# The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial

*Elizabeth G Neal, Hannah Chaffe, Ruby H Schwartz, Margaret S Lawson, Nicole Edwards, Geogianna Fitzsimmons, Andrea Whitney, J Helen Cross*

*Lancet Neurol* 2008; 7: 500–06

Published Online May 3, 2008
DOI:10.1016/S1474-4422(08)70092-9

See Reflection and Reaction page 471

**Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, University College London, London, UK** (E G Neal PhD, H Chaffe BSc, M S Lawson PhD, N Edwards BSc, G Fitzsimmons BSc, A Whitney MRCP, J H Cross FRCPCH); **National Centre for Young People with Epilepsy, Lingfield, UK** (E G Neal, H Chaffe, J H Cross); **and NW London Hospitals NHS Trust, London, UK** (R H Schwartz FRCPCH)

Correspondence to: Elizabeth G Neal, Neurosciences Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
**l.neal@ich.ucl.ac.uk**

## Summary

**Background** **The ketogenic diet has been widely and successfully used to treat children with drug-resistant epilepsy since the 1920s. The aim of this study was to test the efficacy of the ketogenic diet in a randomised controlled trial.**

**Methods** **145 children aged between 2 and 16 years who had at least daily seizures (or more than seven seizures per week), had failed to respond to at least two antiepileptic drugs, and had not been treated previously with the ketogenic diet participated in a randomised controlled trial of its efficacy to control seizures. Enrolment for the trial ran between December, 2001, and July, 2006. Children were seen at one of two hospital centres or a residential centre for young people with epilepsy. Children were randomly assigned to receive a ketogenic diet, either immediately or after a 3-month delay, with no other changes to treatment (control group). Neither the family nor investigators were blinded to the group assignment. Early withdrawals were recorded, and seizure frequency on the diet was assessed after 3 months and compared with that of the controls. The primary endpoint was a reduction in seizures; analysis was intention to treat. Tolerability of the diet was assessed by questionnaire at 3 months. The trial is registered with ClinicalTrials.gov, number NCT00564915.**

**Findings** **73 children were assigned to the ketogenic diet and 72 children to the control group. Data from 103 children were available for analysis: 54 on the ketogenic diet and 49 controls. Of those who did not complete the trial, 16 children did not receive their intervention, 16 did not provide adequate data, and ten withdrew from the treatment before the 3-month review, six because of intolerance. After 3 months, the mean percentage of baseline seizures was significantly lower in the diet group than in the controls (62·0% *vs* 136·9%, 75% decrease, 95% CI 42.4–107.4%; p<0·0001). 28 children (38%) in the diet group had greater than 50% seizure reduction compared with four (6%) controls (p<0·0001), and five children (7%) in the diet group had greater than 90% seizure reduction compared with no controls (p=0·0582). There was no significant difference in the efficacy of the treatment between symptomatic generalised or symptomatic focal syndromes. The most frequent side-effects reported at 3-month review were constipation, vomiting, lack of energy, and hunger.**

**Interpretation** **The results from this trial of the ketogenic diet support its use in children with treatment-intractable epilepsy.**

**Funding** **HSA Charitable Trust; Smiths Charity; Scientific Hospital Supplies; Milk Development Council.**

## Introduction

The ketogenic diet has been widely used as a treatment for drug-resistant childhood epilepsy since the first reports of its beneficial action in seizure control.[1,2] Although the exact mechanism of action is still unclear, the high fat and restricted carbohydrate content of the diet is thought to mimic the biochemical response to starvation, when ketone bodies become the main fuel for the brain's energy demands.[3] The diet has been shown to be effective in retrospective and prospective observational studies: more than half of children who were treated showed a greater than 50% reduction in seizures, and many were seizure free after only 3 months.[4–9] The authors of systematic reviews[10,11] concluded there was sufficient evidence of the efficacy of the diet in children with intractable epilepsy but were concerned by the paucity of controlled trials. A Cochrane review of the ketogenic diet found no reports of randomised controlled trials,[12] despite recommendations by the International League Against Epilepsy (ILAE) that such trials should be included among the required criteria to assess the efficacy and tolerability of all antiepileptic treatments.[13]

