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SYSTEMATIC REVIEW

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The use of ketogenic diets in children living with drug-resistant epilepsy, glucose transporter 1 deficiency syndrome and pyruvate dehydrogenase deficiency: A scoping review

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Abstract

Background: The ketogenic diet (KD) is a high fat, moderate protein and very low carbohydrate diet. It can be used as a medical treatment for drug-resistant epilepsy (DRE), glucose transporter 1 deficiency syndrome and pyruvate dehydrogenase deficiency. The aim of this scoping review was to map the KD literature, with a focus on epilepsy and associated metabolic conditions, to summarise the current evidence-base and identify any gaps.

Methods: This review was conducted using JBI scoping review methodological guidance and the PRISMA extension for scoping reviews reporting guidance. A comprehensive literature search was conducted in September 2021 and updated in February 2024 using MEDLINE, CINAHL, AMED, EmBASE, CAB Abstracts, Scopus and Food Science Source databases.

Results: The initial search yielded 2721 studies and ultimately, data were extracted from 320 studies that fulfilled inclusion criteria for the review. There were five qualitative studies, and the remainder were quantitative, including 23 randomised controlled trials (RCTs) and seven quasi-experimental studies. The USA published the highest number of KD studies followed by China, South Korea and the UK. Most studies focused on the classical KD and DRE. The studies key findings suggest that the KD is efficacious, safe and tolerable.

Conclusions: There are opportunities available to expand the scope of future KD research, particularly to conduct high-quality RCTs and further qualitative research focused on the child's needs and family support to improve the effectiveness of KDs.

KEYWORDS

children, epilepsy, glucose transporter 1 deficiency syndrome, ketogenic diet, pyruvate dehydrogenase deficiency, scoping review

Highlights

- From the studies included in this scoping review, the research is largely quantitative and focuses on efficacy of the ketogenic diet (KD).
- There is a need for high-quality randomised controlled trials and quasi-experimental studies to overcome the limitations of the evidence-base, which at this time is largely descriptive study designs.
- There are five qualitative studies on the KD in children living with drug-resistant epilepsy (DRE). There are no qualitative studies in children living with glucose transporter 1 deficiency syndrome and pyruvate dehydrogenase

deficiency. No studies have explored the needs of families and attrition in KDs.
- Future research should explore the experience of the KD from the perspective of the child living with DRE, glucose transporter 1 deficiency syndrome and pyruvate dehydrogenase deficiency, as well as the family unit supporting them.

INTRODUCTION

Epilepsy is a neurological condition where a person has abnormal neuronal activity in the brain, known as seizures.[1] Epilepsy is one of the most common neurological diseases and the first global report on epilepsy highlights the effects it has on around 50 million people worldwide.[2] Most children living with epilepsy take antiseizure medication (ASM) as the first line treatment to control their seizures; however, drug-resistant epilepsy (DRE) occurs in approximately 30% of these cases.[3] DRE is when the adequate trial of two ASMs has failed to control a person's seizures.[1] Alternative antiseizure treatment options include surgery, neurostimulation devices or ketogenic diet (KD) therapy.[1]

The KD contains high proportions of fat, has a moderate protein allowance for growth and is very low in carbohydrate.[4,5] There are several types of KDs including the classical KD (CKD), medium chain triglyceride (MCT) KD, modified Atkins diet (MAD), modified KD (MKD) and the low glycaemic index treatment (LGIT).[5] The KD requires medical support, including input from a ketogenic dietitian, and nutritional monitoring.[4]

Side effects of the KD include gastrointestinal symptoms, hyperlipidaemia and increased risk of renal stones; however, these can generally be managed with dietary manipulation.[4] The reasons for discontinuing the KD include increased time needed for meal preparation, non-acceptance of KD foods and anxiety around meeting the dietary requirements.[5] This highlights the complex nature of the KD and why the diet cannot be commenced without medical support.

The mechanism of action for the anticonvulsant effect of the KD is still unclear but KDs have been shown to significantly reduce seizures or result in seizure freedom.[4,6] The KD can also be used to supply ketone bodies, which are used as a supplemental fuel to prevent complications and potentially reduce symptoms in two metabolic conditions: glucose transporter 1 deficiency syndrome (GLUT1DS) and pyruvate dehydrogenase deficiency (PDHD).[7,8]

GLUT1DS is a genetic disorder where there is a deficiency in the protein that transports glucose across the blood–brain barrier resulting in seizures and other neurological symptoms.[7] GLUT1DS symptoms include paroxysmal eye movements, infantile-onset epilepsy, deceleration of head growth, impaired development and ataxia. The KD is the gold standard treatment for GLUT1DS but the benefits on ataxia and development are not considered to be as profound as the effects on seizure control.[7,8]

A different mechanism is seen in children living with PDHD who cannot metabolise pyruvate into acetyl coenzyme A. This leads to an increased production of lactate and impaired energy production which results in seizures, neuromuscular and neurological degeneration, and the possibility of death during childhood.[4,5]

Both the National Institute for Health and Care Excellence and the Scottish Intercollegiate Guidelines Network national clinical guidelines recommend that the KD be offered to children with DRE, and that this should be started as soon as possible after diagnosis in GLUT1DS and considered as early as possible for children with PDHD.[9,10]

The aim of this scoping review was to provide a comprehensive map of the increasing evidence-base on KDs, with a focus on DRE and associated metabolic conditions, to summarise the current knowledge base and identify any knowledge gaps. Mapping the evidence was important because of the exponential growth of KD research and the need to direct future pragmatic research instead of repeating similar studies.

