for a KD intervention compared to a usual care group.

Quality of life

In adults, no studies reported this outcome for a KD intervention compared to a usual care group.

Attrition rate

In adults, two studies (n = 141) compared a KD intervention to a usual care group.

The proportion of adults withdrawing from treatment in the MAD group was 35% in both studies compared to a withdrawal rate of 0% to 16% in the usual care groups. Meta-analysis of data for adults indicated that retention favoured the usual care groups, however, the effect was not statistically significant (RR 5.38, 95% CI 0.42 to 69.53; P = 0.20; very low-certainty evidence; Analysis 1.6).

Ketogenic diet versus ketogenic diet for children

Seizure freedom (100% reduction in seizure frequency)

In children, five studies (n = 286) compared different KD interventions (very low-certainty evidence).

- 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.
- 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.
- When investigating the effects of MAD on seizure freedom, Kim 2016 reported a significant difference between classic KD (33%; 17/51 participants) and MAD (25%; 13/53 participants) after three months (P = 0.374), but no difference after six months. When results were divided into subsequent age categories (1 to 2 years, 2 to < 6 years and 6 to 18 years) more children under the age of two years experienced seizure freedom following the classic KD (9/17) compared to the MAD (4/20) (P = 0.047). However, this result is likely to be statistically underpowered.
- 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.

Due to heterogeneity of both interventions and methodology, we could not conduct a meta-analysis for studies comparing different KD interventions in children.

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

In children, five studies (n = 286) compared different KD interventions (very low-certainty evidence).

- 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. Seo 2007 reported that antiepileptic efficacy was significantly greater in the 4:1 KD group than the 3:1 KD group (P = 0.041), but it was unclear as to whether this referred to seizure reduction, seizure freedom or both.
- 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 comparing classic KD to MAD, Kim 2016 reported 43% (22/51) of participants in the classic KD and 42% (22/53) in the MAD group (P = 0.527) reporting greater than 50% seizure reduction. At six months, 39% (20/51) of participants in the

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classic KD group and 36% of the MAD group reported greater than 50% seizure reduction (P = 0.321), therefore no difference was observed between the groups.

- When comparing proportions of carbohydrate in the MAD group, Kossoff 2007 reported a significant difference (P = 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.

Due to heterogeneity of both interventions and methodology, we could not conduct a meta-analysis for studies comparing different KD interventions in children.

Adverse effects

In children, five studies (n = 286) compared different KD interventions for adverse effects.

The most frequent adverse effects reported by children were: vomiting, constipation and diarrhoea. Two studies reported weight loss, with one study stating that weight loss and gastrointestinal disturbances were more frequently reported with 4:1 KD versus 3:1 KD. One study reported a significantly high incidence rate for hypercalcuria amongst children receiving classic KD compared to MAD at three months. There was no significant difference in weight loss between treatment groups given 20 mg/d versus 10 mg/d carbohydrates. Other adverse effects reported included dysphagia, lethargy, lower respiratory tract infection, hyperammonaemic encephalopathy, nausea, infections (pneumonia, sepsis), acute pancreatitis, decrease in bone matrix density, gallstones, fatty liver, nephrocalcinosis, hypercholesterolaemia, status epilepticus, acidosis, dehydration, tachycardia, hypoglycaemia, hunger, abdominal pain, clinically relevant reduction in height, hypercalcinaemia and renal stones.

Cognition and behaviour

No studies reported this outcome.

Quality of life

No studies reported this outcome.

Attrition rate

In children, five studies (286 participants) compared treatment withdrawal across different KD interventions. The proportion of children withdrawing from KD groups were: 8% attrition for gradual-onset KD; 16% attrition on 2:5:1 KD and on 4:1 KD; 17% attrition on fasting-onset KD and on the 3:1 KD; 32% attrition on MAD; and 33% attrition on the classic KD.

Ketogenic diet versus ketogenic diet for adults

Seizure freedom (100% reduction in seizure frequency)

In adults, one study (McDonald 2018) measured seizure freedom when comparing different KD interventions. No adult participants in either treatment groups, MAD plus KetoCal in month one (intervention) or MAD plus KetoCal in month two (control), achieved seizure freedom (very low-certainty evidence).

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

In adults, one study (n = 80) compared different KD interventions (very low-certainty evidence).

- When comparing MAD with KetoCal for month one (intervention), to MAD with KetoCal during month two (control), McDonald 2018 reported 35% (17/40) of the intervention group and 33% (13/40) of the control group to be experiencing greater than 50% reduction in seizures. At two months, 33% (13/40) of the intervention group and 25% (10/40) of the control group were experiencing greater than 50% reduction in seizures. After six months, 25% (10/40) of the intervention group and 25% (10/40) of the control group were experiencing greater than 50% seizure reduction.

Adverse effects

In adults, one study (n = 80) compared different KD interventions.

Constipation was reported more frequently by adults in the MAD plus KetoCal group (17.5%) compared to the MAD only treatment group (5%). Diarrhoea and increase/change in seizure pattern/semiology were also commonly reported (17.5% to 20% of participants). Other less commonly reported adverse effects included: abdominal pain, headache, irregular menses, halitosis, somnolence, nephrolithiasis, kidney infection, nausea, easy bruising, vaginal odour and brittle hair/nails.

Cognition and behaviour

No studies reported this outcome.

Quality of life

No studies reported this outcome.

Attrition rate

In adults, one study (80 participants) compared attrition across different KD interventions. Specifically, 12.5% of adults withdrew from the intervention group (MAD plus KetoCal month 1) compared to 32.5% from the control group (MAD plus KetoCal month 2).

DISCUSSION

Summary of main results

The present update identified two additional randomised controlled trials (RCTs) and, therefore, this review includes 13 RCTs; three of which investigated the effect of MAD in adults with epilepsy (Kverneland 2018; McDonald 2018; Zare 2017).

In relation to children, meta-analysis favoured the use of ketogenic diets (KDs) compared to usual care in promoting seizure freedom (risk ratio (RR) 3.16, 95% confidence interval (CI) 1.20 to 8.35; P = 0.02) and seizure reduction ≥ 50% of baseline (RR 5.80, 95% CI 3.48 to 9.65; P = 0.001). In children, 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). Studies assessing the efficacy of the modified Atkins diet (MAD) in children reported seizure freedom rates of up to 25% and seizure reduction rates of up to 60%.

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

One study reported a significant difference between classic KD and the less restrictive MAD after three months (P = 0.374) in terms of seizure reduction, but no difference after six months (Kim 2016). Of further interest, this study is the first RCT to report on KDs in children under two years of age in relation to seizure freedom, suggesting classical KD may be more effective than MAD (P = 0.047). However, this result is likely to be statistically underpowered and requires further investigation.

In adults, the effect of the MAD is less clear, with no participants experiencing seizure freedom (Kverneland 2018; Zare 2017), and mixed effects noted in seizure reduction of 50% or greater (RR 5.03, 95% CI 0.26 to 97.68; P = 0.29). The first RCT for MAD in adults reported seizure reduction rates of 35% at two months (Zare 2017), which is lower than that of children, but remains statistically significant compared to the usual care group (P = 0.001). However, a more recent study has shown less promising results with 8% of participants experiencing 50% or more seizure reduction compared to usual care (Kverneland 2018). McDonald 2018 found KetoCal to be tolerable by adults for a one-month period, reporting seizure reduction rates of up to 55% during this time.

Adverse effects were fairly consistent across different dietary interventions. The most commonly reported adverse effects were gastrointestinal syndromes. Two of the adult studies reported derangements in lipid profiles (McDonald 2018; Zare 2017), however the clinical significance and long-term effect of this requires further investigation. It was common that adverse effects were the reason for participants dropping out of studies. Other reasons for drop out included lack of efficacy, non-compliance 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 associated with more adverse effects in the majority of studies.

