Classic ketogenic diet versus further antiseizure medicine in infants with drug-resistant epilepsy (KIWE): a UK, multicentre, open-label, randomised clinical trial

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Summary

Background Many infancy-onset epilepsies have poor prognosis for seizure control and neurodevelopmental outcome. Ketogenic diets can improve seizures in children older than 2 years and adults who are unresponsive to antiseizure medicines. We aimed to establish the efficacy of a classic ketogenic diet at reducing seizure frequency compared with further antiseizure medicine in infants with drug-resistant epilepsy.

Methods In this phase 4, open-label, multicentre, randomised clinical trial, infants aged 1–24 months with drug-resistant epilepsy (defined as four or more seizures per week and two or more previous antiseizure medications) were recruited from 19 hospitals in the UK. Following a 1-week or 2-week observation period, participants were randomly assigned using a computer-generated schedule, without stratification, to either a classic ketogenic diet or a further antiseizure medication for 8 weeks. Treatment allocation was masked from research nurses involved in patient care, but not from participants. The primary outcome was the median number of seizures per day, recorded during weeks 6–8. All analyses were by modified intention to treat, which included all participants with available data. Participants were followed for up to 12 months. All serious adverse events were recorded. The trial is registered with the European Union Drug Regulating Authorities Clinical Trials Database (2013–002195–40). The trial was terminated early before all participants had reached 12 months of follow-up because of slow recruitment and end of funding.

Findings Between Jan 1, 2015, and Sept 30, 2021, 155 infants were assessed for eligibility, of whom 136 met inclusion criteria and were randomly assigned; 75 (55%) were male and 61 (45%) were female. 78 infants were assigned to a ketogenic diet and 58 to antiseizure medication, of whom 61 and 47, respectively, had available data and were included in the modified intention-to-treat analysis at week 8. The median number of seizures per day during weeks 6–8, accounting for baseline rate and randomised group, was similar between the ketogenic diet group (5 [IQR 1–16]) and antiseizure medication group (3 [IQR 2–11]; IRR 1·33, 95% CI 0·84–2·11). A similar number of infants with at least one serious adverse event was reported in both groups (40 [51%] of 78 participants in the ketogenic diet group and 26 [45%] of 58 participants in the antiseizure medication group). The most common serious adverse events were seizures in both groups. Three infants died during the trial, all of whom were randomly assigned a ketogenic diet: one child (who also had dystonic cerebral palsy) was found not breathing at home; one child died suddenly and unexpectedly at home; and one child went into cardiac arrest during routine surgery under anaesthetic. The deaths were judged unrelated to treatment by local principal investigators and confirmed by the data safety monitoring committee.

Interpretation In this phase 4 trial, a ketogenic diet did not differ in efficacy and tolerability to a further antiseizure medication, and it appears to be safe to use in infants with drug-resistant epilepsy. A ketogenic diet could be a treatment option in infants whose seizures continue despite previously trying two antiseizure medications.

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Introduction

The incidence of epilepsy is greatest in the first 2 years of life (95% CI 56–88 cases per 100 000 infants per year).[1] These young children with epilepsy remain most at risk for continuing seizures and neurodevelopmental compromise in the long term. Early control of seizures is associated with improved developmental outcome,[2] but many epilepsies presenting in infancy are associated with poor prognosis for seizure control.[3]

A ketogenic diet—ie, a high-fat low-carbohydrate diet designed to mimic the effects of starvation on the body—is a non-pharmacological treatment option for

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed, Ovid, the Cochrane Database of Systematic Reviews, Cochrane CENTRAL, and the National Institutes of Health clinical trial registry from database inception to Oct 16, 2019, with the terms "infant(s)" OR "child(ren)", AND "ketogenic" OR "medium chain triglyceride", AND "epilepsy" OR "spasm(s)" OR "seizure(s)". Of 33 studies identified, two were randomised controlled trials (one compared a classic ketogenic diet with adrenocorticotropic hormone in infants with infantile spasms, and one assessed a classic ketogenic diet with a modified Atkins diet in children, including 37 infants); the remainder were uncontrolled cohort studies. All studies were categorised as low quality. In meta-analyses of uncontrolled studies, about 59% (95% CI 53–65) of infants achieved 50% or more seizure reduction when following a ketogenic diet, and about 33% (26–43) achieved seizure freedom. Randomised controlled trials in older children (aged >2 years) and adults have only compared a ketogenic diet with care as usual. Studies in older children and adults have not compared a ketogenic diet with further antiseizure medication. An adequately powered randomised controlled trial is needed to assess a ketogenic diet versus standard pharmacological treatment in infants with epilepsy with various seizure types who have not responded to first-line treatment.

Added value of this study

This randomised controlled trial is the first to evaluate the effectiveness of a ketogenic diet compared with further antiseizure medicine in infants (aged 1–24 months) with drug-resistant epilepsy. This study was done in infants with epilepsy who were having four or more seizures per week and who had not responded to at least two previous antiseizure medicines. The results provide a valuable evidence base for the treatment of drug-resistant epilepsy in infants in whom few trials have been undertaken previously.

Implications of all the available evidence

Our trial results showed that a ketogenic diet was not more efficacious than a further antiseizure medicine but that the diet was safe to use in infants aged 1–24 months. A ketogenic diet could be considered a treatment option for infants who continue to have seizures despite having tried two antiseizure medications. These results support data from previous low-powered randomised controlled trials in infants with newly diagnosed infantile epilepsy and observational studies in infants with drug-resistant epilepsy.

individuals with drug-resistant epilepsy. There are several versions of the diet, but the one that is most commonly used in infants is based on a ratio between 2:1 to 4:1 of fat (g) and protein and carbohydrate (g), respectively.[4] A Cochrane review[5] of ketogenic diets for epilepsy incorporated data from four randomised controlled trials (RCTs) comparing ketogenic diets with usual care in children, including the first RCT in children aged 2–16 years.[6] Children who received a ketogenic diet were more likely to have 50% or more seizure reduction (risk ratio [RR] 5·80, 95% CI 3·48–9·65; p<0·001) and seizure freedom (RR 3·16, 1·20–8·35; p=0·02). However, the magnitude of these effects might not be considered clinically plausible. The Cochrane review highlighted that evidence for the use of ketogenic diets in infants with epilepsy is scarce.[5]

The efficacy of ketogenic diets cannot be accounted for solely by the accumulation of brain ketones in the body, and various mechanisms of action have been proposed.[7] Medium chain fatty acids, particularly decanoic acid, might enhance neuronal mitochondrial function by stimulating mitochondrial proliferation.[8] Decanoic acid has also been shown to have an antiseizure effect.[9] In younger children (aged <2 years), there is evidence that a switch to fatty acid oxidation occurs more readily than in older children (aged ≥2 years).[10] It should be investigated whether decanoic acid enhances the action of ketogenic diets in infancy, and the biochemical basis for effectiveness should be identified.