The primary review question was "What research has been conducted on the use of the KD in children with DRE, GLUT1DS and PDHD?". The sub-questions helped to guide the review team through the complexity of available research with the goal of identifying potential gaps, comprising: (i) what type of research has been conducted? (ii) where in the world has the research taken place? (iii) what populations have been included in the research? (iv) which KDs have been researched? (v) what are the key findings of the research? and (vi) what are the gaps in the evidence base in relation to the use of the KDs for children with DRE, GLUT1DS and PDHD?

METHODS

An a priori scoping review protocol was registered with Open Science Framework (https://doi.org/10.17605/OSF.IO/S3V5K). The JBI scoping review methodology and PRISMA-ScR Checklist were used to guide conduct and reporting respectively.[11–14] Ethical approval was not required for this review.

ELIGIBILITY CRITERIA

The inclusion criteria for the scoping review followed the JBI Manual for Evidence Synthesis[13] recommended structure of Participants, Concept and Context.

Participants

Male and female children, defined as aged 18 years or younger with a diagnosis of DRE, GLUT1DS or PDHD were included. Studies on mixed populations or age groups were included if data on children comprised 70% or more of the study sample, or where the data on children were reported separately.

Concept

The concept of interest was any type of KD (i.e. CKD, MCT KD, MAD, MKD and LGIT). Studies that focused on one or multiple KDs were considered for inclusion. Studies where a KD was used in isolation or as an adjunct to other medical interventions were considered for inclusion.

Context

This scoping review considered studies from any geographical location and any setting (e.g., hospital, community).

Types of studies

This scoping review considered systematic reviews (SRs) and any type of primary research published in the English language for inclusion. Grey literature, conference abstracts and single case studies were excluded. There was no restriction placed on the date of publication.

SEARCH STRATEGY AND DATA SYNTHESIS

A preliminary search was conducted to determine relevant studies and identify keywords and index terms. These were then used to construct a detailed search strategy that was applied to the following databases: MEDLINE, CINAHL, AMED, EmBASE, CAB Abstracts, Scopus and Food Science Source. These databases were searched for relevant studies in the English language from database inception to September 2021 and were uploaded to Covidence and duplicates removed (veritas Health Innovation, Melbourne, Australia) (https://www.covidence.org).[15]

TABLE 1 Search strategy. MEDLINE, EBSCO HOST, September 2021.

No.	Search terms	Records retrieved
1	Diet, Ketogenic [mh]	1691
2	Ketogenic Diet [tiab]	3360
3	Classical Ketogenic Diet [tx]	49
4	Medium-chain triglyceride ketogenic diet [tx]	98
5	Modified ketogenic diet [tx]	130
6	Modified atkins diet [tx]	249
7	Low glyc*emic index treatment [tx]	80
8	Diet therapy [mh]	10,797
9	Nutrition therapy [mh]	2790
10	Carbohydrate restricted diet [tx]	2066
11	Low carb* diet [tx]	4401
12	High fat diet [tx]	48,312
13	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12**	68,141
14	Epilepsy [mh]	78,729
15	Epileptic [tx]	50,254
16	Seizures [mh]	56,889
17	Status epilepticus [tx]	15,374
18	Drug resistant epilepsy [mh]	2645
19	Intractable epilepsy [tx]	6302
20	Spasms, Infantile [mh]	3801
21	Glut 1 deficiency syndrome [tx]	8
22	Glucose 1 transporter disorder [tx]	11
23	Glucose transporter type 1 [tx]	4576
24	Pyruvate dehydrogenase deficiency [tx]	666
25	PDHD [tx]	38
26	**14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25**	169,123
27	**13 AND 26**	1995
28	**27 AND CHILDREN 0-18**	1004

Reference lists of the articles included at full-text screening were manually hand-searched to ensure that every study was given the opportunity to be included. Subsequently the search was updated to include literature published up to 17 February 2024. The full electronic search from MEDLINE (EBSCO host) is available to view (Table 1).

SELECTION OF SOURCES OF EVIDENCE

Two reviewers (TC and KC) independently screened titles and abstracts using the predetermined inclusion and exclusion criteria. Conflicts were resolved by discussion or by a third reviewer (KA). Following piloting of a data extraction tool and establishing 98% agreement, full-text screening was conducted by one reviewer (TC) with a second reviewer (KC) checking 10% of studies, with no conflicts arising.

DATA CHARTING PROCESS

The review team created a data extraction tool in Excel to extract relevant information from the selected studies.[16] Information extracted included: title, authors, year published, country, study design, setting, KD type, participants and authors key findings. The scoping review aimed to map the current available literature related to the use of KDs in DRE, GLUT1DS and PDHD; therefore, the quality of the research methodology was not scrutinised.