Only one study assessed the effect of dietary interventions on quality of life and found no difference between quality-adjusted life years (QALYs) when comparing KD to usual care (Lambrechts 2017). This study is also the only study to report upon cognitive or behavioural functioning, suggesting the KD group to be more active, more productive and less anxious. However, given the limitations of the study, further evidence investigating the effects of KDs on quality of life and cognitive and behavioural functioning would be beneficial before drawing conclusions.

Overall completeness and applicability of evidence

The present review identified 13 RCTs with a total sample size of 932 people with epilepsy, three of which were in adult populations. The effect of KDs for adults remains unclear, highlighting the need for further research in this field. Additionally, more studies that investigate the use of KDs in children are required to expand and improve the certainty of the evidence available for paediatric populations.

We also require more studies that evaluate the effects of KDs on cognitive and behavioural outcome and on quality of life. Currently, only one study has assessed cognitive and behavioral outcomes in a RCT of KD, and only one other separate study has reported quality of life. The evidence we have acquired is therefore inadequate to inform clinical practice about the effects of KDs on these outcomes.

The studies in both adults and children were all of short duration, with none longer than 16 months. The evidence therefore is restricted to the short-term effects of KDs and is unable to provide information on the long-term efficacy or tolerability of KDs.

Notably, meta-analysis for all planned comparisons was not possible due to the clinical and methodological heterogeneity observed and the limited data available. Thus, meta-analysis was restricted to studies comparing KDs with a usual care group. For the purposes of this meta-analysis, we considered it appropriate to group all variations of the KD together as a single ketogenic intervention. The effects of the intervention were then compared against the continuation of usual care without dietary intervention. Similarly, we did not feel that it was appropriate to combine the data from adults and children into a single meta-analysis, due to the obvious heterogeneity between the treatment effects estimated.

Certainty of the evidence

The certainty of evidence judgements for all GRADE-assessed outcomes for the four comparisons are displayed in Summary of findings 1, Summary of findings 2, Summary of findings 3, and Summary of findings 4.

We GRADE-assessed the majority of outcomes as being derived from very low-certainty evidence. Consequently, this means that we are very uncertain whether the findings that we have reported for these outcomes are accurate of the true effect; the true effect could likely be substantially different from that described in this review. We rated the evidence for three outcomes as low certainty, meaning that we are uncertain about the accuracy of the effect estimate we have provided (seizure reduction, adverse effects and attrition for 'Ketogenic diet compared to usual care for children with drug-resistant epilepsy'; (Summary of findings 1)). There is a possibility that the effect estimate could be considerably different from the true effect, but we are unsure.

We downgraded all outcomes across the four comparisons once for risk of bias after we detected significant risk of bias across all included studies. This was largely due to a lack of blinding and unclear methodological reporting. There was also an issue with missing data for several of the included studies. The studies either did not complete intention-to-treat (ITT) analysis or did not clarify whether or not it was used.

Another common issue that impacted the majority of outcomes was imprecision. Specifically, there were limited data available, regarding KDs, with a restricted number of events reported for many outcomes. Consequently, the suggested optimal information size was not satisfied on most occasions. This thus implied that the analysis may not have been adequately powered. We also found it necessary to downgrade for imprecision due to the data synthesis conducted. Certain outcomes, such as cognition and behaviour, and quality of life, required a narrative synthesis due to the heterogenous approaches used to assess them. A narrative synthesis does not estimate a weighted effect size, and therefore is not an accurate representation of the true effect. This hence results in a downgrading for imprecision. With regard to dichotomous outcomes, such as seizure freedom for the comparison 'Ketogenic

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diet compared with other ketogenic diets for children with drug-resistant epilepsy' (Summary of findings 3), unfortunately, due to the heterogeneity in the interventions of the included studies, we judged that it was inappropriate to combine data into a meta-analysis. Instead, we performed a narrative synthesis. This again contributed to a downgrading of evidence.

The heterogeneity observed in data sets also negatively impacted another GRADE-assessed domain, inconsistency. Specifically, two outcomes, seizure reduction and treatment withdrawal for the comparison 'Ketogenic diet compared to usual care for adults with drug-resistant epilepsy' (Summary of findings 2), displayed significant statistical heterogeneity, and therefore we downgraded once for inconsistency. It was necessary to downgrade the certainty of evidence for multiple outcomes for the comparisons, 'Ketogenic diets compared with other ketogenic diets for children with drug-resistant epilepsy' (Summary of findings 3) and 'Ketogenic diets compared with other ketogenic diets for adults with drug-resistant epilepsy' (Summary of findings 4), due to the observed heterogeneity in interventions used.

Overall, the certainty of evidence for this review has been limited by the associated risk of bias, the observed heterogeneity between studies, and the low number of participants recruited to study populations.

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 we identify further data following publication of this review, we will incorporate it 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.

We also encountered issues with young adults being incorporated into both the adult and child study populations for the trials that we included in this review. One adult study included participants as young as 16 years old (Kverneland 2018), whilst three of the child studies included participants up to the age of 18 years old (Kim 2016; Kossoff 2007; Lambrechts 2017). Consequently, data from people with drug-resistant epilepsy, aged 16 to 18 years old, has been considered and analysed in both of our comparisons. Although this is not useful to young adults with drug-resistant epilepsy and their clinicians who are deciding whether a KD will be beneficial, it is reflective of current clinical practice, whereby the age for transition from paediatric to adult health services is variable.

Agreements and disagreements with other studies or reviews

We found, and excluded, two prospective, but not RCTs investigating the effect of KD 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 (9 participants). Dropout rates varied between 30% and 77%, reportedly due to feelings 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 efficacy findings of Kossoff 2008 were similar to those of the included paediatric RCTs discussed above, but greater than what is observed in studies comparing KDs to usual care (Kverneland 2018; Zare 2017). However, attrition rates experienced by Moesk 2009 were considerably higher than the RCTs conducted on children or the adult RCTs, which may suggest tolerability of a 4:1 KD or lack of efficacy to be problematic in the adult population. We note however, that the adult RCTs included in this review are of short duration, three months or less.

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 35% and 58% of children to have greater than 50% seizure reduction following six months of KD (DiMario 2002; Kang 2005). However, given the time scale, direct comparisons of results are difficult. Adverse effects in both studies were mild and self-limited. Kang 2005 reported a 32% dropout rate, which is slightly greater than the included RCTs, reportedly due to complications and dietary intolerances. However, four participants were also reported to have 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 collective evidence presented in this review suggests an effect for ketogenic diets (KDs) for epilepsy in children. The limited number of studies in both adults and children, small sample sizes and generally short-term follow-up, however, resulted in low- to very low-certainty evidence for the majority of outcomes.

All studies comparing all KD variations reported adverse effects, from short-term gastrointestinal-related disturbances, to longer-term complications. The adverse effects associated with the modified Atkins diet (MAD) may initially appear lower than the classic KD, but further studies are required.

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

One study found no significant difference in seizure reduction between gradual-onset and fasting-onset KD, further analysis would be beneficial to assess cost-effectiveness. However, further large-scale studies are required.

The effect of KDs on quality of life, cognition and behaviour requires further investigation.

There was a lack of evidence for the use of KDs in adults or infants with epilepsy, therefore, further research would be of benefit.

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

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For people who have medically intractable epilepsy or people who are not suitable for surgical intervention, KDs remain 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.
- Further studies utilising economic modelling (quality-adjusted life years; QALYs) would be of benefit.
- Consistency in outcomes across RCTs would be beneficial through a core outcome set, for example it would 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. 6 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 MAD).
- The present review highlighted a paucity of evidence for the use of the KD in adults and infants. Therefore, future studies should investigate the use and potential adverse effects of KDs in adults and infants with epilepsy.
- Large-scale RCTs would be of benefit.