We designed a phase 4 randomised trial in infants aged 1–24 months with drug-resistant epilepsy (defined as four or more seizures per week and at least two previous antiseizure medicines). We aimed to assess the efficacy of a classic ketogenic diet on the number of seizures per day, compared with further antiseizure medication.

Methods

Study design

We did a phase 4, open-label, multicentre, randomised clinical trial at 19 hospitals in the UK (all sites and principal investigators are listed in the appendix, p 129). The Research Ethics Committee provided full ethics approval (14/LO/1230) before the trial start. The Medicines and Healthcare products Regulatory Agency provided approval with annual review because medicinal compounds without marketing authorisations in the target population were used as the comparator. The protocol has been published (appendix pp 1–51).[11]

Participants

Participants were infants (aged 1–24 months) with a confirmed diagnosis of epilepsy and with four or more seizures per week at baseline, who did not respond to two or more pharmacological treatments (antiseizure medication or corticosteroids). Exclusion criteria included diagnosis of a metabolic disease contraindicating use

of ketogenic diets, progressive neurological disease, severe gastroesophageal reflux, or previous treatment with ketogenic diets. A complete list of eligibility criteria is provided in the appendix (pp 20–69).

Parents or guardians of potential participants were approached initially by a member of their direct health-care team. Written informed consent was obtained from each parent or guardian before undergoing baseline assessment, following a face-to-face or tele-phone consultation with an adequate explanation of the aims, methods, anticipated benefits, and potential adverse events of the study. Consent was obtained by the local site principal investigator (paediatric neurologist) or delegate. Sex, as reported in local hospital records, was filled on paper case report forms by the paediatric neurologist, alongside other study data. Categories for ethnicity were White, Black, Asian, and Other.

Randomisation and masking

Participants were randomly assigned to either a classic ketogenic diet or a further antiseizure medication using a web-based randomisation service. The randomisation schedule was computer generated using a simple randomisation method with no stratification. Allo-cations were released via email to centres after the research nurse had entered participant information onto the randomisation website. This process concealed treatment allocation from research nurses involved in patient care. Success of masking was not measured. Although it was not possible to mask participants to treatment allocation, efforts were made to minimise expectation bias by emphasising in the patient information sheet that evidence supporting ketogenic diets for seizure control is scarce. Serious adverse events were initially assessed by local investigators, but they were masked from the safety monitoring board for further review. Treatment procedures started within 5 days of randomisation.

Procedures

Before randomisation, participants were observed for 2 weeks (or 1 week if the infant was prone to more than two seizures per day), during which time no changes were made to regular antiseizure medication; emergency seizure treatments continued as required. Seizure types or frequency, number of emergency seizure treatments required, and health-care system contacts due to exacerbation were recorded by parents or guardians in a seizure diary. The paediatric neurologist or research nurse assessed all infants using the Infant Toddler Quality of Life Questionnaire (ITQOL-97)[12] and Vineland Adaptive Behaviour Scales (Vineland-II).[13] ITQOL-97 is a questionnaire to measure physical, mental, and social wellbeing, with scores on a scale from 0 (worst health) to 100 (best health). Vineland-II is a scale to support the diagnosis of

intellectual and developmental disabilities, with scores on domains including communication, daily living, socialisation, and motor skills. Scores ranged from 20 to 160 (mean 100 [SD 15]). A low score was classified as less than 85. Clinical laboratory assessments were done at local laboratories (appendix pp 76–77). Parents or guardians returned food diaries required for diet calculation at a maximum of 1 week into the observation period.

For infants who were assigned a ketogenic diet, the components of the diet were calculated by a paediatric dietitian and were specific to the infant, accounting for the food diary, daily calorie requirements, adequate protein intake for growth, and vitamin and mineral supplementation. All diets were implemented according to a classic ketogenic diet protocol, based on a ratio (usually between 2:1 and 4:1) of fat (g) to carbohydrate and protein (g), with non-fasting initiation. Further adjustments to the ketogenic diet were established through regular growth monitoring, seizure diaries, and daily home measurement of urine or concentrations of blood ketones. Parents or guardians of infants assigned a ketogenic diet underwent a thorough teaching programme before starting the diet, including how to manage potential early side-effects, such as excess ketosis and hypoglycaemia. Infants who were younger than 12 months were admitted for diet initiation. An intervention manual (appendix pp 44–50, 95–99) was provided to sites to ensure consistent ketogenic diet implementation and was discussed with local dietitians and the dietetic assistant. All dietitians involved in the study were in regular contact with the dietetic assistant, and meetings were organised to ensure continued cross-site consistency. Consistency of ketogenic diet implementation was monitored after the 8-week and 12-month visits by the dietetic assistant.

For infants who were assigned a further antiseizure medication, the clinician who was responsible for managing the infant's epilepsy prescribed the most appropriate drug, which was selected depending on presenting seizures, epilepsy syndrome, and previous drugs used. Paediatric neurologists attended an initial meeting to discuss clinical practice, forming the basis of a consensus protocol to ensure consistent delivery of antiseizure medication (appendix pp 51, 100). Cross-site consistency of antiseizure medication prescription, according to the protocol, was monitored by the dietetic assistant. A general discussion about infant or toddler nutrition, including details such as promotion of breastfeeding, age-appropriate texture progression for weaning, food groups, and the importance of iron-rich foods, was done with families of infants in the antiseizure medication group at the randomisation visit. If the infant had local dietetic support, it was ensured that this monitoring continued, and a referral was made if required.

Follow-up visits were arranged at 4 weeks, 8 weeks, 6 months, 9 months, and 12 months. Assessments at

these visits included clinical review, physical examination, documentation of seizure frequency from seizure diaries, review of adverse events and concomitant medication, clinical laboratory assessments

Figure: Trial profile
*Some infants with missing data for the primary outcome analysis had data available for secondary outcomes at 8 weeks. †At 12 months, full data for secondary outcomes were only available for 31 infants (missing or incomplete data n=12) in the ketogenic diet group and 25 infants (missing or incomplete data n=7) in the antiseizure medication group.