SYNTHESIS OF RESULTS

The resulting data were charted in graphs and tables. The results of the scoping review were summarised and are discussed in an accompanying narrative.

RESULTS

Selection of sources of evidence

Search results are mapped in a Prisma flow diagram (Figure 1) yielding 4703 studies that were uploaded to Covidence. There were 1982 duplicates removed. Title and abstract screening of 2721 studies was completed and 2389 were excluded. After full-text review of 332 studies, 80 were excluded for the following reasons: wrong concept ($n = 46$), wrong study design ($n = 15$), wrong population ($n = 8$), full text was unavailable ($n = 7$) and duplicate studies ($n = 4$). There remained 252 studies that met the inclusion criteria and these were included in the scoping review. Hand-searching reference lists of included studies resulted in an additional 13 studies. Because it was over 2 years since the original search, it

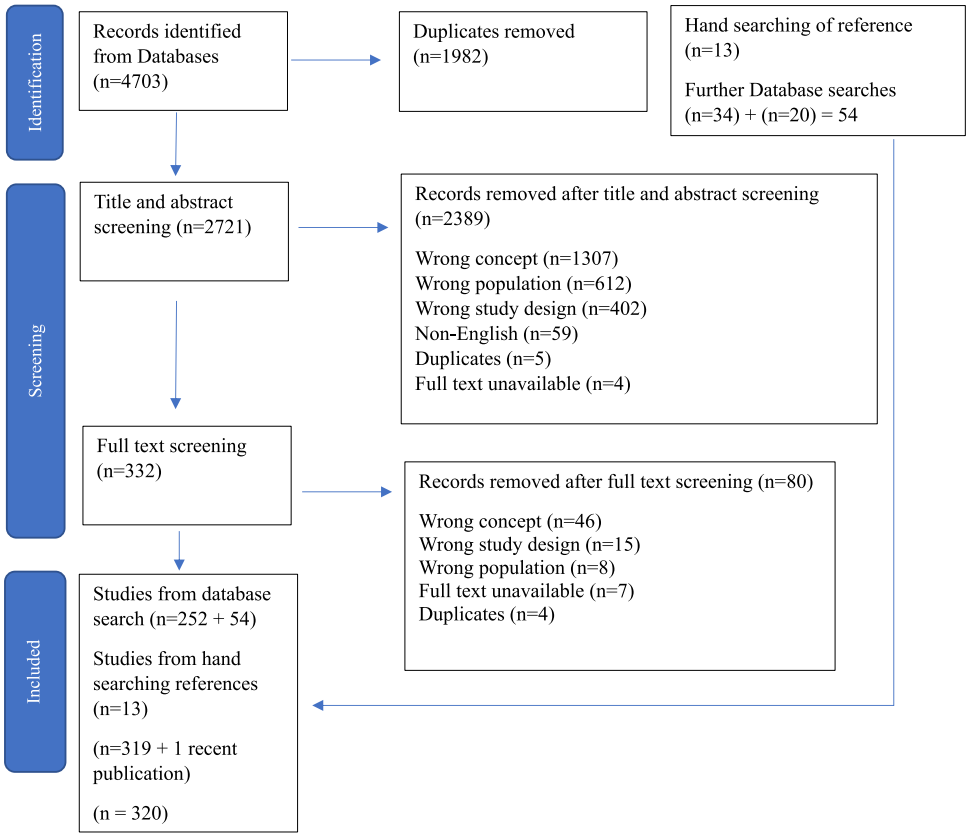

FIGURE 1 PRISMA flowchart outlining the identification and inclusion of studies.

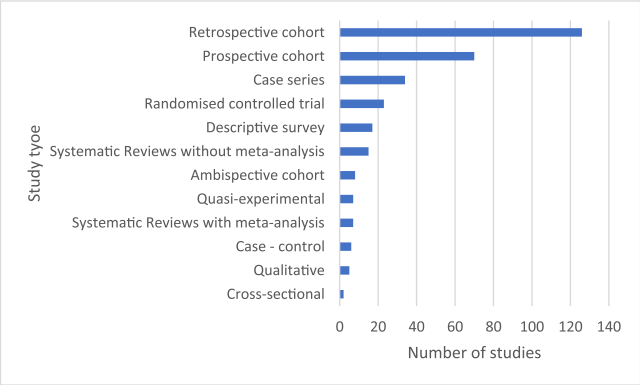

FIGURE 2 Types of studies included in the scoping review.

was updated across all databases and a further 34 studies were included in February 2023 and an additional 20 were included after a second search on the 17 February 2024. One additional qualitative study was included on publication in April 2024. Therefore, 320 studies met the inclusion criteria and are reported in this scoping review (see Supporting information, Table S1).

What type of research has been conducted?