ACKNOWLEDGEMENTS

We would like to thank Cerian Jackson, Pratima Giri and Jennifer Pulman for contributions to previous versions of this review and Dr Elizabeth Neal for providing her expert opinion regarding included studies in this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bergqvist 2005

Study characteristics	
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 undertaken in Philadelphia, USA. All generalised and focal seizures included; • Exclusion criteria: children with metabolic disorders, genetic disorders and known or suspected neurodegenerative disorders. 42% of children included in the study had cerebral palsy.

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Bergqvist 2005 *(Continued)*

Interventions	Speed of introduction of KD: Fast KD (< 48 hour fast, followed by 4:1 KD with increase in portion size over 6 days) or Grad KD (gradual increase in KD ratio from 1:1 to 4:1 over 6 days)
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; • This study was supported in part by RRK-23 16074 and General Clinical Research Center (MO1R-R00240), the Nutrition Center of the Children's Hospital of Philadelphia, P30 HD26979, and the Catharine Brown Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants stratified by age (1 to 2 years and 2 to 14 years); randomisation in permuted blocks of random size (2 to 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 of participants and personnel (performance bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of participants and study personnel does not seem possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of outcome assessors does not seem possible.
Incomplete outcome data (attrition bias)	Unclear risk	Similar attrition rate in both groups, numbers too small for statistical analysis. No ITT analysis completed.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable.
Other bias	Low risk	All participants admitted received same care; no other bias identified.

El-Rashidy 2013

Study characteristics

Methods	Single-centre randomised controlled trial to comparing two different dietary interventions (MAD and classic KD in form of 4:1 liquid diet) and a control group (AED polytherapy).
Participants	• 40 children aged 12-36 months (mean 27.13, SD 6.63) with symptomatic intractable epilepsy. Study undertaken in Egypt; • Exclusion criteria: children < 1 year, diagnosed with idiopathic epilepsy or with other systemic chronic conditions;

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El-Rashidy 2013 *(Continued)*

	• Two children in the classic group had infantile spasms and one child in the classic group had myoclonic encephalopathy.
Interventions	• Participants were randomised into 1 of 3 groups; MAD (15 participants), KD (10 participants) and control (polytherapy) (15 participants); • 4:1 refers to 4 g fat to 1 g of carbohydrate and protein combined.
Outcomes	• Reduction in seizure frequency; • Adverse effects; • Attrition rate. Data were collected at 3 and 6 months.
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; • No external funding support was received for this study beyond the treating hospital (Children's hospital, Faculty of Medicine, Ain Shams University).

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 of participants and personnel (performance bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of participants and study personnel does not seem possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of outcome assessors does not seem possible.
Incomplete outcome data (attrition bias)	High risk	Study attrition was reported but ITT 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.

Kim 2016

Study characteristics

Methods	Prospective, single-centre, randomised trial to compare MAD (75% energy restriction) to classic KD (4:1 ratio). Four week baseline period completed.

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Kim 2016 *(Continued)*

Participants	• 104 participants aged 1 to 18 years, with drug-resistant epilepsy, experiencing more than 4 seizures per month, with treatment failure following 2 or more AEDs. Study was conducted in Korea; • Exclusion criteria: history of previous diet therapy, hyperlipidaemia, renal calculi, any other medical contraindications for diet therapy; • Epilepsy syndromes included Lennox-Gastaut syndrome (10 participants in the MAD and 8 participants in the KD group), West syndrome (8 participants in the MAD and 12 participants in the KD group), myoclonic astatic epilepsy (1 participant in each group) and Dravet syndrome (2 participants in the MAD and 4 participants in the KD group).
Interventions	• Randomised into 1 of 2 groups; MAD (10 g carbohydrate per day for the first month, followed by increase to 10% of total energy requirements, with energy restriction to 75% of recommended daily intake) and classic KD (4:1 ratio) for a 6-month period; • 4:1 refers to 4 g fat to 1 g of carbohydrate and protein combined. All recruited participants were hospitalised to commence the diet and followed a non-fasted initiation protocol.
Outcomes	• Seizure reduction; • Seziure freedom; • Adverse effects; • Compliance; • Attrition.
Notes	• At 3 months 12 participants had discontinued the classic KD; 1 due to inefficacy, 7 due to intolerance and 4 due to side effects. In the MAD group 6 participants had discontinued diet; 3 due to inefficacy, 2 due to intolerance and 1 due to side effects. By 6 months a further 5 participants discontinued to classic KD; 1 due to inefficacy, 1 due to intolerance and 3 due to side effects. In the MAD group 11 had discontinued diet; 3 due to inefficacy, 6 due to intolerance and 2 due to side effects; • This study was supported financially by the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified permuted block randomisation using statistical software. Minimisation method used to adjust for age (1 to 2 years, 2 to 6 years, 6 to 18 years).
Allocation concealment (selection bias)	Low risk	Independent medical personnel were responsible for allocating participants to treatment groups and were blind to participants' identity.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of participants and study personnel does not seem possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of outcome assessors does not seem possible.
Incomplete outcome data (attrition bias)	Unclear risk	Study attrition reported and unclear if ITT analysis carried out.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable.
Other bias	High risk	An energy restriction of 75% of recommended daily intake applied to MAD group and not classical KD group. Significant difference noted in the children

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Kim 2016 *(Continued)*

	under 2 years of age in favour of the classical KD likely to be underpowered due to subgroup analysis.

Kossoff 2007

Study characteristics	
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; • Exclusion criteria: children with prior experience of the diet for > 7 days, hypercholesterolaemia, kidney dysfunction, BMI < 3% for age and children with heart disease; • Epilepsy syndromes included were idiopathic (15 children), Rett syndrome (2 children), cortical dysplasia (2 children) and tuberous sclerosis complex (1 child).
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 = 0.33). Reasons for drop out were not stated; • Funding support for this study was not stated.

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study meaning participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study meaning outcome assessors were not blinded.
Incomplete outcome data (attrition bias)	Unclear 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 = 0.33. No ITT analysis completed.
Selective reporting (reporting bias)	Low risk	Protocol received. No evidence to suggest selective reporting.

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Kossoff 2007 *(Continued)*

Other bias	Low risk	Same care to both groups.

Kverneland 2018

Study characteristics	
Methods	Prospective, randomised controlled trial comparing MAD (up to 16 g carbohydrate per day, excluding fibre) to a usual care over a three-month period.
Participants	• 75 adult participants aged 16 years or over, with focal or multifocal epilepsy, at least three countable seizures per month, tried at least three AEDs, BMI > 18.5kg/m^2, motivated and capable of adhering to the diet, with assistance if required. Participants were referred from across Norway; • Exclusion criteria: pregnancy, previous use of KD in past 12 months, change of AED treatment, non-epileptic seizures, status epilepticus in past six months, resective surgery or vagal nerve stimulation in past 12 months or comorbidities that contraindicate use of the KD.
Interventions	MAD (up to 16 g carbohydrate per day, excluding fibre; 37 participants) compared to usual care (38 participants) over a three-month period.
Outcomes	• Seizure reduction; • Adverse effects; • Changes in body weight; • Changes in selected biomarkers.
Notes	• 13 participants dropped out from the treatment arm; 9 did not receive the diet and 4 were lost to follow-up. In the usual care arm 6 participants dropped out; 3 did not start the treatment period, 1 was excluded as commenced diet during the control period and 2 were lost to follow-up. • No funding was received for this study.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Manual random allocation sequence.
Allocation concealment (selection bias)	Low risk	Researcher not involved in study.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of participants and study personnel does not seem possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of outcome assessors does not seem possible.
Incomplete outcome data (attrition bias)	Unclear risk	Unclear if ITT used.
Selective reporting (reporting bias)	Low risk	Protocol received. No evidence to suggest selective reporting.