Most studies report the use of the classical ketogenic diet,[10,11] which has been used since the 1920s and is based on a ratio of fat:carbohydrate and protein of 3:1 or 4:1.[14] A modification to this diet that used medium-chain triglycerides (MCT) as an alternative fat source was introduced in the 1970s.[15,16] MCT yield more ketones per kilocalorie of energy provided than long-chain triglycerides (LCT) do, they are absorbed more efficiently, and are carried directly from the digestive system to the liver by the portal vein. The increased ketogenic potential of MCT means less total fat is needed in the MCT diet, which enables the inclusion of more carbohydrate and protein. Although both types of

diet are effective for treating seizures,[17] there are no randomised controlled trials that compare the classical and the MCT ketogenic diets.

The ketogenic diet was traditionally thought to be most successful for treating patients with myoclonic seizures, atonic seizures, or the mixed seizures seen in Lennox–Gastaut syndrome; however, more recent studies have found no significant difference in efficacy between seizure types, including focal seizures.[4,5,8] The authors of a study that compared children who showed a dramatic early response to diet treatment with a control group of children who had no response to the ketogenic diet found the only significant difference to be the absence of complex partial seizures in the early responders.[18] The successful use of the diet has also been reported in children with infantile spasms,[19] severe myoclonic epilepsy of infancy,[20] tuberous sclerosis complex,[21] and myoclonic astatic epilepsy.[22,23]

Owing to the lack of randomised controlled trials in children on any type of ketogenic diet, the aim of this study was to investigate whether there are clear benefits in terms of seizure control in children with epilepsy who were treated with the ketogenic diet for 3 months compared with a control group of children whose treatment did not change.

## Methods

### Participants

Children were recruited from referrals from epilepsy clinics at Great Ormond Street Hospital and from paediatric neurologists and paediatricians around the UK. Children aged between 2 and 16 years who had seizures at least daily or more than seven seizures per week, had not responded to at least two antiepileptic drugs, and had not previously been treated with the ketogenic diet were eligible for inclusion. Exclusion criteria were a history of hyperlipidaemia, renal stones, or organic-acid-deficiency syndromes: these did not apply to any referred children. Families or other carers were made to understand the implications of the diet, were prepared to bring the child to the trial centre, and were available for regular home monitoring of the child. Before an initial screening appointment, families were sent an information sheet that explained the ketogenic diet and the trial. Children were then assessed with regard to epilepsy diagnosis (syndrome diagnosis was defined, where possible, in accord with the International League Against Epilepsy[24,25]) and fulfilment of entry criteria by one of two consultant paediatric neurologists. The main centre was Great Ormond Street Hospital for Children, London; a few children were seen at either Central Middlesex Hospital, London, or at a residential centre (the National Centre for Young People with Epilepsy, Surrey). Children were randomly assigned to groups by use of a computer program (Minim, University of York, UK) that used the minimisation method to ensure a close balance between the treatment groups for three defined age-groups (2–6 years, 7–11 years, and 12–16 years) and that took into account whether the child was at the residential centre or not. The program randomly assigned the children to start the diet either after a 4-week baseline period or after the baseline and a further 3 months of seizure records with no changes in treatment; the latter group acted as controls during the 3-month pre-diet period. Children were also randomly assigned to receive either the classical or MCT versions of the diet; the results of this comparison will be reported separately. Neither the ketogenic diet team nor the parents or carers of the children were blinded to which intervention was allocated.

Permission for the study was obtained from the ethics committees at each of the three centres. Parents or carers of all children were asked to give written consent before their child was enrolled in the study. When appropriate, children were also asked to give their consent to treatment.