The literature search provided a wide variety of study designs (Figure 2). Seven (2.2%) were SRs with meta-analyses[17–23] whereas 15 (4.7%) were SRs without a meta-analysis.[24–38] There were 23 (7.2%) randomised controlled trials (RCTs)[39–61] and seven (2.2%) quasi-experimental studies.[62–68]

The most common research type was retrospective cohort study (39.4%, $n = 126$),[69–194] followed by prospective cohort study (21.9%, $n = 70$).[195–264] The remaining quantitative study designs included case series (10.7%, $n = 34$),[265–298] descriptive survey (5.3%, $n = 17$),[299–315] ambispective cohort (2.5%, $n = 8$),[316–323] case–control (1.9%, $n = 6$)[324–329] and cross-sectional (0.6%, $n = 2$).[330,331] The remaining 1.6% ($n = 5$) were qualitative in design.[332–336]

Where in the world has the research taken place?

The use of KDs and research into this medical treatment has increased over the years.[211,300,308,313,316,322] In total, there are 36 countries that have published research (Table 2), some involving multiple countries and KD centres (3.8%, $n = 12$). The USA has produced the most studies (28.4%, $n = 91$) followed by China (8.1%, $n = 26$), South Korea (6.9%, $n = 22$) and the UK (5.9%, $n = 19$).

What KD types have been researched?

Removing SRs to avoid double-counting of primary studies resulted in 298 studies remaining. The most common KD type (Figure 3) was the CKD, used in 60.1% of studies ($n = 179$), followed by the MAD in 10.1% ($n = 30$), LGIT in 3.7% ($n = 11$) and the MCT KD in 1.7% ($n = 5$). There was one study (0.3%) on the use of MKD. Multiple KDs were studied in 21.1% ($n = 63$) and, in 1.7% ($n = 5$), the studies explored involved expectations of parents, attitude and experiences of parents, and country experiences therefore did not include dietary specifics. Finally 1.3% ($n = 4$) of studies did not describe the KD in sufficient detail to be able to define it.

The 21.1% ($n = 63$) of studies that included multiple KDs reviewed either two, three or four KDs, but never all five. Studies with multiple KDs highlighted the use of CKD and MAD in 11.4% ($n = 34$) of these, followed by 4.4% in CKD and MCT KD ($n = 13$). Additional variations were CKD, MAD and MCT KD ($n = 4$; 1.3%); CKD, MAD, MCT KD and LGIT ($n = 3$; 1%); CKD, MAD and LGIT; CKD, MCT KD and MKD; CKD and MKD ($n = 2$; 0.7%); CKD, MAD and MKD; CKD, MCT KD, LGIT and MKD; and MAD and LGIT ($n = 1$; 0.3%).

TABLE 2 Countries that have published ketogenic diet studies.

Country	Number of articles
USA	91
China	26
South Korea	22
UK	19
India	17
Argentina	14
Iran, Multicentre	12
The Netherlands	11
France, Japan	9
Italy, Turkey	8
Austria	7
Canada, Denmark	6
Australia, Egypt	5
Brazil, Saudi Arabia	4
Spain, Taiwan, Thailand	3
Greece, Sweden	2
Belgium, Germany, Indonesia, Kenya, Kingdom of Bahrain, Malaysia, Norway, Pakistan, Poland, Portugal, Vietnam, Zambia	1

What populations have been included in the research?

Removing SRs to avoid double-counting of primary studies resulted in 298 studies remaining. Most studies

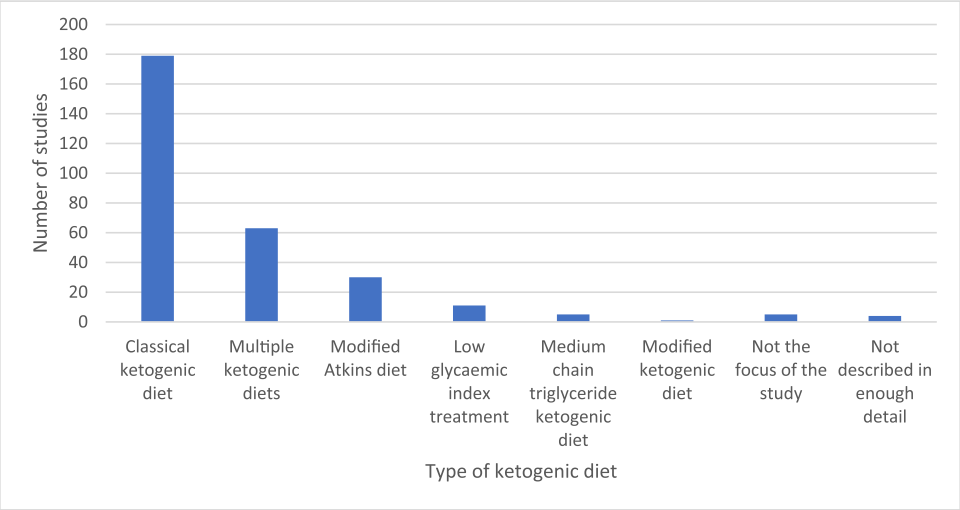

FIGURE 3 Types of ketogenic diet reported by studies included in the scoping review.