(at 8 weeks, 6 months, and 12 months), completion of the tolerability questionnaire by parents or guardians with research nurses, and completion of ITQOL-97 (at 8 weeks and 12 months) and Vineland-II (at 12 months).

Parents or guardians were asked to keep daily seizure diaries for 8 weeks; thereafter, they were requested to reduce seizure recording to at least 1–2 days per week, as clinically indicated, until 28 days before the final 12-month visit, when daily seizure recording recommenced. After the 8-week assessment, according to the infant's clinical response to treatment (seizure outcome and tolerability), a ketogenic diet or antiseizure medication was continued or changed. Infants in the antiseizure medication group who did not have seizure control at 8 weeks were offered the chance to switch to a ketogenic diet outside the context of the trial, depending on waiting lists for ketogenic diet at the study site. Infants on a ketogenic diet without seizure improvement at the 8-week assessment continued clinical management with antiseizure medication, as per clinician decision.

During the COVID-19 pandemic, visits were conducted remotely by telephone or secure videoconference facility if the parents or guardians did not wish to travel or bring the child to hospital (or both), or if there were concerns about adverse events, as advised by the local study team. Remote methods were also used for issuing and collecting seizure diaries and completing questionnaires. Blood tests could be done locally, and existing laboratory samples used for screening if samples were no older than 6 weeks. Other protocol amendments during the study included reducing the inclusion age from 3 months to 1 month, giving the option of a minimum of a 1 week baseline instead of 2 weeks for participants who had a seizure frequency of more than two seizures per day, and several extensions to the recruitment end date. A summary of protocol amendments can be found in the appendix (pp 110–18).

Outcomes

The primary outcome was the number of seizures recorded during weeks 6–8, accounting for the baseline rate and randomised group. Secondary outcomes at 8 weeks were the number of infants who were seizure-free during weeks 6–8 of the intervention, responder rate (defined as the number of infants with >50% improvement from baseline in seizure frequency), tolerance to a ketogenic diet (as assessed by questionnaire or blood results), and the association between concentration of medium chain fatty acids and seizure control. Secondary outcomes at 12 months were treatment retention (defined as the number of infants who remained on a ketogenic diet; intervention group only), quality of life (ITQOL-97 subscales were also analysed separately), and neurodevelopmental outcome (using Vineland-II, with domains also analysed
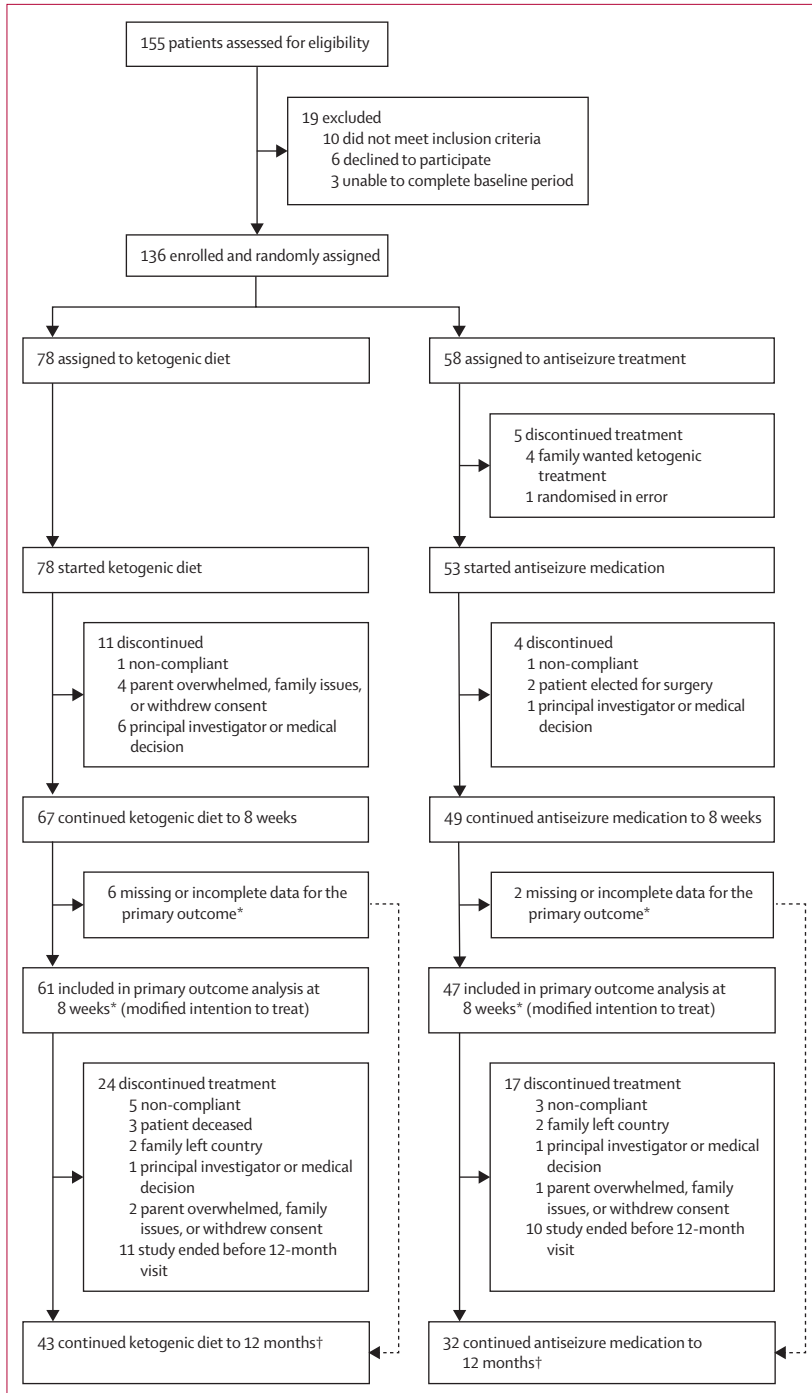
separately). Adverse events were recorded throughout the trial. Serious adverse events were reported to the study sponsor. The local principal investigator reviewed the adverse events and decided whether they were related to the study intervention. Serious adverse events were reviewed by the data monitoring committee. Adverse events were coded according to MedDRA for the purpose of reporting.