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Kverneland 2018 *(Continued)*

Other bias	High risk	Study discontinued after 6 years due to limited recruitment; initial study powered to 92 participants (75 were recruited). Female dominant intervention group at baseline.

Lambrechts 2017

Study characteristics

Methods	Prospective, single-centre, non-blinded, randomised controlled trial to compare KD (classic KD and MCT KD) to a control (usual care) group over a 4-month period. Follow-on studies then compared long-term clinical outcomes at 16 months, cognitive and behavioural impacts and an economic evaluation. A 4-week baseline period was completed.
Participants	• 57 participants aged 1 to 18 years with drug-resistant epilepsy, seizures not adequately controlled by 2 or more AEDs and surgical remedial causes of epilepsy not viable. Study was conducted in the Netherlands; • Exclusion criteria: medical contraindications, behavioural or motivational problems that would preclude compliance; • Epilepsy syndromes included West syndrome (3 participants in KD group and 2 participants in usual care group), Lennox-Gastaut syndrome (1 participant in KD group), Doose syndrome (3 participants in KD group and 2 participants in usual care group), Dravet syndrome (1 participant in KD group), childhood absence epilepsy (1 participant in KD group), epilepsy with myoclonic absences (1 participant in KD group), generalised epilepsies (4 participants in KD group and 6 participants in usual care group) and localisation-related epilepsies (12 participants in each group).
Interventions	Randomised into 1 of 2 groups; KD (classic KD and MCT KD) and control (usual care) for a four-month period
Outcomes	• Seizure reduction; • Adverse effects; • Attrition; • Quality of life; • Cost-effectiveness; • Cognitive and behavioural changes.
Notes	• 7 participants in the KD group dropped out by 4 months; 1 due to compliance, 1 due to ineffectiveness, 1 due to ineffectiveness combined with adverse effects, 2 due to adverse effects alone, 1 due to change in seizure pattern and 1 due to withdrawn consent. In the usual care group 9 participants dropped out, all 9 due to dissatisfaction with randomisation arm. By 16 months, a further 4 participants had discontinued KD; 2 due to compliance, 1 due to ineffectiveness and 1 due to ineffectiveness combined with adverse effects. Data at 16 months for the usual care group is not presented as the usual care arm had no option to commence KD after the initial 4-month treatment period was completed; • Differences in baseline demographics between groups for gender (18 male in KD group and 9 male in usual care group), daily seizures (10 participants in KD group and 3 participants in usual care group), almost daily seizures (5 participants in KD group and 10 participants in usual care group) and etiology (9 genetic aetiology in KD group and 1 in usual care group; 2 structural aetiology in KD group and 10 structural in usual care group); • The study was supported financially by the Netherlands Organisation for Health Research and Development.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Lambrechts 2017 *(Continued)*

Random sequence generation (selection bias)	Low risk	ALEA, minimisation method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of participants and study personnel does not seem possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of outcome assessors does not seem possible.
Incomplete outcome data (attrition bias)	Low risk	Study attrition reported and ITT analysis carried out.
Selective reporting (reporting bias)	Low risk	Protocol published. No evidence to suggest selective reporting bias.
Other bias	High risk	Excluded participants with motivational or behavioural problems. Baseline differences in mood and behaviour scores, gender balance and seizure frequency (no significance value reported to fully assess extent). Gastrointestinal problems greater at baseline in KD group compared to usual care ($P < 0.05$). Underpowered to assess QALYs and tool extrapolated from adult tariffs.

McDonald 2018

Study characteristics	
Methods	Prospective, randomised controlled trial, single-centre, comparing two MAD interventions: 1) MAD plus KetoCal during first month, followed by MAD alone in second month (intervention) to 2) MAD alone in the first month, followed by MAD plus KetoCal during second month (control) with MAD consisting of 20 g net carbohydrates per day. The intervention was conducted for two months, with a six-month follow-up period.
Participants	• 80 adult participants aged 18 years and over, four quantifiable seizures per month minimum, failed trial of two or more AEDs. Participants were recruited from Johns Hopkins Hospital, USA; • Exclusion criteria included: unwillingness to restrict carbohydrate, BMI < 18.5kg/m^2, pregnant, history of kidney disease, hypercholesterolaemia, milk allergy, metabolic or mitochondrial disorder in which KDs are contraindicated, prior use of MAD for two days or more, use of KetoCal at any time, use of classical KD in the past year.
Interventions	A comparison of two MAD interventions: 1. MAD plus KetoCal during first month, followed by MAD alone in second month (intervention) to 2. MAD alone in the first month, followed by MAD plus KetoCal during second month (control) with MAD consisting of 20 g net carbohydrates per day. The intervention was conducted for two months, with a six-month follow-up period.
Outcomes	• Seizure reduction; • Dietary adherence; • Tolerability; • Adverse effects.

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McDonald 2018 *(Continued)*

Notes	• From the treatment arm, 5 participants dropped out: 1 lost to follow-up; and 4 discontinued the intervention. Four were excluded from the 1-month analysis due to incomplete seizure logs or change in medication. In the control arm, 13 participants dropped out: 4 elected not to start the control diet; 4 lost to follow-up; and 5 did not adhere to the intervention. Two were excluded from the 1-month analysis due to lack of seizure log or changes to medication; • Differences is baseline demographics were noted for mean weight (185.3 +/- 48.5 lbs in the control group and 162.3 +/- 49.7 lbs in the intervention group; P = 0.039) and mean BMI (30.3 lbs/in^2 in control group; 25.9 lbs/in^2 in intervention group; P = 0.007). carbohydrate, BMI <18.5kg/m^2; • This study was supported financially by Nutricia North America.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number allocation.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of participants and study personnel does not seem possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of outcome assessors does not seem possible.
Incomplete outcome data (attrition bias)	Unclear risk	Unclear if ITT used in study analysis.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable.
Other bias	High risk	Power calculation based on 85% retention rate (70% retention achieved in study). Significant differences in baseline weight and BMI.

Neal 2008

Study characteristics

Methods	Prospective, randomised, non-blinded, controlled trial comparing KD (classic (4:1) and MCT combined) to usual care 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; • Exclusion criteria: hyperlipidaemia, renal stones or organic acid deficiency syndromes.
Interventions	• Participants were randomised to commence a KD (either classic or MCT) immediately (73 participants) or after a further 3 months of seizure recording (usual care group, 72 participants). Those in the KD arm were then randomised to receive classical KD or MCT; • 4:1 refers to 4 g fat to 1 g of carbohydrate and protein combined.

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Neal 2008 *(Continued)*

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; • This study received financial support from HSA, Smiths Charity, Scientific Hospital Supplies, and the Milk Development Council. University College London Institute of Child Health received funding as a National Institute for Health and Research Specialist Biomedical Research Centre.

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 programme assigned children to treatment group.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study meaning participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study meaning outcome assessors were not blinded.
Incomplete outcome data (attrition bias)	Low risk	High level of missing data in usual care group, however, completed ITT.
Selective reporting (reporting bias)	Low risk	Initial application protocol received. No evidence to suggest selective reporting.
Other bias	Low risk	Same care to both groups.