### Procedures

All ketogenic diets were calculated on an individual basis by a dietitian after a telephone consultation with the parents or carers with regard to the child's current food preferences. The children's pre-study calorific intake was calculated with a computer program (Com-peat Pro version 5.8; Nutrition Systems, Banbury, UK) from a 4-day food record. The initial calorie prescription for the ketogenic diets was based on an average between their pre-diet intake and the recommendations for energy requirements on the ketogenic diet[26] and taking into account current and previous weight and height, UK recommended calorific requirements, levels of physical activity, seizure activity, and medications. Ketogenic diets were started at home after a full day outpatient visit for education and baseline electroencephalographic and blood tests. A non-fasting initiation protocol was used, and no changes to the child's normal diet were advised before starting the ketogenic diet treatment. Classical diets were started at a 2:1 ratio (fat:protein and carbohydrate) and gradually increased to a 3:1 or 4:1 ratio over 1–2 weeks, as tolerated; protein content was generally kept at WHO minimum requirements for age.[27] MCT diets were started on a full prescription for carbohydrate (generally 15% of total energy), protein (usually 10% of total energy) and long-chain fat (usually 30% of total energy). The MCT fat content was increased incrementally over 7–10 days, as tolerated, to an initial level that was usually 45% of total dietary energy. Alterations were made to the calorie prescriptions as needed during the follow-up. These were generally done in increases or decreases of 100-kcal increments with at least a 2-week lag period before any further changes were made; 50-kcal increments were used in children with a low daily energy prescription, for example, the very young or non-ambulant. Diets were fully supplemented with vitamins and minerals.

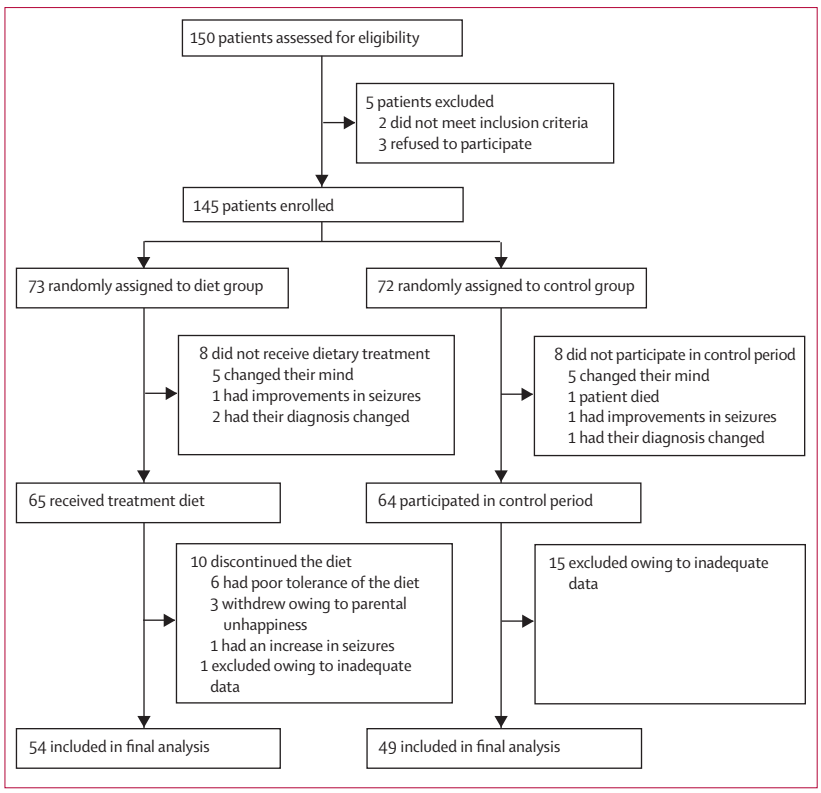


*Figure:* **Trial profile**

Children were reviewed as outpatients at 6 weeks and 3 months. They were also closely monitored by telephone call between clinic visits. In the diet group, changes were made to the diet as necessary during the telephone consultation to improve ketosis and optimise seizure control. Protein intake was increased as needed to meet recommended requirements, and modifications were made to fluid intake and meal distribution when necessary. The control group received their normal diet with no dietetic input, and remained on the same antiepileptic medication for the 3 months.