Statistical analysis

For the primary outcome, based on data from our previous study,[6] a mean percentage change of 62% (SD 45) in seizures from baseline in the ketogenic diet group was used, assuming a change of 90% (SD 50) from the baseline seizure level in the comparison group (100% was no change in frequency of seizures from baseline) at 90% power and 5% significance, with a superiority study design. An inflation factor of 1·35 was used to account for therapist effect (dietitian), assuming nine centres with an average cluster size of eight and an intraclass correlation coefficient of 0·05. We also inflated for 10% dropout or other methodological challenges. We calculated a sample size of 68 participants in the antiseizure medication group and 92 participants in the ketogenic diet group (160 in total). Due to slow recruitment, the sample size was recalculated assuming 25% dropout but keeping all other parameters the same as in the original sample size. With 75 participants in the ketogenic diet group and 62 participants in the antiseizure medication group (137 in total), the primary outcome was powered at 80%. Type 1 error was two-tailed.

Primary outcome data were analysed using a Poisson mixed model, accounting for clustering by centre (synonymous with therapist). Random allocation and timepoint (baseline or 8 weeks) were entered into the model as fixed effects, and centre was entered as a random effect. Log_e of number of days' data included in the analysis from 6 weeks to 8 weeks was included as an offset. Secondary outcomes were analysed using random effects logistic models, with centres as the random effects and randomised group as a fixed effect. The process outcome relating to tolerability, quality of life, and neurodevelopment was analysed using random effects linear modelling. Two stopping rules were established for the data monitoring committee: the O'Brien-Fleming[14] type rule for efficacy and a power family with an exponent of 1·5 for adverse events. Data were analysed twice for the data monitoring committee. All analyses were by modified intention to treat, which included all randomly assigned participants who had data available for the primary endpoint.

STATA 17 was used for all analyses except for SAS 9.4, which was also used for the primary outcome. The statistical analysis plan is provided in the appendix (pp 101–09).

This trial is registered with ClinicalTrials.gov (NCT02205931) and EudraCT (2013–002195–40).

	Antiseizure medication group (n=58)	Ketogenic diet group (n=78)
Age at randomisation, years	1·10 (0·48)	1·23 (0·54)
Sex		
Male	36/58 (62%)	39/78 (50%)
Female	22/58 (38%)	39/78 (50%)
Ethnicity		
White	40/55 (73%)	59/75 (79%)
Other	15/55 (27%)	16/75 (21%)
EEG abnormal	45/51 (88%)	59/68 (87%)
Epilepsy syndrome diagnosis	29/43 (67%)	45/67 (67%)
Epilepsy syndrome or type		
Early myoclonic encephalopathy	0/38 (0%)	1/46 (2%)
Early infantile epileptic encephalopathy	11/38 (29%)	13/46 (28%)
Migrating focal seizures of infancy	1/38 (3%)	0/46 (0%)
Infantile epileptic spasms syndrome	19/38 (50%)	23/46 (50%)
Dravet syndrome	1/38 (3%)	2/46 (4%)
Epilepsy with myoclonic atonic seizures (Doose syndrome)	1/38 (3%)	0/46 (0%)
Lesional focal epilepsy	5/38 (13%)	7/46 (15%)
Genetic diagnosis	14/54 (26%)	18/68 (26%)
Other neurological diagnosis	19/54 (35%)	26/67 (39%)
Developmental delay (reported by medical team)	49/55 (89%)	65/73 (89%)
Hemiplegia	3/55 (5%)	8/72 (11%)
Seizure type		
Focal	22/52 (42%)	30/69 (43%)
Spasms	30/52 (58%)	41/69 (59%)
Absence	6/52 (12%)	4/69 (6%)
Myoclonic	10/52 (19%)	9/70 (13%)
Clonic	3/52 (6%)	4/69 (6%)
Tonic	10/52 (19%)	18/69 (26%)
Tonic clonic	10/52 (19%)	7/69 (10%)
Atonic	4/52 (8%)	3/69 (4%)
Seizures per day	9 (3–19)	7 (4–21)
Systolic blood pressure, mm Hg	94 (13)	98 (16)
Diastolic blood pressure, mm Hg	56 (13)	62 (16)
Pulse, beats per min	126 (17)	126 (22)
Temperature, °C	36·8 (0·3)	36·6 (0·4)
Weight, kg	9·9 (2·9)	9·6 (2·7)
Weight, SDS	–0·02 (1·76)	–0·09 (1·52)
Length, m	0·75 (0·11)	0·76 (0·09)
Length, SDS	–0·45 (1·90)	–0·27 (1·79)
Head circumference, cm	44·1 (4·1)	44·1 (3·5)
Head circumference, SDS	–1·07 (2·58)	1·08 (2·28)

(Table 1 continues on next page)

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 2015, and Sept 30, 2021, 155 infants were assessed for eligibility, of whom 136 met inclusion

	Antiseizure medication group (n=58)	Ketogenic diet group (n=78)
(Continued from previous page)		
ITQOL-97: child's current health		
Overall health	60 (30–60)	60 (30–60)
Physical abilities	25 (10–56)	23 (10–62)
Parent's or guardian's satisfaction with child's overall growth and development	45 (33–58)	51 (39–70)
Pain	58 (42–75)	58 (42–75)
Temperament and mood	56 (45–66)	61 (47–72)
Overall behaviour	65 (58–79)	69 (56–81)
Global behaviour	85 (60–85)	73 (60–100)
Getting on with others	60 (50–66)	55 (48–70)
Parent's or guardian's perceptions of child's general health	36 (25–54)	41 (27–50)
ITQOL-97: change in child's health		
Much worse than 1 year ago	8/29 (28%)	7/43 (16%)
Somewhat worse than 1 year ago	3/29 (10%)	7/43 (16%)
About the same as 1 year ago	11/29 (38%)	10/43 (23%)
Somewhat better than 1 year ago	3/29 (10%)	11/43 (26%)
Much better than 1 year ago	4/29 (14%)	8/43 (19%)
ITQOL-97: effect on parent or guardian		
Emotional effect	39 (21–54)	50 (29–64)
Effect on their time	52 (33–71)	62 (33–76)
Family cohesion	85 (85–100)	85 (60–100)
Vineland-II: communication skills		
Receptive communication, v-scale score	7 (5–10)	8 (6–10)
Expressive communication, v-scale score	6 (4–11)	8 (6–11)
Overall, v-scale score	12 (9–19)	16 (11–20)
Communication domain, standard score	44 (37–62)	60 (46–66)
Vineland-II: daily living skills		
Personal, v-scale score	9 (8–11)	9 (8–12)
Domestic, v-scale score	12 (6–13)	11 (0–12)
Community, v-scale score	10 (0–10)	10 (0–10)
Overall, v-scale score	29 (10–32)	26 (10–32)
Daily living domain, standard score	66 (57–72)	68 (61–75)
Vineland-II: socialisation skills		
Interpersonal relationships, v-scale score	7 (5–9)	8 (5–10)
Play, v-scale score	8 (7–10)	9 (7–10)
Coping, v-scale score	0 (0–9)	0 (0–9)
Overall, v-scale score	21 (18–26)	22 (19–26)
Socialisation domain, standard score	59 (53–65)	65 (54–73)
Vineland-II: motor skills		
Gross, v-scale score	6 (5–8)	6 (6–8)
Fine, v-scale score	6 (6–8)	7 (6–9)
Overall, v-scale score	12 (10–15)	14 (12–19)
Motor skills domain, standard score	50 (49–55)	55 (50–61)
Overall Vineland-II score		
Sum of domain standard scores or adaptive behaviour composite	228 (199–244)	236 (208–276)
Standardised score	54 (48–58)	56 (50–66)