Raju 2011

Study characteristics

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 drug-resistant epilepsy, at least 2 seizures/month, despite appropriate use of at least 2 AEDs and at least 1 newer AED. Study undertaken in India; • Exclusion criteria: known or suspected inborn errors of metabolism, systemic illness or surgical remediable causes of epilepsy; • Epilepsy syndromes included were West syndrome (9 participants in 4:1 KD group and 7 participants in 2.5:1 KD group), Lennox-Gastaut syndrome (8 participants in 4:1 KD group and 9 participants in 2.5:1 KD group), Doose (no participants in 4:1 KD group and 2 participants in 2.5:1 KD group) and unclassified syndromes (2 participants in 4:1 KD group and 1 participant in 2.5:1 KD group). The trial included participants with cerebral palsy (15 participants in 4:1 KD group and 9 participants in 2.5:1 KD group).

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Raju 2011 *(Continued)*

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; • 4:1 refers to 4 g fat to 1 g of carbohydrate and protein combined. 2.5:1 refers to 2.5 g fat to 1 g of carbohydrate and protein combined.
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; • No funding was received for this study.

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study meaning participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study meaning outcome assessors were not blinded.
Incomplete outcome data (attrition bias)	Low risk	Attrition was reported and was fairly equal across the groups. ITT 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 comorbidity.

Seo 2007

Study characteristics

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/month and seizures were not controlled by at least 3 AEDs. Study completed in Korea. All seizure types included; • Exclusion criteria: children with metabolic disorders, known or suspected neurological degenerative disorders, or both;

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Seo 2007 *(Continued)*

	• Epilepsy syndromes included Lennox-Gastaut syndrome and the study also included participants with infantile spasms
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; • 4:1 refers to 4 g fat to 1 g of carbohydrate and protein combined. 3:1 refers to 3 g fat to 1 g carbohydrate and protein combined; • 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.
Outcomes	• Seizure reduction rate; • Tolerability.
Notes	• 6 participants dropped out in both of the original groups. 2 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; • This study was financially supported by Yonsei University Research Fund of 2003.

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 of participants and personnel (performance bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of participants and study personnel does not seem possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not discussed in this paper, but considering the design of the study, blinding of outcome assessors does not seem possible.
Incomplete outcome data (attrition bias)	Low risk	Number of dropouts and reasons for dropouts were reported and an ITT analysis was completed.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable.
Other bias	Low risk	No other sources of bias identified.

Sharma 2013

Study characteristics

Methods	Open-label, single-centre, parallel-group, randomised controlled trial, to compare the MAD to a usual care 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 drug-resistant epilepsy and 2-14 daily seizures, having previously tried 3 AEDs. Study conducted in India;

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Sharma 2013 *(Continued)*

	• Exclusion criteria: known or suspected inborn errors of metabolism, systemic illness or motivational issues the family that would prelude compliance; • Epilepsy syndromes included: West syndrome (9 participants in the MAD group and 10 participants in usual care group) and myoclonic astatic epilepsy (2 participants in the MAD group and 3 participants in usual care group).
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 usual care group, 3 participants were lost to follow-up; • The lead author (Sharma) was financially supported as a Senior Research Associate in the "Scientists pool scheme" of the Council for Scientific and Industrial Research (CSIR), Government. of India, for this study.

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study meaning participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study meaning outcome assessors were not blinded.
Incomplete outcome data (attrition bias)	Low risk	Study attrition reported and ITT analysis carried out.
Selective reporting (reporting bias)	Low risk	Protocol available 15 August 2015 (NCT00836836).
Other bias	High risk	Excluded participants where motivational issues within the family were noted.

Sharma 2016

Study characteristics

Methods	Prospective, randomised, non-blinded controlled trial to compare sMAD to usual care (normal diet). Four-week baseline period completed.
Participants	• 81 participants aged 2-14 years, with drug-resistant epilepsy, experiencing daily seizures (or more than 7 seizures per week) despite 2 or more AEDs. Study was conducted in India;

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Sharma 2016 *(Continued)*

	• Exclusion criteria: known or suspected inborn errors of metabolism, systemic illness, surgically remediable causes of epilepsy, motivational issues in the family that would preclude compliance; • Epilepsy syndromes included West syndrome (22 participants in sMAD and 25 participants in the normal diet group) and Lennox-Gastaut syndrome (14 participants in sMAD and 13 participants in usual care group).
Interventions	• Randomised into 1 of 2 groups; sMAD (10 g carbohydrate per day, delivered with simplified dietary methods) and usual care (normal diet) for a 3-month period; • This study modified the traditional educational techniques used to implement the diet, to promote the inclusion of children with parents who have low levels of literacy and who are of poor socioeconomic status.
Outcomes	• Seizure reduction; • Adverse effects; • Non-seizure domains; • Tolerability.
Notes	• At 3 months 5 participants dropped out of the trial in the sMAD arm; 1 participant 'changed their mind' after randomisation, 2 were lost to follow-up and 2 discontinued the diet. Reasons for discontinuation included refusal to eat and anorexia with lethargy. In the usual care group 1 participant was lost to follow-up; • This study was supported by the Indian Council of Medical Research (ICMR).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Variable block randomisation (2, 6 and 6 block sizes), using computer generated randomisation sequence.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study meaning participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study meaning outcome assessors were not blinded.
Incomplete outcome data (attrition bias)	Low risk	Study attrition reported and ITT analysis carried out.
Selective reporting (reporting bias)	Low risk	Protocol received. No evidence to suggest selective reporting.
Other bias	Low risk	A subjective, non-validated tool was used to assess alertness, speech, sleeping, social and behavioural changes, results of which not included in this review.

Zare 2017

Study characteristics

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Zare 2017 *(Continued)*

Methods	Prospective, randomised, non-blinded, controlled trial to compare MAD to usual care over a 2-month period.
Participants	• 66 adult participants aged 18 years or over, with drug-resistant epilepsy (2 or more AEDs and 2 or more seizures per month). Study was conducted in Iran; • Exclusion criteria: prior use of the Atkins' diet or MAD for 1 week or more, use of KD within the last year, heart disease, renal disease, hypercholesterolaemia, coronary heart diease, cerebral vascular disease, peripheral vascular disease, atherosclerosis, myocardial infarction, pregnancy, BMI < 18.5 kg/m^2, status epilepticus in last 6 months and 2-week seizure-free period in last 6 months.
Interventions	Randomised into 1 of 2 groups; MAD (carbohydrates limited to 15 g per day; approximate macronutrient intakes as a percentage of total energy: 4% to 6% carbohydrate, 20% to 30% protein, 60% to 70% fat) and usual care for a 2-month period.
Outcomes	• Seizure reduction; • Adverse effects.
Notes	• At 2 months 12 participants dropped out of the MAD arm, all due to non-compliance; • The study was supported by the Plastic Surgery Research Centre, Isfahan University of Medical Sciences, Isfahan.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study meaning participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study meaning outcome assessors were not blinded.
Incomplete outcome data (attrition bias)	Low risk	Study attrition reported and ITT analysis carried out.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable.
Other bias	High risk	Numerical errors with the article. No power calculation stated. Low levels of urinary ketosis achieved, may impact efficacy data. Unknown if baseline period completed prior to commencing diet.

AED: antiepileptic drug; BMI: body mass index; Fast FD: fasting-onset ketogenic diet; Grad KD: gradual-onset ketogenic diet; ITT: intention-to-treat; KD: ketogenic diet; MAD: modified Atkins diet; MCT: medium-chain triglyceride; QALYs: quality-adjusted life years; SD: standard deviation; sMAD: simplified modified Atkins diet.

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

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Study	Reason for exclusion
Dressler 2015	Irrelevant study population - infantile spasms.
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	Drug-resistant infantile spasm population, outcome measures did not match inclusion criteria for this review.
NCT03183076	We suspect that the study was non-randomised.
Singh 2015	Abstract only. Unable to obtain further data.
Smith 2011	Not a randomised controlled trial.