($n = 182$; 61.1%) focused on a diagnosis of DRE, of which 17 (5.7%) were DRE in infants under 2 years of age, and did not limit recruitment to specific epilepsy syndromes, seizure types or aetiology. There are studies focused on status epilepticus (SE), super-refractory status epileptics (SRSE) or febrile infection-related epilepsy syndrome (FIRES) ($n = 22$; 7.4%), infantile epileptic spasm syndrome (formerly known as West syndrome or infantile spasms [IS]) ($n = 16$; 5.4%), GLUT1DS ($n = 15$; 5%), Dravet syndrome (DS) ($n = 8$; 2.7%), Lennox–Gastaut syndrome (LGS) ($n = 7$; 2.3%), PDHD ($n = 5$; 1.7%), tuberous sclerosis complex (TSC) ($n = 5$; 1.7%), mitochondrial conditions ($n = 4$; 1.3%) (arginosuccinate lyase deficiency [$n = 1$], LGS with mitochondrial dysfunction [$n = 1$], DRE with respiratory chain defects [$n = 1$] and various mitochondrial conditions [$n = 1$]), epilepsy with myoclonic atonic seizures formerly known as DOOSE ($n = 4$; 1.3%), Angelman syndrome ($n = 2$; 0.7%), genetic aetiology ($n = 2$; 0.7%), malformation of cortical development ($n = 2$; 0.7%), and epilepsy of infancy with migrating focal seizures ($n = 2$; 0.7%).

Single studies ($n = 1$; 0.3%) have been conducted with KD and CDKL5-developmental and epileptic encephalopathy (DEE), PIGA deficiency, seizures as a result of hypothalamic hamartoma, infantile Alexander disease, Rett syndrome, Sturge–Weber syndrome, Aicardi syndrome, Jeavons syndrome, STXBP1-DEE, acquired epileptic aphasia, ALG3-CDG mutation, SMC1A-DEE mutation, hyperinsulinaemic hypoglycaemia caused by glucokinase mutations, North Sea progressive myoclonus epilepsy, SCN2A mutation, DEPDC5-related epilepsy, DEE, juvenile myoclonic epilepsy, myoclonic status in non-progressive encephalopathy, symptomatic or cryptogenic focal epilepsy, refractory continuous spikes and waves during sleep, and detectable somatic mammalian target of rapamycin pathway mutations.

What are the key findings of the research?

The first Cochrane SR was published in 2003 and there were no RCTs included, but five subsequent SRs highlight the increasing number of RCTs.[25,27,28,30,33] The 2020 SR included 13 RCTs, but sample sizes were small; therefore, it was concluded that evidence available on the use of KDs was low to very low-quality, but if children living with DRE are unsuitable for surgical intervention then KDs should be offered as a treatment option.[33] There was sufficient data to include a meta-analysis, KDs versus care as usual, and the main finding was that children randomised to KD treatment were three times more likely to become seizure-free and children who receive KD treatment were six times more likely to have a 50% or more reduction in seizures.[33]

Additional SRs in children with DRE and KD,[26] as well as different combinations of diet, including CKD and MAD[18,19,22]; CKD and MCT[17,24]; CKD, MAD and LGIT[37]; CKD, MAD and MCT[21,34]; CKD, MAD, MCT KD and LGIT[23]; and LGIT[31] all concluded that the KD is effective and should be considered as a treatment option. The findings from two SRs and meta-analyses demonstrated that the CKD was superior to MAD in achieving >50% seizure reduction but comparable for >90% seizure reduction, as well as seizure freedom at 6 months.[19,22] In comparison, a recent SR and network meta-analysis reported short-term effectiveness for the CKD, MAD and LGIT, but MAD was tolerated better, and had a higher probability of >50% reduction in seizures and comparable probability for 90% or higher seizure reduction.[23]

In addition, there are SRs concentrating on IS, SE and SRSE. In infants, one SR assessed the efficacy of KD as an adjunctive treatment and it was suggested there is a potential benefit in using KDs for drug-resistant IS.[29] The other SR included 33 studies that reported a response to

KD, included two RCTs, and it was indicated that KDs were tolerable, safe and could be effective, although high-quality evidence was not available.[20]

Schoeler et al.[36] included 31 studies in their SR and proposed that evidence for KD use in SRSE was limited and low quality but suggestive of benefits, whereas Dozières-Puyravel et al.[38] reviewed 15 studies and advised that there was preliminary data available to validate the safety and feasibility of KD use in SE, and SRSE.[36,38]

One SR examined the evidence of the KDs impact on children living with epilepsy and the effect on quality of life.[32] Eighteen studies were included, including seven RCTs or quasi-experimental studies, and it was advised that KD researchers should focus more on the diet's efficacy and less on quality of life and wellbeing of the child or family members. The SR concluded that parents required more understanding before starting the KD, support from experienced families, and that the child's diet was ultimately a key component of family life.[32]

There was an additional SR for KD and mitochondrial disease (MD), which included 14 paediatric case reports and concluded that the data was insufficient for general KD recommendations in this vulnerable group, but that KD treatment should be considered in MD DRE if there are no contraindications.[35]