Data are n/N (%), mean (SD), or median (IQR). SDS=standard deviation score. ITQOL-97=Infant Toddler Quality of Life questionnaire, 97-item full-length version. Vineland-II=Vineland adaptive behaviour scales, 2nd edn.

Table 1: Clinical and demographic characteristics at screening or baseline

criteria and were randomly assigned. 78 infants were assigned to a ketogenic diet and 58 to further antiseizure medication (figure). 75 (55%) infants were male and 61 (45%) were female. Baseline clinical and demographic characteristics, including quality of life (ITQOL-97) and neurodevelopment (Vineland-II), were similar between the ketogenic diet group and antiseizure medication group (table 1), as were baseline clinical laboratory parameters (appendix pp 119–21).

All 78 infants who were assigned to the ketogenic diet group started the diet. 67 (86%) of 78 infants continued to 8 weeks, of whom 61 (78%) had primary outcome data available and were included in the modified intention-to-treat analysis. Some infants with missing data for the primary outcome had available data for secondary outcomes at 8 weeks. Of 58 infants assigned to further antiseizure medication, 53 (91%) commenced treatment, 49 (84%) continued to 8 weeks, and 47 (81%) had primary outcome data available.

The trial was terminated before all participants could attain 12 months of follow-up data because of slow recruitment and end of funding. Of 67 infants who were randomly assigned to a ketogenic diet more than 12 months before the study end date (and who therefore had a full 12 months of follow-up), 43 (64%) continued the diet to 12 months and 31 (47%) had available data. Of 48 infants randomised to further antiseizure medication more than 12 months before the study end date, 32 (67%) continued antiseizure medication to 12 months and 25 (52%) had available data.

Median follow-up was 11·3 months (IQR 2·7–12·1). At 8 weeks, the median number of seizures per day compared with baseline was similar in the ketogenic diet group and antiseizure medication group (5 [IQR 1–16] and 3 [IQR 2–11]; IRR 1·33, 95% CI 0·84–2·11; table 2). Of 63 infants in the ketogenic diet group with available data for the responder rate analysis at 8 weeks, 28 (44%) had more than 50% seizure reduction compared with 19 (40%) of 47 infants in the antiseizure medication group (OR 1·21, 95% CI 0·55–2·65). Seven (11%) of 63 infants in the ketogenic diet group were seizure-free at 8 weeks compared with six (13%) of 48 infants in the antiseizure medication group (OR 0·88, 0·27–2·80). The tolerability score was similar in both groups at the week 8 outcome analysis and at other timepoints (table 3).

No differences between groups were noted for any concept within the ITQOL-97 at 12 months, except for the child's temperament and mood (β coefficient −6·09, 95% CI −11·63 to −0·54) and the child getting along with others (β coefficient −6·79, −12·97 to −0·60), which favoured the antiseizure medication group (table 2). A similar proportion of parents or guardians in both groups perceived their child's health to be much better than 1 year ago (12 [50%] of 24 in the antiseizure medication group and 11 [37%] of 30 in the ketogenic diet group) or much worse than 1 year ago (none [0%] of 24 and one [3%] of 30).

At 8 weeks, median scores in the ITQOL-97 were numerically higher (suggesting better health) in the ketogenic diet group than the antiseizure medication group for seven of the 12 concepts (appendix p 128). Child's pain, child's global behaviour, effect on parental time, and family cohesion were equal between the groups, although general perceptions of the child's health was numerically higher in the antiseizure medication group. At 12 months, a numerically larger proportion of infant's parents or guardians in the ketogenic diet group perceived their child's health to be much better than 1 year ago than in the antiseizure medication group (ten [25%] of 40 individuals vs three [9%] of 32 individuals). By contrast, numerically more parents or guardians in the antiseizure medication group perceived their child's health to be much worse than 1 year ago than those in the ketogenic diet group (eight [25%] of 32 vs two [5%] of 40; appendix p 128).

No differences between groups were noted in the Vineland-II overall standardised score or in the domain standard score at 12 months (table 2). The overall daily living v-scale score was nominally improved in the antiseizure medication group (β coefficient 2·23, 95% CI −4·22 to −0·25).

A total of 73 serious adverse events were reported in the antiseizure medication group and 161 were reported in the ketogenic diet group. The proportion of serious adverse events classified into each Medical Dictionary for Regulatory Activities (MedDRA) system organ was similar in each group (table 4). Three infants died during the trial, all of whom were randomly assigned to the ketogenic diet group; deaths were judged unrelated to the treatment. One child with epilepsy and dystonic cerebral palsy was found not breathing at home; cardiopulmonary resuscitation was attempted without success in the emergency department. One child died suddenly and unexpectedly at home, a known risk of complex epilepsy. The third child was no longer on a ketogenic diet at the time of the event; they became bradycardic and went into cardiac arrest during routine surgery under anaesthetic.

A higher proportion of infants in the antiseizure medication group had changes to the number or dose of concurrent antiseizure medications during the study compared with the ketogenic diet group (24 [50%] of 48 infants vs nine [14%] of 66 infants). These modifications included dose increases of concurrent antiseizure medications or short courses of new antiseizure medications due to seizure escalation or prophylaxis for planned admission, except for one (2%) of 66 infants in the ketogenic diet group and two (4%) of 48 infants in the antiseizure medication group, for whom the dose of a concurrent antiseizure medication was decreased during the study. Concomitant (non-antiseizure) medications were changed in a similar proportion of infants in both groups (25 [53%] of 47 infants in the antiseizure medication group and 33 [49%] of 67 infants in ketogenic diet group).