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

CTRI/2015/07/006048

Study name	Modified Atkins diet in adolescence and adults with drug-resistant epilepsy
Methods	An unblinded, randomised controlled trial.
Participants	Aimed to recruit 160 people, aged 10 to 55 years, with drug-resistant epilepsy. Included participants experiencing persistent, daily countable seizures (more than 2 per month for 6 months), willing to attend regular follow-up and maintain seizure frequency accurately and willing to perform induction phase of diet. Potencial participants excluded if less than 10 years of age, surgically remediable causes of epilepsy, clinical features of inborn metabolism, suspicion of a metabolic disorder, refusal to give consent, tried KD in past year, BMI < 18 and > 30 kg/m^2, two or more of the following: high blood ammonia (> 80 mmol/L), high arterial lactate (> 2 mmol/L), metabolic acidosis (pH > 7.2), hypoglycaemia (< 40 mg/dL)
Interventions	• Intervention group treated with MAD (20 g carbohydrate per day) for 6 months; • Control arm receive normal diet with no dietetic input for 6 months, following which MAD can be offered.
Outcomes	Primary outcome: • Greater than 50% seizure reduction at 6 months; Secondary outcomes: • Rate and characteristics of short-term adverse effects while on MAD; • Rate of withdrawal from the MAD diet during the study period and reasons for withdrawal; • Change in quality of life of both groups during the study period.
Starting date	18 August 2015
Contact information	manjari2tripathi@gmail.com
Notes	Recruitment expected to be complete June 2018.

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CTRI/2017/12/010898

Study name	Effect of modified Atkins diet when compared to low glycemic index diet in controlling seizures in children with epilepsy who do not respond to conventional anti epileptic drugs
Methods	A randomised, controlled, parallel group trial.
Participants	• Intends to recruit 90 children, aged 6 months to 5 years old with drug-resistant epilepsy (failure of adequate trials of two tolerated, appropriately chosen drug schedules); • Exclusion criteria: Children with renal, pulmonary, cardiac or hepatic dysfunction, severe malnutrition (according to the World Health Organization).
Interventions	• Intervention group treated with MAD (10 to 20 mg carbohydrate per day); • Control arm treated with low glycaemic index foods.
Outcomes	Primary outcome: • Seizure freedom (as per parental reports) at 4 weeks and 12 weeks; Secondary outcomes: • Rate and characteristics of adverse effects while on MAD at 4 weeks and 12 weeks; • Greater than 50% seizure reduction (as per parental reports) at 4 weeks and 12 weeks; • Greater than 90% seizure reduction (as per parental reports) at 4 weeks and 12 weeks.
Starting date	1 January 2018
Contact information	jayashankarkaushik@gmail.com
Notes	The principle investigator for the study has self-funded the trial.

Hulshof 2017

Study name	The modified Atkins diet in patients with refractory epilepsy and intellectual disability: a randomised controlled trial
Methods	A single-centre, parallel, unblinded randomised controlled trial.
Participants	• Aimed to recruit 54 people, aged > 18 years, adults with drug-resistant epilepsy that was controlled by 2 AEDs; • Included participants must have had ≥ 2 seizures/month and have moderate-to-severe intellectual disability; • Exclusion criteria: participants who have 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 outcome: • Number of responders 4 months after randomisation, compared between the intervention and the control group. Responder is defined by > 50% reduction in seizure frequency;

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Hulshof 2017 *(Continued)*

	Secondary outcomes: • Retention of the diet; • Change in daily functioning; • Feasibility of the MAD in this population and setting; • Adverse effects attributable to the MAD; • Predictive factors of efficacy of the diet.
Starting date	Unknown
Contact information	Unknown
Notes	On 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. No further update was received from the study authors for this update.

NCT02708030

Study name	Dietary therapy in epilepsy treatment (Diet-trial): a randomised non-inferiority trial comparing KD, MAD and LGIT for drug resistant epilepsy
Methods	A randomised, parallel-group trial.
Participants	Intend to recruit 170 children aged 1 to 15 years, who experience four seizures or more per month, despite treatment with two or more AEDs and who have not previously tried a KD, MAD or LGIT diet
Interventions	• First intervention group received KD for 24 months; • Second intervention group received MAD for 24 months; • Third intervention group received LGIT for 24 months.
Outcomes	Primary outcome: • Percentage seizure reduction from baseline at 24 months; Secondary outcomes: • Adverse effects.
Starting date	April 2016
Contact information	Prof Sheffali Gulati
Notes	Recruitment status was unknown at the time of publication. ClinicalTrials.gov last updated July 2017.

NCT03464487

Study name	Comparison between efficacy of daily and intermittent low glycaemic index therapy diet among children with drug resistant epilepsy aged 1-15 years: an open labeled randomized controlled parallel design non-inferiority trial
Methods	An open-label, randomised, controlled, parallel-group design, non-inferiority trial.

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NCT03464487 *(Continued)*

Participants	• Aim to enrol 110 children, aged 1 to 15 years, with drug-resistant epilepsy who were willing to attend regular follow-up; • Exclusion criteria: if there was a surgically remediable cause for their epilepsy, a proven inborn error of metabolism except in which dietary therapy for epilepsy is indicated (i.e. pyruvate carboxylase deficiency and glucose transporter type 1 (GLUT 1) deficiency), previously received KD, MAD or LGIT diet, had chronic kidney disease, chronic liver disease/gastrointestinal illness, chronic heart disease (congenital and acquired), or a chronic respiratory illness.
Interventions	• Intervention group received daily LGIT, alongside AEDs (40 g to 60 g carbohydrate per day, carbohydrates required to have glycemic index less than 50) for 6 months; • Intervention group received daily LGIT for five days of each week, alongside AEDs, plus two days of liberal diet (40 g to 60 g carbohydrate per day for five days per week, carbohydrates required to have glycemic index less than 50) for 6 months.
Outcomes	Primary outcome: • Percentage of seizure reduction from baseline at 24 weeks; Secondary outcomes: • Greater than 50% seizure reduction at 6 months; • Improvement in social quotient at 6 months, measured by Vineland Social Maturity scale; • Rate of adverse effects at 3 months and 6 months; • Correlation between seizure frequency and change with blood haemoglobin A1c levels at 3 months and 6 months; • Correlation between seizure frequency and change with blood betahydroxybutyrate levels at 3 months and 6 months; • Rate of biochemical adverse effects at 6 months.
Starting date	15/02/2018
Contact information	sheffaligulati@gmail.com
Notes	Estimated study completion date was January 2019 however, at the time of publishing, the ClinicalTrials.gov entry reported that the study was still recruiting participants.

NCT03764956

Study name	Comparison of efficacy of LGIT and MAD among children with drug resistant epilepsy
Methods	An open-label randomised, non-inferiority trial with parallel-group design
Participants	• Intend to enrol 110 children, aged 1 to 15 years with drug-resistant epilepsy, willing to come for regular follow-up, seizure frequency > 4 seizures per month, receiving optimal doses of ≥ 2 AEDs. For West syndrome, participants required to have ≥ 4 spasm cluster per month despite treatment with AEDs and adrenocorticotrophic hormone or vigabatrin; • Participants excluded if they had a surgically remediable cause for their epilepsy, an inborn error of metabolism, previously received KD, MAD or LGIT diet, had chronic kidney disease, chronic liver disease/gastrointestinal illness, chronic heart disease (congenital and acquired), or a chronic respiratory illness.
Interventions	• Intervention group received LGIT (food items with glycaemic index < 50 only) for 24 weeks; • Intervention group received MAD (20 g carbohydrate per day, increased fat and protein ratio) for 24 weeks.