A comparison of KDs to care as usual in RCTs reported KDs to be an effective therapy.[42,51] In addition, with a focus of the RCT on the MAD, it was concluded that it was effective and tolerated in DRE and in drug refractory IS.[41,48,56] A simplified MAD for parents with low levels of literacy was reported as being feasible and efficacious.[50] A study reporting results from a crossover RCT summarised that a 10 g of carbohydrate as the MAD starting point may be ideal with the option of a less restricted 20 g of carbohydrate at 3 months.[41] In a RCT in children aged 2–8 years following a LGIT, this was reported to be more efficacious as an add-on treatment compared to the control group.[55] KDs were also reported to be efficacious and safe for children with epilepsy related to their MD.[57]

The CKD and MCT KD were shown to be comparable in one study.[44] The CKD and MAD were shown to be tolerable, safe and effective but the CKD may be more suitable in infants under 2 years of age and the MAD more favourable in children.[47,49,59,61] Seizure freedom was comparable in the MAD and LGIT at 12 weeks of treatment.[54] A RCT comparing three KDs concluded that the CKD, MAD and LGIT significantly reduced seizure burden but the LGIT had the least number and least severe side effects.[53]

Comparison of CKD ratios (fat:protein + carbohydrate) in RCTs reported the 4:1 CKD having greater efficacy compared to 3:1 CKD but the benefits largely remained when reducing the ratio.[40] A later RCT found a potential efficacy at a ratio of 2.5:1 with the added benefit of less side effects.[46] One RCT focused on fasting versus gradual initiation of the CKD and concluded that fasting was not necessary for the KD to be efficacious.[39] The following RCT focused on length of CKD when used to treat IS and confirmed that a short-term (8 months) compared to the usual 2-year timeframe had a similar relapse rate and short-term KD use may reduce side effects.[45]

In RCTs comparing KD to ASM, authors reported that the addition of the MAD to treat DRE was superior to the ASM Levetiracetam, and that KD is as effective as adrenocorticotropic hormone use in the long-term for IS as an appropriate second-line option after the ASM, vigabatrin.[52,58] A recent RCT looked to establish the efficacy of CKD compared with addition of another ASM in infants under 2 years of age. It was concluded that addition of the CKD did not alter the efficacy or tolerability of treatment compared to a further ASM.[60]

There were five qualitative studies (1.6%) identified in the scoping review. They were conducted in the UK, Saudi Arabia, Kenya, USA and most recently again in the UK, had sample sizes of 12, 30, 17, 17 and 21, respectively, and used semistructured interviews to gather data on the lived experiences of families in each country.[332–336]

The first UK study explored the KD and parenting from a grounded theory worldview and thematic analysis developed the themes: food as medicine, fat is good and food as symbol of inclusion.[332] In Saudi Arabia, attitudes and experiences of parents towards epilepsy were examined after KD use.[333] Parental expectations and experiences were explored in the USA.[335] Themes that arose from the analysis included social impact, physical and emotional impact for both parents and parental reporting for their child. Parents also felt that the demands of epilepsy and the KD led to impact on their finances and work.[335]

Furthermore, Carroll et al.[336] investigated parents experiences of treating epilepsy with KD from an interpretive description methodology that generates knowledge for clinical application. The themes described were “epilepsy is all consuming”, which shows parental focus on caring for their child, and “opening the window to new opportunities”, which highlighted the benefits observed from KD use such as increased social relationships, learning new skills and engaging in activities.[336] The “reality of KD therapy” describes the challenges experienced by families whereas the final theme “looking to the future” explains the worry of weaning from the KD and fear of increased seizure activity.[336]

These studies were parent proxy reports except the Kenyan study which explored the feasibility and acceptance of MAD in Kenyan parents and three adolescents.[334] Parents from the Kenyan study reported that treatment with KDs resulted in the avoidance of social gatherings, changes to shopping patterns and costs involved, and increased their time for meal preparation.[334] Adolescents following a KD discussed avoiding foods they disliked and found carrying snacks and meals

to school to be an inconvenience, although they were aware of the benefits they experienced.[334]

Children and young people living with a diagnosis of GLUT1DS and PDHD may have been included in studies under the umbrella term of DRE, but there are a handful of studies that focused specifically on these populations. An overview of these studies is provided below.

Out of the 15 quantitative studies focusing on GLUT1DS, none were RCTs or quasi-experimental in design. The included studies were retrospective ($n = 4$), prospective ($n = 1$) and ambispective ($n = 1$), case series ($n = 5$), and descriptive surveys ($n = 4$). There were studies reporting that all of their participants became seizure free,[186,272] whereas other studies reported seizure freedom in 83%[286] and 80%.[208] A survey of parents of children living with GLUT1DS and KD reported a variety of KD types (CKD, MAD, MCT KD and LGIT) resulting in seizure freedom.[310] Reasons for poorer outcomes were attributed to poor ketosis, older age at diagnosis and KD side effects.[151]

Paroxysmal movement disorder was reported to have improved after KD in 1/5 (20%) and 4/5 (80%).[151,322] Conversely, another study reported that ataxia was as responsive to the KD (79%) as seizures (80%).[307] Survey results indicated that 53% still experience ataxia despite KD use.[312]