The primary outcome was efficacy—a decrease in seizure frequency. This was assessed by the parent or carer in accordance with seizure records on the basis of a chart with six categories of seizure (absence, myoclonic, atonic, tonic, tonic–clonic, and focal). The definitions of the different seizure types were clarified with parents at the start. Seizure frequencies were recorded daily for the 4-week baseline period and the study period. The number of seizures in the 28 days before a timepoint was used to calculate the mean seizure number at that timepoint, which was expressed as a percentage of the mean baseline number of daily seizures (ie, the number of seizures during the 4 weeks before the child started either the diet or the control phase of the study). No changes were made to the child's antiepileptic medication during the 4-week baseline or the 3-month study periods.

Follow-up outpatient assessment and a standardised questionnaire completed by the parents were used to assess the tolerability of the diet. Ketosis was assessed by twice-daily home urine testing with Ketostix (Bayer, Germany) and by measurement of blood ketone concentrations at clinic appointments. Weight and height were recorded at all hospital visits.[28]

### Statistical analysis

This trial was designed as a comparative test of the hypothesis that the ketogenic diet might be more efficacious than the continuation of antiepileptic medication with no other changes. By use of a null hypothesis that the two groups would not have a significant difference in seizure control outcome, and by defining 25% as the minimum outcome difference of clinical importance, the sample size formula to compare two means calculated a necessary sample of 47 patients per group to enable the detection of a difference that was significant at 5% with a power of 90%. The calculation was based on an expected outcome range of mean percentages of baseline seizures from 0% to 150% (SD 37·5%). A sample of this size would enable detection of a 25% or more difference in mean percentage of baseline seizures between the groups; any difference greater than this would be regarded as clinically significant.

Mean percentage of baseline seizures at 3 months between children on the ketogenic diet and controls were compared with the unpaired *t* test and verified with the Mann-Whitney *U* test, owing to the skewed data. Multiple linear regression was used to assess the association between diet and the percentage of baseline seizures, taking into account the sex of the child and which of the three age-groups they were in. Responder rates of greater than either 50% or 90% seizure reduction were set, and Fisher's exact test was used to calculate the differences between the diet and control groups with regard to these cut-off points. Epilepsy syndromes were combined into two categories: those that have generalised symptoms and those that have focal symptoms. The unpaired *t* test was used to compare mean percentage of baseline seizures between the groups with generalised and focal symptoms in the diet and control groups at 3 months.

### Role of the funding source

The funding sources had no role in study design, data collection, data analysis, interpretation of the results, report writing, or the decision to submit the manuscript for publication. The corresponding author had full access to all the data and had final responsibility for the decision to publish.

## Results

Children were recruited to the trial between December, 2001, and July, 2006, and randomly assigned to either

the diet or control groups (figure, table 1). 37 children in the diet group were assigned to a classical (LCT) ketogenic diet and 36 children were assigned to a MCT ketogenic diet.

Baseline demographic characteristics of children who were randomly assigned to each of the study groups and those included in the final analysis are given in table 1. 78 children had generalised epilepsy (39 in the diet groups and 39 in the control group) and 57 children had a focal epilepsy (27 in the diet groups and 30 in the control group). The specific epilepsy syndromes are shown in table 2. Further diagnoses included seven children with severe myoclonic epilepsy of infancy and three children who were later found to have a neurodegenerative disease, who had their diagnosis changed. At entry, six children were on no epilepsy medications because previous treatments had had no effect and were withdrawn, 20 children were on one medication, 53 children were on two medications, 54 children were on three medications, 11 children were on four medications, and one child was on five medications. The children had a mean of 11·6 seizures per day (13·3 in the diet group and 10·1 in the control group). Eight children were recruited from the residential centre; all others attended the hospital as outpatients while they lived at home.