	Antiseizure medicine group (n=58)	Ketogenic diet group (n=78)	IRR, OR, or β coefficient (95% CI)
Number of seizures at 8 weeks (primary outcome)	3 (2 to 11)	5 (1 to 16)	IRR 1·33 (0·84 to 2·11)
Seizure free at 8 weeks	6/48 (13%)	7/63 (11%)	OR 0·88 (0·27 to 2·80)
Treatment responsive at 8 weeks	19/47 (40%)	28/63 (44%)	OR 1·21 (0·55 to 2·65)
ITQOL-97: child's current health at 12 months			
Overall health	30 (30 to 85); n=24	60 (30 to 60); n=28	β coefficient 1·23 (−12·70 to 15·17)
Physical abilities	47 (7 to 70); n=24	27 (13 to 58); n=22	β coefficient −0·59 (−14·58 to 13·40)
Satisfaction with child's overall growth and development	58 (38 to 78); n=24	45 (38 to 70); n=30	β coefficient −4·14 (−14·22 to 5·94)
Pain	75 (50 to 83); n=24	67 (33 to 83); n=30	β coefficient −11·14 (−24·65 to 2·36)
Temperament and mood	68 (60 to 79); n=23	65 (56 to 71); n=30	β coefficient −6·09 (−11·63 to −0·54)
Overall behaviour	67 (60 to 83); n=14	65 (56 to 77); n=14	β coefficient −7·23 (−15·96 to 1·50)
Global behaviour	85 (60 to 100); n=14	85 (60 to 100); n=14	β coefficient 12·72 (−1·56 to 27·00)
Getting on with others	65 (52 to 72); n=12	58 (50 to 66); n=16	β coefficient −6·79 (−12·97 to −0·60)
Perceptions of child's general health	41 (30 to 52); n=24	30 (16 to 52); n=30	β coefficient −6·37 (−14·29 to 1·56)
ITQOL-97: effect on parent or guardian at 12 months			
Emotional effect	57 (36 to 79); n=24	54 (39 to 68); n=30	β coefficient −5·00 (−15·52 to 5·53)
Effect on their time	62 (33 to 90); n=24	57 (43 to 76); n=30	β coefficient −3·11 (−16·80 to 10·58)
Family cohesion	85 (60 to 85); n=24	85 (60 to 100); n=30	β coefficient −1·52 (−9·48 to 6·45)
Vineland-II: communication skills at 12 months			
Receptive communication, v-scale score	7 (7 to 8); n=9	7 (5 to 7); n=8	β coefficient 0·09 (−1·22 to 1·39)
Expressive communication, v-scale score	5 (3 to 7); n=9	5 (3 to 8); n=14	β coefficient 0·68 (−1·49 to 2·85)
Overall communication, v-scale score	10 (8 to 14); n=5	11 (9 to 13); n=5	β coefficient 1·17 (−3·42 to 5·77)
Communication domain, standard score	48 (43 to 59); n=5	49 (44 to 55); n=5	β coefficient 2·79 (−8·14 to 13·72)
Vineland-II: daily living skills at 12 months			
Personal, v-scale score	6 (5 to 7); n=11	5 (4 to 7); n=9	β coefficient −1·53 (−3·38 to 0·32)
Domestic, v-scale score	10 (9 to 11); n=21	11 (9 to 11); n=20	β coefficient 0·01 (−0·38 to 0·41)
Community, v-scale score	10 (9 to 10); n=17	10 (9 to 10); n=22	β coefficient 0·22 (−0·22 to 0·67)
Overall, v-scale score	16 (15 to 17); n=10	15 (13 to 16); n=8	β coefficient −2·23 (−4·22 to −0·25)
Daily living domain, standard score	25 (21 to 34); n=10	25 (21 to 28); n=8	β coefficient −0·69 (−7·68 to 6·31)

(Table 2 continues on next page)

Mean measurements for laboratory parameters, blood pressure, pulse, and body temperature were mostly similar in both groups at 8 weeks (appendix pp 122–24). Differences were noted between groups in concentrations

	Antiseizure medicine group (n=58)	Ketogenic diet group (n=78)	IRR, OR, or β coefficient (95% CI)
(Continued from previous page)			
Vineland-II: socialisation skills at 12 months			
Interpersonal relationships, v-scale score	6 (5 to 9); n=12	6 (3 to 7); n=12	β coefficient –1·30 (–3·17 to 0·57)
Play, v-scale score	8 (7 to 9); n=13	8 (7 to 9); n=12	β coefficient 0·77 (–1·12 to 2·66)
Coping, v-scale score	9 (8 to 9); n=11	9 (8 to 9); n=16	β coefficient –0·07 (–0·99 to 0·84)
Overall, v-scale score	21 (18 to 23); n=5	22 (19 to 24); n=5	β coefficient 1·55 (–4·04 to 7·14)
Socialisation domain, standard score	56 (47 to 59); n=5	54 (53 to 58); n=5	β coefficient 1·12 (–17·13 to 19·36)
Vineland-II: motor skills at 12 months			
Gross, v-scale score	5 (4 to 7); n=18	5 (4 to 6); n=19	β coefficient –0·53 (–1·54 to 0·48)
Fine, v-scale score	5 (4 to 7); n=15	5 (3 to 6); n=18	β coefficient –0·33 (–1·85 to 1·19)
Overall, v-scale scores	9 (9 to 12); n=14	9 (8 to 10); n=15	β coefficient –0·46 (–1·95 to 1·03)
Motor skills domain, standard score	48 (45 to 54); n=14	43 (45 to 50); n=15	β coefficient –1·53 (–5·94 to 2·88)
Vineland-II: overall scores at 12 months			
Domain standard score or adaptive behaviour composite	165 (160 to 171); n=4	168 (162 to 176); n=2	β coefficient 0·96 (–18·12 to 20·03)
Standardised score	40 (39 to 41); n=4	41 (39 to 43); n=2	β coefficient 0·16 (–5·34 to 5·67)

Data are median (IQR) or n/N (%), unless specified otherwise. The secondary outcomes ITQOL-97 and Vineland-II were analysed at 12 months. The number of infants included in these analyses are small due to missing data or not meeting the minimum requirement for analysis. ITQOL-97=Infant Toddler Quality of Life questionnaire, 97-item full-length version. Vineland-II=Vineland adaptive behaviour scales, 2nd edn. IRR=incidence rate ratio. OR=odds ratio.