Caregivers reported improved physical endurance, cognition, alertness and demeanour after KD therapy.[151,208,286,292] Parent's and children living with GUT1DS and CKD had impaired global scores for quality of life but this was comparable to other chronic diseases.[312] It was recommended that the KD be used life-long in GLUT1DS.[322]

The following quantitative studies ($n = 5$) were available on PDHD and KD: prospective ($n = 2$), ambispective ($n = 1$) and case series ($n = 2$). It was advised that KD may improve neurological outcome and longevity, have positive effects on epilepsy, sleep and language development, and reduce hospital admissions, but complications such as acute pancreatitis were noted.[200,247,265,296]

DISCUSSION

To the best of our knowledge, this is the first scoping review to have comprehensively mapped the evidence on the use of KDs in 320 studies of children with DRE, GLUT1DS and PDHD.

Where in the world has the research taken place?

Our findings indicate that 36 countries across the globe have been involved in the research of KDs which indicates widespread use, in different societies and cultures. However, the USA has published the highest proportion of studies (28.4%). In 2005, there were 41 countries out-with the USA offering KDs compared to the International League against Epilepsy (ILAE) listed centres from 78 countries in 2020.[337] The ILAE, as well as the emergence of global symposia and development of the International Neurological Ketogenic Society, in addition to the work of charitable bodies, has likely contributed to the increase in KD centres, patient numbers and studies worldwide.[313]

What KDs have been researched?

The KD has been used in the treatment of DRE since the 1920s when Wilder, proposed that if ketonemia was produced in the absence of starvation then seizure activity would improve, and he subsequently described the CKD in 1921.[338] This scoping review highlights that the CKD has been most widely researched, in 60.1% of studies.

The MCT KD was then described by Huttenlocher, University of Chicago, in 1971 but, despite being the second KD protocol described, it was only present in 1.7% of studies included in this scoping review.[338] This could be a result of the gastrointestinal side effects of MCT or because it is less used in practice.[313] Because of the development of ASMs, KD use declined until it re-emerged in the 1990s.[338] Studies from the USA include The John Hopkins Hospital Team who brought the MAD to the forefront and Massachusetts General Hospital who first described the use of the LGIT.[84,269] The MKD was developed by UK dietitians with the aim to simplify the treatment with Martin-McGill et al.[311] describing it as "MKD offers the dietary 'control' offered by CKD, the flexibility of MAD and the supplemental benefits of MCT KD".

What populations have been included in the research?

Most studies have been conducted under the umbrella term of DRE (61.1%) but there are studies in epilepsy syndromes and conditions where the KD is considered to be more beneficial (> 70% seizure reduction), which has resulted in them being highlighted in the International KD Study Group recommendations for earlier initiation[4]: These include Angelman syndrome, DS, and epilepsy with myoclonic atonic seizures formerly known as DOOSE, GLUT1DS, FIRES, IS syndrome, PDHD, SRSE and TSC. Ohtahara syndrome is also included in this group within the recommendations, but the search did not locate any studies on Ohtahara syndrome that met the inclusion criteria for this review.

There are fewer studies on KDs in the rare metabolic conditions, GLUT1DS and PDHD, which is likely a result of the smaller population size, challenge in recruiting to studies, and the poor prognosis of neonatal and infantile-onset PDHD. GLUT1DS was discovered by

Dr Darryl DeVivo in 1991[338,339] and guidance has been published but this focuses more on the medical management of GLUT1DS rather than KD recommendations.[7]

What are the key findings of the research?

The scoping review did not critically appraise or assess the quality of studies and is unable to make recommendations for practice. However, there is a large body of evidence that reports KDs as being effective and that they should be considered as a treatment option in DRE despite low levels of evidence which is a result of the study designs available, small sample sizes and reported unclear methods described in the RCTs.[33]

There is less evidence available on GLUT1DS and PDHD. In GLUT1DS, the KD was seen to be beneficial, and there were positive improvements in seizure activity and movement disorders. Despite lower amounts of evidence, KD is the current standard of care for GLUT1DS.[7] Studies in PDHD suggest clinical improvement in seizure activity, lactic acidosis and sleep, and also that KD should be considered as a treatment option.

The studies included in the scoping review suggest that KDs are efficacious and safe to use in infants, children and adolescents, and there are studies describing oral, enteral and parenteral KDs. Studies highlight that the need for a fasting KD initiation is not necessary for KD efficacy and it was proposed that fasting increases the risk of hypoglycaemia.[39,73,77,85,141,182]

Studies also propose the use of KDs earlier on in the epileptic journey,[83,91,99,122,149,156,185,291,299] specifically in LGS,[233] TSC,[271] infants,[60,75,119,161,282,329] DS,[118,163] DOOSE,[144,209] CDKL5,[140] FIRES and SRSE,[36,160,169,256,280,283] and the metabolic conditions GLUT1DS[114,272,286] and PDHD.[247,296] Recommendations for treating new onset-refractory SE, including FIRES, includes the advice to escalate treatment from ASMs not only to immunotherapy, but also to KD, as soon as possible in the treatment course.[340] This key finding highlights the importance of early KD referral and is an important learning point for clinical practice.