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NCT03764956 *(Continued)*

Outcomes	Primary outcome: • Percentage seizure reduction from baseline to 24 weeks; Secondary outcomes: • Greater than 50% seizure reduction at 24 weeks; • Rate of adverse effects at 24 weeks; • Compliance assessed each week (satisfactory or unsatisfactory); • Change in social quotient at 24 weeks measured by Vineland Social Maturity scale; • Change in quality of life of participants < 4 years measured by Pediatric Quality of Life inventory at 24 weeks; • Change in quality of life of participants ≥ 4 years measured by Quality of Life in Childhood Epilepsy questionnaire at 24 weeks; • Change in quality of life of caregivers measured by the World Health Organization Quality of Life questionnaire at 24 weeks; • Gut microbiota analysis pre- and post-dietary therapy at 24 weeks; • Change in behavioural abnormalities at 24 weeks.
Starting date	26/12/2018
Contact information	sheffaligulati@gmail.com drvyshakhanandmp@gmail.com
Notes	

NCT03807141

Study name	Evaluation of the modified Atkins diet in children with epileptic spasms refractory to hormonal therapy: a randomised controlled trial
Methods	An open-label, randomised, controlled, parallel-group design trial.
Participants	• Intend to enrol 90 children, aged 9 months to 3 years, with epileptic spasms in clusters and evidence of hypsarrhythmia or its variants on EEG, at least one or more cluster(s) per day despite treatment with oral corticosteroids or adrenocorticotrophic hormone (ACTH) and one additional anticonvulsant (valproate/benzodiazepine/vigabatrin/topiramate/zonisamide/levetiracetam) for at least 4 weeks; • Exclusion criteria: Children with an error of known or suspected metabolism, or they had renal, pulmonary, cardiac, or hepatic dysfunction, severe malnutrition, motivational or psychosocial issues in the family which may affect compliance.
Interventions	• Intervention group are treated with MAD (10 g carbohydrate per day) for 1 month; • Control arm receive normal diet with no dietetic input for 1 month.
Outcomes	Primary outcome: • Seizure freedom (as per parental reports) at 4 weeks; Secondary outcomes: • Greater than 50% seizure reduction (as per parental reports) at 4 weeks; • Resolution of hypsarrhythmia on EEG at 4 weeks; • Rate and characteristics of adverse effects as (per parental reports) while on MAD.

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NCT03807141 *(Continued)*

Starting date	15 January 2019
Contact information	sharma.suvasini@gmail.com
Notes	The study is estimated to be completed 31 March 2022. Sponsors and Collaborators includes Mary Hardinge Medical College.

Titre-Johnson 2017

Study name	Ketogenic diet in the treatment of epilepsy in children under the age of 2 years:
Methods	An open-label, randomised, controlled, multi-centre trial.
Participants	Intend to recruit 160 children, aged 3 months up to 24 months, with confirmed diagnosis of epilepsy, specifically, drug-resistant epilepsy (failure of two AEDs) and includes infantile spasms. Seizure frequency required to be ≥ 4 seizures per week on average.
Interventions	• Intervention group treated with classical ketogenic diet (at least a 3:1 ratio for fat to carbohydrate and protein) for 8 weeks up to 12 months; • Control arm will receive further antiepileptic drugs (the most appropriate further AED for the individual child as chosen by the expert clinician) plus a discussion regarding diet and healthy eating.
Outcomes	Primary outcome: • Change in seizure frequency from baseline to weeks 6-8; Secondary outcomes: • Seizure freedom at 8 weeks; • Greater than 50% seizure reduction at 8 weeks; • Tolerance to KD (assessed by adverse effects questionnaire) at 8 weeks; • Rate of biochemical adverse effects at 8 weeks; • Relationship between medium-chain fatty acids and seizure control at 8 weeks; • Retention rate at 12 months; • Quality of life (Infant Toddler Quality of Life Questionnaire) at 12 months; • Neurodevelopmental outcome (Vineland Adaptive Behaviour Scales) at 12 months.
Starting date	January 2015
Contact information	s.titre-johnson@ucl.ac.uk
Notes	• ClinicalTrials.gov identifier (NCT number): NCT02205931; • Estimated study completion was June 2019, however, at the time of publishing, the ClinicalTrials.gov entry reported that the study was still recruiting participants.

AED: antiepileptic drug; BMI: body mass index; EEG: electroencephalogram; KD: ketogenic diet; LGIT: low glycaemic index treatment; MAD: modified Atkins diet.

DATA AND ANALYSES

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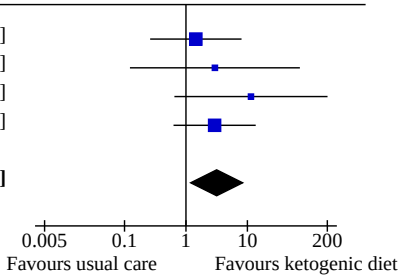
Comparison 1. Ketogenic diet versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Seizure freedom: children	4	385	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [1.20, 8.35]
1.2 Seizure freedom: adults	2	141	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 50% or greater reduction in seizure frequency: children	4	385	Risk Ratio (M-H, Fixed, 95% CI)	5.80 [3.48, 9.65]
1.4 50% or greater reduction in seizure frequency: adults	2	141	Risk Ratio (M-H, Random, 95% CI)	5.03 [0.26, 97.68]
1.5 Treatment withdrawal: children	5	425	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.74, 1.57]
1.6 Treatment withdrawal: adults	2	141	Risk Ratio (M-H, Random, 95% CI)	5.38 [0.42, 69.53]

Analysis 1.1. Comparison 1: Ketogenic diet versus usual care, Outcome 1: Seizure freedom: children

	Ketogenic diet		Usual care			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Lambrechts 2017	3	29	2	28	40.3%	1.45 [0.26 , 8.02]	
Neal 2008	1	73	0	72	10.0%	2.96 [0.12 , 71.47]	
Sharma 2013	5	50	0	52	9.7%	11.43 [0.65 , 201.50]	
Sharma 2016	6	41	2	40	40.1%	2.93 [0.63 , 13.65]	
Total (95% CI)		**193**		**192**	**100.0%**	**3.16 [1.20 , 8.35]**	
Total events:	15		4				

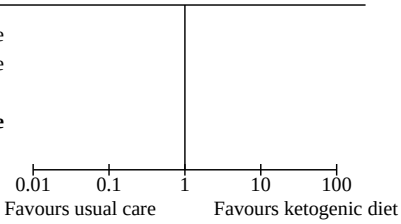
Heterogeneity: Chi² = 1.58, df = 3 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Ketogenic diet versus usual care, Outcome 2: Seizure freedom: adults

	Ketogenic diet		Usual care			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kverneland 2018	0	37	0	38		Not estimable	
Zare 2017	0	34	0	32		Not estimable	
Total (95% CI)		**71**		**70**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



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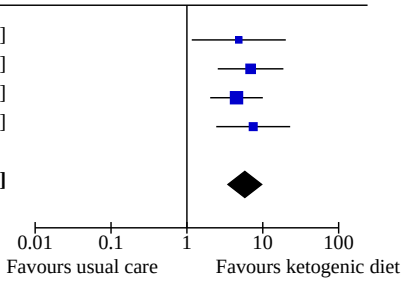
Analysis 1.3. Comparison 1: Ketogenic diet versus usual care, Outcome 3: 50% or greater reduction in seizure frequency: children