Table 2: Primary and secondary outcomes

	Antiseizure medicine group (n=58)	Ketogenic diet group (n=78)
4 weeks	44 (41–44)	40 (36–42)
8 weeks*	41 (39–44)	40 (38–42)
6 months	40 (4)	39 (4)
9 months	41 (3)	41 (3)
12 months	41 (39–43)	40 (36–42)

Data are median (IQR) or mean (SD). A lower score refers to increased symptoms or increased severity of symptoms (or both). *Prespecified secondary outcome.

Table 3: Tolerability questionnaire scores by randomised group

	Antiseizure medicine group (n=58)	Ketogenic diet group (n=78)
At least one serious adverse event at any time	26/58 (45%)	40/78 (51%)
Number of serious adverse events	73	161
MedDRA system organ class*		
Cardiac disorders	0/73 (0%)	1/161 (1%)
Gastrointestinal disorders	7/73 (10%)	8/161 (5%)
General disorders and administration site conditions	3/73 (4%)	2/161 (1%)
General system disorders	1/73 (1%)	0/161 (0%)
Immune system disorders	1/73 (1%)	0/161 (0%)
Infections and infestations	11/73 (15%)	64/161 (40%)
Injury, poisoning, and procedural complications	1/73 (1%)	0/161 (0%)
Investigations	1/73 (1%)	2/161 (1%)
Metabolism and nutrition disorders	1/73 (1%)	9/161 (6%)
Nervous system disorders	34/73 (47%)	56/161 (35%)
Respiratory, thoracic, and mediastinal disorders	10/73 (14%)	23/161 (14%)
Surgical and medical procedures	5/73 (7%)	2/161 (1%)
Vascular disorders	0/73 (0%)	1/161 (1%)

Examples of MedDRA codes included in each system organ class are: cardiac arrest (cardiac disorders); vomiting, diarrhoea, and haematemesis (gastrointestinal disorders); pyrexia (general disorders and administration site conditions); chest discomfort (general system disorders); allergic dermatitis (immune system disorders); pneumonia, viral bronchitis, and lower or upper respiratory tract infection (infections and infestations); shunt malfunction (injury, poisoning, and procedural complications); weight decreased (investigations); dehydration, hypoglycaemia, and metabolic acidosis (metabolism and nutrition disorders); seizure, status epilepticus, and increased intracranial pressure (nervous system disorders); pneumonia aspiration, and abnormal respiration (respiratory, thoracic, and mediastinal disorders); gastrostomy and oesophagogastric fundoplasty (surgical and medical procedures); and oesophageal varices (vascular disorders). MedDRA=Medical Dictionary for Regulatory Activities. *MedDRA system class totals do not add up to 73 and 161 respectively as some participants had more than one classification within a single serious adverse event.

Table 4: Serious adverse events in 12 months by randomised group

of β-hydroxybutyrate, glucose, bicarbonate, urate, creatinine, free carnitine, urine organic acids, urine-to-creatinine ratio, lipids, and acylcarnitine, but these changes were as would be expected for individuals following a ketogenic diet. No out-of-range laboratory parameters were considered clinically significant in either group. Mean measurements for laboratory parameters, anthropometry SD scores, blood pressure, pulse, and body temperature were similar in both groups at 12 months (appendix pp 125–27).

71 plasma samples were sent for medium chain fatty acid analysis. Stability was compromised in 39 samples in storage, so data were available for only 17 samples at baseline and 15 samples at 8 weeks from infants on a ketogenic diet. There was a wide range of baseline plasma concentrations of medium chain fatty acids, and an increase in octanoic acid and decanoic acid concentrations in samples taken at 8 weeks (n=15; table 5). Dodecanoic acid concentrations were similar in baseline and post-intervention samples. In view of the small number of samples available for analysis, no attempt was made to perform any statistical analysis to establish whether there was an association between seizures and fatty acid concentrations.

Discussion

To our knowledge, this study is the first randomised trial in infants (aged 1–24 months) with drug-resistant

	Baseline (n=17)	8 weeks (n=15)
Octanoic acid (μmol/L)	6·7 (2·4–9·1)	10·1 (4·2–14·8)
Decanoic acid (μmol/L)	4·3 (3·2–6·6)	10·2 (4·2–18·1)
Dodecanoic acid (μmol/L)	11·6 (8·1–21·9)	12·9 (9·2–18·5)

Data are median (IQR).

Table 5: Concentrations of plasma medium chain fatty acids at baseline and 8 weeks in infants assigned to ketogenic diet

epilepsy (defined as four or more seizures per week and at least two previous antiseizure medicines) to assess the efficacy of a classic ketogenic diet versus further antiseizure medication. Although it was designed as a superiority study, no evidence was found that a ketogenic diet was better than additional antiseizure medication at achieving seizure control in infants aged 1–24 months, and the two treatments were similarly tolerated. Although the study was not powered for non-inferiority, a ketogenic diet was numerically similar in efficacy and tolerability to further antiseizure medication and appeared safe to use in this age group. A ketogenic diet might be considered as a treatment option with standard antiseizure medication for infants who continue to have seizures after having tried two antiseizure medications.

Our responder rate of approximately 40% is consistent with other ketogenic diet studies. RCTs comparing a ketogenic diet with usual care in older children (aged 2–16 years) report responder rates of 34–50% after 3–4 months;[5] a meta-analysis conducted by the KIWE study group of uncontrolled studies of ketogenic diets in infants with epilepsy estimated a responder rate of 59%.[15] The seizure freedom rate was at the higher end of the range reported in previous RCTs of older children (1–10%) yet lower than that reported in uncontrolled studies in infants (33%). It should be acknowledged that false-negative results can occur if seizures were not seen or recorded (or both) within the intervention period, but this would apply to individuals in both groups, as well as throughout the study (baseline and intervention periods), as with all clinical trials. One further RCT examined the efficacy of a ketogenic diet versus adrenocorticotropic hormone in infantile spasms not previously trialled on steroids (a standard treatment for this seizure type). Ten (62%) of 16 infants on a ketogenic diet were in electroclinical remission at 28 days compared with 11 (69%) of 16 on adrenocorticotropic hormone; relapse rates were similar between groups (40% *vs* 36%).[16] However, this study was done in infants with new-onset spasms (a single seizure type) and was underpowered with small numbers. This population was different to that in our study in which infants with different seizure types were included and those with spasms had not responded to standard steroid and vigabatrin treatment.