Table 3 shows the results for percentage of baseline seizure numbers in both groups at 3 months. Mean seizure frequency was reduced by 38% in the treatment group and increased by 37% in the control group. The difference between the mean percentage of baseline seizures at 3 months in the diet and control groups was 74·9% (95% CI 42·4–107·4%; p<0·0001). Although the data distribution is clearly skewed by a number of outliers and a digression between mean and median values for both groups, the difference remained significant when tested with non-parametric methods. The difference between the mean percentage baseline seizures in the diet and control groups increased slightly to 76·6% (44·4–108·9; p<0·0001) when calculated with a linear regression model. There were three extreme outliers in the control group who had increases in seizure numbers of more than 400% in the 3-month period. Removal of these outliers before analysis lowered the mean percentage of baseline seizures in the control group to 112·9% and reduced the mean difference between the groups to 50·9% (30·7–71·2; p<0·0001). Although the wide confidence intervals are compatible with a broad range of clinical scenarios, the diet group had a considerably better outcome in terms of efficacy compared with the control group.

At 3 months, freedom from seizures was attained in one child in the diet group and none of the children in the control group. Table 4 shows the rates in the diet and control groups of children who achieved greater than either 50% or 90% reduction in seizures after 3 months, with the total number of children allocated to each treatment group used as the denominator.

Ten children withdrew from dietary treatment before 3 months: three because of parental unhappiness with the restrictions, two with behavioural food refusal, and one each with increased seizures, extreme drowsiness, constipation, vomiting, and diarrhoea. One child was found to have haematuria after a few weeks on dietary treatment, and a renal ultrasound detected debris that indicated there was a risk of kidney stone formation. After treatment with potassium citrate, the child remained on the diet without any recurrence of the problem. Table 5 shows the reported side-effects during the previous 3 months, as reported on the questionnaire completed by the parent or carer. Few of the adverse

| | Diet group | | Control group | |
|---|---|---|---|---|
| | Allocated to study group (n=73) | Included in final analysis (n=54) | Allocated to study group (n=72) | Included in final analysis (n=49) |
| **Sex** | | | | |
| Male | 38 (52%) | 30 (56%) | 38 (53%) | 25 (51%) |
| Female | 35 (48%) | 24 (44%) | 34 (47%) | 24 (49%) |
| **Age** | | | | |
| 2–6 years | 37 (51%) | 28 (52%) | 29 (40%) | 20 (41%) |
| 7–11 years | 27 (37%) | 20 (37%) | 32 (44%) | 20 (41%) |
| 12–16 years | 9 (12%) | 6 (11%) | 11 (15%) | 9 (18%) |

*Table 1:* **Baseline characteristics of children allocated to each study group and included in final analysis**

| | Number of children |
|---|---|
| **Generalised epilepsy** | |
| Lennox–Gastaut syndrome | 14 |
| West syndrome (with continued spasms) | 11 |
| Myoclonic absence epilepsy | 7 |
| Unspecified myoclonic epilepsy | 8 |
| Myoclonic astatic epilepsy | 8 |
| Atypical absence seizures | 3 |
| Continuous spike wave of slow sleep | 2 |
| Childhood absence epilepsy | 2 |
| Myoclonic encephalopathy | 1 |
| No specific syndrome diagnosis | 22 |
| **Focal epilepsy** | |
| Structural brain abnormalities | 27 |
| Presumed focal | 16 |
| Multifocal | 14 |

*Table 2:* **Number of children in each epilepsy syndrome category**

| | Diet group (n=54) | Control group (n=49) |
|---|---|---|
| Mean percentage of baseline seizures after 3 months (95% CI) | 62·0% (50–74%) | 136·9% (105–169%) |
| Median percentage of baseline seizures after 3 months (SD, IQR) | 47·7% (43, 0–200%) | 106·3% (111, 28–575%) |

*Table 3:* **Comparison of seizures as a percentage of baseline after 3 months**

| | Patients who achieved cut-off points | | p value |
|---|---|---|---|
| | Diet group (n=73) | Control group (n=72) | |
| >90% reduction in seizures | 5 (7%) | 0 (0%) | 0·0582 |
| >50% reduction in seizures* | 28 (38%) | 4 (6%) | <0·0001 |
| <50% reduction in seizures† | 45 (62%) | 68 (94%) | <0·0001 |

Percentages based on numbers allocated to each intervention. *Includes patients who reported >90% reduction. †Includes 71 patients with data and 42 unknown (16 did not recieve treatment, 10 discontinued treatment, 16 with no data).