Study or Subgroup	Ketogenic diet Events	Ketogenic diet Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lambrechts 2017	10	29	2	28	13.6%	4.83 [1.16 , 20.10]
Neal 2008	28	73	4	72	26.9%	6.90 [2.55 , 18.69]
Sharma 2013	26	50	6	52	39.3%	4.51 [2.03 , 10.01]
Sharma 2016	23	41	3	40	20.3%	7.48 [2.44 , 22.96]
Total (95% CI)		**193**		**192**	**100.0%**	**5.80 [3.48 , 9.65]**
Total events:	87		15			

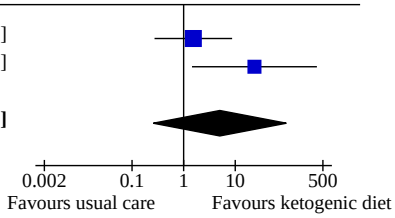
Heterogeneity: Chi² = 0.76, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 6.76 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Ketogenic diet versus usual care, Outcome 4: 50% or greater reduction in seizure frequency: adults

Study or Subgroup	Ketogenic diet Events	Ketogenic diet Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Kverneland 2018	3	37	2	38	56.7%	1.54 [0.27 , 8.70]
Zare 2017	12	34	0	32	43.3%	23.57 [1.45 , 382.39]
Total (95% CI)		**71**		**70**	**100.0%**	**5.03 [0.26 , 97.68]**
Total events:	15		2			

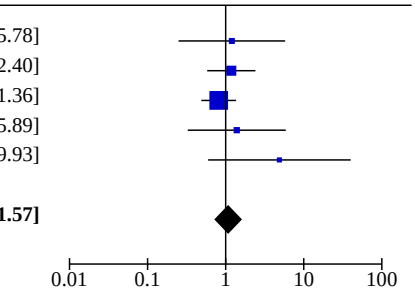
Heterogeneity: Tau² = 3.27; Chi² = 3.33, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 1.07 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Ketogenic diet versus usual care, Outcome 5: Treatment withdrawal: children

Study or Subgroup	Ketogenic diet Events	Ketogenic diet Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
El-Rashidy 2013	4	25	2	15	6.4%	1.20 [0.25 , 5.78]
Lambrechts 2017	11	29	9	28	23.6%	1.18 [0.58 , 2.40]
Neal 2008	19	73	23	72	59.7%	0.81 [0.49 , 1.36]
Sharma 2013	4	50	3	52	7.6%	1.39 [0.33 , 5.89]
Sharma 2016	5	41	1	40	2.6%	4.88 [0.60 , 39.93]
Total (95% CI)		**218**		**207**	**100.0%**	**1.08 [0.74 , 1.57]**
Total events:	43		38			

Heterogeneity: Chi² = 3.31, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Not applicable



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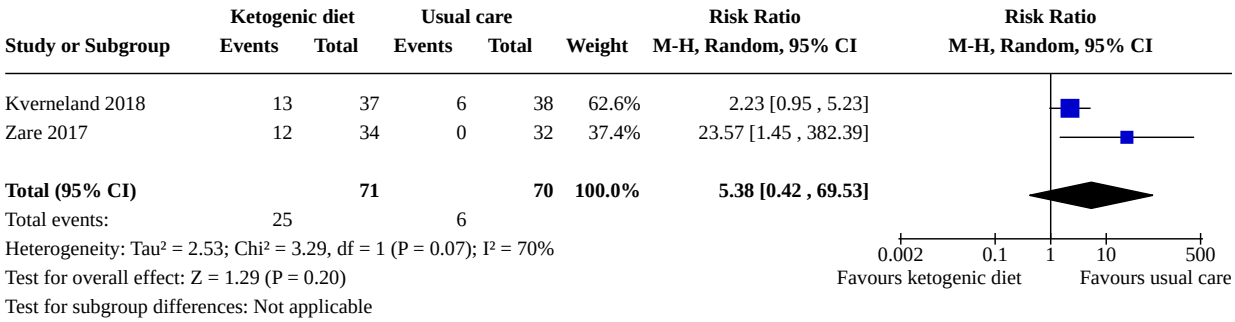
Analysis 1.6. Comparison 1: Ketogenic diet versus usual care, Outcome 6: Treatment withdrawal: adults



APPENDICES

Appendix 1. CRS Web search strategy

1. MESH DESCRIPTOR Epilepsy EXPLODE ALL WITH QUALIFIER DH AND CENTRAL:TARGET

2. MESH DESCRIPTOR Seizures EXPLODE ALL WITH QUALIFIER DH AND CENTRAL:TARGET

3. #1 OR #2

4. MESH DESCRIPTOR Diet Therapy EXPLODE ALL AND CENTRAL:TARGET

5. MESH DESCRIPTOR Fasting EXPLODE ALL AND CENTRAL:TARGET

6. (ketogenic* OR diet OR diets OR dieting):AB,KW,MC,MH,TI AND CENTRAL:TARGET

7. #4 OR #5 OR #6

8. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET

9. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET

10. (epilep* OR seizure* OR convuls*):AB,KW,MC,MH,TI AND CENTRAL:TARGET

11. #8 OR #9 OR #10 AND CENTRAL:TARGET

12. #7 AND #11

13. #3 OR #12

Appendix 2. 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/

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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 or pragmatic 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

23. remove duplicates from 22

WHAT'S NEW

Date	Event	Description
29 April 2019	New search has been performed	We updated the searches on 29 April 2019 and included two new studies (Kverneland 2018; McDonald 2018)
29 April 2019	New citation required but conclusions have not changed	Conclusions are unchanged

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 3, 2003

Date	Event	Description
11 April 2017	New citation required but conclusions have not changed	Conclusions are unchanged
11 April 2017	New search has been performed	We updated the searches on 11 April 2017 and included four new studies (Lambrechts 2017; Kim 2016; Singh 2015; Zare 2017)
30 March 2015	New citation required but conclusions have not changed	Conclusions are unchanged
30 March 2015	New search has been performed	We updated the searches on 30 March 2015 and included three new studies (El-Rashidy 2013; Raju 2011; Sharma 2013)

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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	We updated this review. We included four new RCTs. We also identified seven prospective studies and four retrospective studies.

CONTRIBUTIONS OF AUTHORS

Kirsty J Martin-McGill (KM) was responsible for the update of this review.

Rebecca Bresnahan (RB) provided support for the update of this review.

Robert G Levy (RL) provided expert opinion and feedback for the update of this review.

Paul N Cooper (PC) provided expert opinion and feedback for the update of this review.

DECLARATIONS OF INTEREST

KM: received PhD funding from The University of Liverpool.

RB: 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

  This review update was funded by the National Institute for Health Research (NIHR) [Clinically effective treatments for central nervous system disorders in the NHS, with a focus on epilepsy and Movement Disorders] (SRPG project 16/114/26). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated the methods, results, discussion, conclusion and recommendation sections due to the addition of new studies. This is the second title change since the protocol was published.

This most recent review update was undertaken at the request of the National Institute for Health and Care Excellence (NICE). NICE guidelines include pathways for epilepsy populations with intellectual disabilities. Consequently, for this review update, we also attempted to assess KD interventions in this epilepsy population specifically for the first time.

INDEX TERMS

Medical Subject Headings (MeSH)

Age Factors; Diet, Carbohydrate-Restricted [methods]; Diet, High-Protein Low-Carbohydrate [methods]; Diet, Ketogenic [adverse effects] [*methods]; Dietary Carbohydrates [*administration & dosage]; Dietary Fats [*administration & dosage]; Drug Resistant Epilepsy [*diet therapy]; Intention to Treat Analysis; Prospective Studies; Quality of Life; Randomized Controlled Trials as Topic; Retrospective Studies; Sample Size

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MeSH check words

Adolescent; Adult; Aged; Child; Child, Preschool; Humans; Infant; Middle Aged; Young Adult

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