Despite the similar seizure frequencies in both groups in our study, more infants who were assigned to further antiseizure medication required medication changes during the intervention compared with those randomly assigned to a ketogenic diet, suggesting that infants on a ketogenic diet might have been more clinically stable. We acknowledge that a ketogenic diet might take time to be effective, but this delay could also occur with up-titrating antiseizure medication. Moreover, as the protocol stated that baseline antiseizure medications should not change during baseline and intervention periods, any changes to antiseizure medications would be for emergency rescue or dose adjustment of existing medications for ongoing seizures. In view of the randomisation and complexity of the epilepsy in these children, a similar degree of severity of epilepsy syndrome and need for medication change would have been expected in both groups.

In this study, we used 8 weeks as the primary outcome period rather than the standard 3 months used in other RCTs. In infants, many epilepsy syndromes are characterised by high seizure frequency, and 8 weeks was considered the longest tolerable period for assessment and justifiable time to leave concurrent antiseizure medications unchanged. In our clinical experience, seizure response to a ketogenic diet or an antiseizure medication is generally established within 4 weeks in infants (although longer might be needed for some antiseizure medications due to slow titration periods), which leaves 2–4 weeks for seizure assessment following the initial titration period. Previous antiseizure medication studies in this age group have used standardised titration periods of 1 day to 4 weeks, with 4-day to 4-week stabilisation periods.[17–19]

Most sections of the ITQOL-97 quality-of-life measure at 8 weeks showed a favourable trend towards the ketogenic diet group, and more parents or guardians perceived their child's health to be much better at 12 months versus baseline, compared with those in the antiseizure medication group. The feeling of the parents or guardians of doing something worthwhile when administering a ketogenic diet (despite the common perception that dietary treatment is an imposition on parents) and their perception of its benefit for their child should not be ignored,[20] independent of its efficacy in terms of seizure reduction. However, the potential placebo effect of any unblinded treatment should be considered.

Quality-of-life and neurodevelopmental measures at 12 months (ITQOL-97 and Vineland-II) should be interpreted with caution due to substantial loss to follow-up, which challenges internal validity and statistical precision. Communication and socialisation skills being numerically in favour of the ketogenic diet group at 12 months is consistent with the only RCT assessing quality-of-life and cognitive and behavioural functioning on ketogenic diet compared with usual care at 4 months and 16 months. A trend was reported towards improved activation, increased productivity, and decreased anxiety and mood-disturbed behaviour,[21]

although no difference was found between quality-adjusted life-years when comparing ketogenic diet with usual care.[22]

Consistent with uncontrolled studies on the use of ketogenic diets in infants,[15] clinical or laboratory parameters were not clinically significantly different between groups, except for those that would be expected when following a ketogenic diet. The proportion of individuals with results out of normal range differed between groups only for specific clinical or laboratory parameters at varying timepoints relevant to ketogenic diet use. Serious adverse events were as expected in both groups: most commonly an increase in seizures, followed by infections, which were both thought to be unrelated to treatment.

Retention rates of approximately 50% at 12 months in this study are similar to those reported in uncontrolled studies of infants on a ketogenic diet (aggregated rate of 43% at 12 months).[15] RCTs of a ketogenic diet versus usual care in children with epilepsy also found similar retention rates between groups (RR 1·08, 95% CI 0·74–1·57; p=0·71).[5] Studies evaluating the efficacy of antiseizure medications in infancy are scarce. Protocols that were used in studies that assessed first-line treatment in people with spasms required a short time for intervention and outcome, making longer term retention rates irrelevant. Only a few studies have been done of second-line treatments in infants, in which efficacy was reviewed over a short period. Therefore, our data are the first to provide information about retention rates in infants.

More infants in the antiseizure medication group switched to a ketogenic diet compared with infants in the ketogenic diet group who switched to antiseizure medication at 8 weeks. Although changes to antiseizure medications for infants assigned to further antiseizure medication were not recommended in the protocol (dose of concurrent antiseizure medications might be decreased due to drug interactions, especially if a high dose was being taken), medications or doses were changed more often in the antiseizure medication group than in the ketogenic diet group. Although efficacy was not different between groups, parent or guardian satisfaction or infant stability might have been higher in the ketogenic diet group than the antiseizure medication group.

Recruitment was slower than anticipated. Infants presenting with epilepsy often have a high burden of seizures; physicians, thus, perceived an urgent need to treat or change treatment rather than wait to document the baseline rate of seizures. The study was also introduced to families at a late stage during treatment—ie, not after two antiseizure medications when further treatment options are limited. Therefore, we reduced the baseline period to 1 week for infants with frequent seizures and increased the number of sites to aid recruitment. An alternative trial design might be required for infants. One design has been proposed in which baseline duration is adjusted on the basis of individual seizure burden, and treatment duration is based on seizure response according to the timing of seizure occurrence rather than using the number of seizures over a set time period as the primary outcome.[23] Furthermore, we had scant medium chain fatty acid data, because the stability of many samples was compromised due to storage issues, preventing meaningful analysis of these data. Future studies should allow resources to aid with sample logistics to prevent such difficulties, particularly when samples are being transported from other sites.

Although we started the study with 12 sites, we invited all UK ketogenic diet centres to participate and included 19 sites nationwide, encompassing secondary and tertiary centres from south England to north Scotland, with varying sizes of ketogenic diet service. Including all centres not only optimised recruitment but also ensured that the range of sociodemographic and clinical diversity encountered in this population was reflected in our cohort. As expected, infantile epileptic spasms syndrome was the most common presenting epilepsy syndrome, as is seen in epidemiological studies,[1] but there were no obvious differences in characteristics between groups. Study visits and assessments were conducted online during the COVID-19 pandemic when possible, and interpreters were available as required.

In this first RCT assessing the use of a ketogenic diet in infants (aged 1–24 months) with drug-resistant epilepsy, we report that a classic ketogenic diet was not more efficacious than antiseizure medication. A ketogenic diet was tolerable and safe to use in this age group. Ketogenic diets might be a treatment option in infants who continue to have seizures despite having tried two antiseizure medications. Many parents or guardians viewed a ketogenic diet as positive, even if it did not stop their child's seizures. A ketogenic diet might also improve some aspects of quality-of-life and neurodevelopment, but further trials are needed with larger cohorts at 12-month follow-up and thereafter, perhaps with an alternative study design.

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