*Table 4:* **Number of children in each group who achieved 50% and 90% seizure reduction at 3 months**

| | Patients who reported side-effect* |
|---|---|
| Vomiting | 13 (24%) |
| Diarrhoea | 7 (13%) |
| Abdominal pain | 5 (9%) |
| Constipation | 18 (33%) |
| Medication for constipation needed | 13 (24%) |
| Lack of energy | 13 (24%) |
| Hunger | 12 (22%) |

*Data are number (%) of the 55 children who continued on the diet for 3 months.

*Table 5:* **Side-effects reported after 3 months on the ketogenic diet.**

effects led to withdrawal of treatment and most could be treated with dietary adjustment.

The numbers of children who provided data in individual syndrome groups were too small for between-group statistical analysis. The five children who had a greater than 90% reduction in seizures had infantile spasms, unspecified symptomatic generalised epilepsy, continuous spike wave of slow sleep, myoclonic astatic epilepsy, and multifocal epilepsy, respectively; the child with myoclonic astatic epilepsy was seizure free.

Two additional categories were defined: all epilepsy syndrome groups that could be grouped together as being symptomatic generalised in origin, and all seizure syndrome groups that could be grouped together as being symptomatic focal in origin. Not all epilepsy syndromes could be included: 51 of 54 children in the diet group for whom data were available for analysis were able to have their seizures broadly classified in this way (27 as symptomatic generalised and 24 as symptomatic focal) as were 41 of 49 children in the control group (19 as symptomatic generalised and 22 as symptomatic focal). After 3 months of dietary treatment, the mean percentage of baseline seizures was 62·3% in the symptomatic generalised group and 64·9% in the symptomatic focal group (p=0·865). In the control group, the mean percentage of baseline seizures was 160·5% in the symptomatic generalised group and 121·2% in the symptomatic focal group (p=0·285) after 3 months.

## Discussion

We report the results of a randomised controlled trial to assess the efficacy of the ketogenic diet to treat drug-resistant epilepsy in children. Our results clearly show the benefits of the ketogenic diet over no change in treatment: seizures in the 54 children on the diet fell to a mean of 62% of baseline, and increased to 137% of baseline in the control group. Responder rates (table 4) were similar to those seen in randomised controlled trials of newer antiepileptic drugs versus placebo.[29,30] The increase in seizure frequency in the control group, whose treatment did not change, is a surprise. The most probable explanation is the unusual increase in seizure frequency in three of the children; when these data were excluded, the increase in seizure frequency in the control group over 3 months was only 12%. There is also likely to be an improvement in within-person seizure recording over time, which might have led to an underestimation of the benefit of the diet during the initial 3-month period. When children with seizures of symptomatic generalised origin were compared with children with seizures of symptomatic focal origin, the results show no difference. Further conclusions on the differences in efficacy between epilepsy syndromes will be made when the 6-month and 12-month analyses of the completed data set are available.

The response rates in this study are lower than other reported rates, at both the 50% and 90% seizure reduction.[4–9,31] The differences could be accounted for, to some degree, by the fact that our group might have been more drug resistant because the diet was started late in the clinical course. There might also have been selection bias in some of the other studies, with the diet offered to children with a type of epilepsy that was presumed to be more responsive to the dietary treatment. Furthermore, children under 2 years were not included in our study, despite anecdotal evidence that this age-group might respond more favourably than older children do.[19,32] This age discrepancy needs to be investigated further. Direct comparisons of the results of this study with those previously reported is difficult in view of the major differences in study design and the lack of randomised controlled studies. The randomisation process to allocate children by use of a minimisation method that accounts for age-group and treatment location avoided any selection bias between the study groups.

Our study had a high number of non-starters and withdrawers, which was difficult to predict and not reported in other studies of the ketogenic diet. This has important implications for the careful use of scarce dietetic resources because the initial ketogenic calculations and monitoring are time consuming. The initial assessment and screening process is vital, and future inclusion criteria should ensure that children with pre-existing behavioural feeding problems are appropriately treated before they embark on a restricted diet. The willingness and full understanding of parents

and carers to comply with restrictions and monitoring is also paramount.

Just under a quarter of the 55 children who were on a ketogenic diet until 3 months reported problems such as vomiting, lack of energy, or hunger; slightly fewer reported diarrhoea, abdominal pain, or taste problems at some point during treatment. In most cases the tolerance problems were resolved by adjustment of the diet, and in none of the children were the problems so extensive that they led to withdrawal of the diet at 3 months. Constipation was the most reported problem; a third of the children in the diet group reported this as a side-effect. Although cited as a reason to stop the diet in only one of the children who withdrew before 3 months, about a quarter of the children who stayed on the diet for 3 months needed medication to treat this problem.

The scientific weight of this study could have been improved by the inclusion of prospective seizure data on the children who either did not start treatment or who withdrew before 3 months; for the purpose of analysing the 50% and 90% responder rates as an intention to treat, these withdrawals are counted as non-responders. The study would also have been improved by a double-blind, randomisation process, as recommended by Glauser and colleagues[33] for all class I or II scientific evidence. However, it would have been impossible to blind the parents, carers, and children because this was a prescribed diet that requires their close cooperation; furthermore, the dietitian who prescribed the diets was also involved in data collection and would not have been able to be blinded. An improvement would have been to have an independent person who was blinded to the group allocation to collect and analyse the data. The use of parental or carer seizure records will probably miss some nocturnal seizures and runs the risk of introducing subjective errors. Within-person recording was thought to be consistent over the study period, although this might improve with time, which might explain the increase in seizure frequency seen in the control group. Long-term outcome data on dietary efficacy would have been of benefit, and will be included in the separately reported comparison of the classical and MCT versions of the diet.

Despite these limitations, this study presents evidence from a randomised controlled trial on the ketogenic diet. We have shown that the diet has efficacy and should be included in the management of children who have drug-resistant epilepsy. However, the diet is not without possible side-effects, which should be considered alongside the risk–benefit of other treatments when planning the management of such children.

#### Contributors

All authors participated in the clinical work and data collection for this study. The data analysis and the writing of this report were done by EGN and JHC.

#### Conflicts of interest

JHC has received educational grants and honoraria for educational talks from UCB, Janssen Cilag, Eisai, and SHS International.

#### Acknowledgments

Funding was received for this project from HSA, Smiths Charity, Scientific Hospital Supplies, and the Milk Development Council. UCL Institute of Child Health received funding as a National Institute for Health & Research Specialist Biomedical Research Centre. Annie Jones provided some editorial advice on the structure of the manuscript.

#### References

1 Wilder RM. The effects of ketonemia on the course of epilepsy. *May Clin Proc* 1921; **2:** 307–08.
2 Peterman MG. The ketogenic diet in epilepsy. *JAMA* 1925; **84:** 1979–83.
3 Hartman AL, Gasior M, Vining EP, Rogawski MA. The neuropharmacology of the ketogenic diet. *Pediatr Neurol* 2007; **36:** 281–92.
4 Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. The efficacy of the ketogenic diet 1998: a prospective evaluation of intervention in 150 children. *Pediatrics* 1998; **102:** 1358–63.
5 Kang HC, Kim YJ, Kim DW, Kim HD. Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multicentric experience. *Epilepsia* 2005; **46:** 272–79.
6 Coppola G, Veggiotti P, Cusmai R, et al. The ketogenic diet in children, adolescents and young adults with refractory epilepsy: an Italian multicentric experience. *Epilepsy Res* 2002; **48:** 221–27.
7 Kankirawatana P, Jirapinyo P, Kankirawatana S, Wongarn R, Thamanasiri N. Ketogenic diet: an alternative treatment for refractory epilepsy in children. *J Med Assoc Thai* 2001; **84:** 1027–32.
8 Maydell BV, Wyllie E, Akhtar N, et al. Efficacy of the ketogenic diet in focal versus generalized seizures. *Pediatr Neurol* 2001; **25:** 208–12.
9 Vining EP, Freeman JM, Ballaban-Gil K, et al. A multicenter study of the efficacy of the ketogenic diet. *Arch Neurol* 1998; **55:** 1433–37.
10 Keene DL. A systematic review of the use of the ketogenic diet in childhood epilepsy. *Pediatr Neurol* 2006; **35:** 1–5.
11 Lefevre F, Aronson N. Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. *Pediatrics* 2000; **105:** E46.
12 Levy R, Cooper P. Ketogenic diet for epilepsy. *Cochrane Database Syst Rev* 2003; **3:** CD001903.
13 Commission on antiepileptic drugs of the International League Against Epilepsy. Guidelines for clinical evaluation of antiepileptic drugs. *Epilepsia* 1989; **30:** 400–08.
14 Vining EP. Clinical efficacy of the ketogenic diet. *Epilepsy Res* 1999; **37:** 181–90.
15 Huttenlocher PR. Ketonemia and seizures: metabolic and anticonvulsant effects of two ketogenic diets in childhood epilepsy. *Pediatr Res* 1976; **10:** 536–40.
16 Huttenlocher PR, Wilbourn AJ, Signore JM. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. *Neurology* 1971; **21:** 1097–103.
17 Schwartz RM, Eaton J, Bower BD, Aynsley-Green A. Ketogenic diets in the treatment of epilepsy: short term clinical effects. *Dev Med Child Neurol* 1989; **31:** 145–51.
18 Than KD, Kossoff EH, Rubenstein JE, Pyzik P, McGrogan JR, Vining EPG. Can you predict an immediate, complete and sustained response to the ketogenic diet? *Epilepsia* 2005; **46:** 580–82.
19 Kossoff EH, Pyzik PL, McGrogan JR, Vining EP, Freeman JM. Efficacy of the ketogenic diet for infantile spasms. *Pediatrics* 2002; **109:** 780–83.
20 Caraballo RH, Cersosimo RO, Sakr D, Cresta A, Escobal N, Fejerman N. Ketogenic diet in patients with Dravet syndrome. *Epilepsia* 2005; **46:** 1539–44.
21 Kossoff EH, Thiele EA, Pfeifer HH, McGrogan JR, Freeman JM. Tuberous sclerosis complex and the ketogenic diet. *Epilepsia* 2005; **46:** 1684–86.
22 Oguni H, Tanaka T, Hayashi K, et al. Treatment and long-term prognosis of myoclonic–astatic epilepsy of early childhood. *Neuropediatrics* 2002; **33:** 122–32.

23 Kilaru S, Bergquist AGK. Current treatment of myoclonic astatic epilepsy: clinical experience at the Children's Hospital of Philadelphia. *Epilepsia* 2007; **48:** 1703–07.

24 Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989: **30:** 389–99.

25 Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. *Epilepsia* 2001; **42:** 796–803.

26 Freeman JM, Freeman JB, Kelly MT. The ketogenic diet: a treatment for epilepsy, 3rd edn. New York: Demos, 2000.

27 World Health Organisation. Energy and protein requirements. Report of a Joint FAO/WHO/UNU expert consultation. *Technical Report Series* 1985; **724**.

28 Neal EG, Chaffe HM, Edwards N, Lawson M, Schwartz R, Cross JH (2008). Growth of children on classical and medium-chain triglyceride ketogenic diets. *Pediatrics* (in press).

29 Motte J, Trevathan E, Arvidsson JF, et al. Lamotrigine for generalized seizures associated with Lennox–Gastaut syndrome. *N Engl J Med* 1997; **337:** 1807–12.

30 Biton V, Montouris GD, Ritter F, et al. A randomised, placebo-controlled study of topiramate in primary generalised tonic–clonic seizures. *Neurology* 1999; **52:** 1330–37.

31 Henderson CB, Filloux FM, Alder SC, Lyon JL, Caplin DA. Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. *J Child Neurology* 2006; **21:** 193–98.

32 Nordli DR Jr, Kuroda MM, Carroll J, et al. Experience with the ketogenic diet in infants. *Pediatrics* 2001; **108:** 129–33.

33 Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006; **47:** 1094–120.