Historically, the KD was not recommended for use in infants under 2 years of age because of their nutritional requirements and because this time is crucial for development, whereas more recently KD has been demonstrated to be safe and effective in this specific patient group[20,60] and there are potential benefits.[29] The increased use of KDs in infants has led to the publication of guidelines for infants living with DRE.[341] The literature also suggests that breast feeding or expressed breast milk can be safely incorporated in KD regimes.[98,153,284,319]

A clinical practice guideline for the use of human milk and breastfeeding during KD in infants has been developed and provides practical strategies for clinicians.[342]

Multiple studies have described the efficacy of the CKD,[40,42,44,46,49,53] MCT KD,[42,44] MAD,[48,49,53,54] and LGIT,[53–55] and reported that the less restrictive dietary options, LGIT,[53,84,138,258] have less side-effects and increased compliance but even the higher carbohydrate and protein options have high rates of attrition.[93,104,235]

What are the gaps in the evidence base in relation to the use of the KD for children with DRE, GLUT1DS and PDHD?

Despite retrieving 320 studies on the use of KD, gaps in knowledge remain.

There is a small body of evidence with regards to enteral and parenteral KD use but there is no sole research into the use of blended KD via enteral feeding tubes, which would help guide clinical practice and guidelines. Future research could focus on the positive and negative aspects, and any potential benefits over commercially made KD enteral powder and liquid.

There are also gaps in knowledge with regards to children living with metabolic conditions, GLUT1DS and PDHD, and the KD. Single case studies or case series of KD use in children living with PDHD and GLUT1DS, or prospective cohort studies, would provide valuable quantitative data for clinicians and strengthen the evidence for considering KD as a treatment option.

An additional knowledge gap is the small number of RCTs and quasi-experimental studies. The need for high-quality RCTs and quasi-experimental studies would help to establish the effectiveness of KD and overcome the limitations of the evidence-base, which at this time is largely descriptive study designs.

One of the main gaps in knowledge arguably stems from the limited number of qualitative studies identified by this comprehensive literature search. The restrictive nature of KDs and high attrition rates are often reported, and so it is somewhat surprising that there have been so few qualitative studies exploring the lives and experiences of families and children living with DRE, GLUT1DS or PDHD and KD. Consequently, we lack understanding of the relationships within families managing the KD, and why some excel and others struggle. Future research should focus on the rich data that research on lived experiences can provide.

There are many complex factors involved when medical diets are used for chronic illness, including parent feeding practices and the child's eating behaviours, social eating and dietary stigma, parent–child relationships, siblings as carers, wider family or other caring roles, parental stress and the burden of responsibility, and food insecurity.[321,343–346] These factors have the potential to impact the lived experience of children living with DRE, GLUT1DS and PDHD, as well as their families.

The following key points were highlighted from authors interviews with parents: (i) diet is a key component of family[332]; (ii) perceptions of food, particularly fat, can change over time[332]; and (iii) families

want to know the real-life impact the KD would have on their family life, from the supplies required to changes in shopping, KD preparation and the time required.[304,330,335,336] These research findings highlight the complexity of food and diet-related medical treatments, and also indicate that little is known about children and KDs, in addition to why KDs are successful for some families and not others.

There is therefore a lack of rich data available on the complex factors experienced by children living with DRE, GLUT1DS or PDHD, and families supporting them that are available to guide clinicians, dietitians and families who are considering using KDs as a medical treatment. Our future work seeks to address this gap in knowledge by conducting primary qualitative research with the main caregivers, extended family and the child living with the KD as medical management for DRE, GLUT1DS or PDHD.

LIMITATIONS

There was a comprehensive search strategy and thorough extraction of data, which is a strength of this review. Efforts were made to obtain all studies related to the scoping review question, but study limitations still exist. The included studies were not critically appraised. This is standard for a scoping review that aims to map the evidence base and not to rate the studies quality or make recommendations for practice.

The search was restricted to studies published in the English language only because this was the language of the review team and translation services were not available. This removed a total of 59 studies published in Spanish ($n = 22$), French ($n = 8$), Japanese ($n = 6$), Chinese ($n = 6$), German ($n = 4$), Norwegian, Danish, Italian and Portuguese ($n = 2$), and Russian, Polish, Swedish, Czechoslovakian and Turkish ($n = 1$), which would have increased the overall studies and number of countries publishing research. Arguably, these excluded studies may have provided additional findings, except for one qualitative study; however, there was significant repetition in the 320 studies that we data extracted from, and so the likelihood is low.

There was no date restriction applied to the search, but older studies ($n = 4$) from the 1970–1980s were unable to be located. Because of their age, these are also arguably unlikely to have altered the findings. Also, the selection of online databases could have reduced the results but those chosen were considered to hold most journals related to KD research.

AUTHOR CONTRIBUTIONS

All authors contributed to the planning, design and completion of the scoping review. Tracy Cameron completed the literature searches, screened all the studies, extracted all the data and drafted the manuscript. Kay Cooper contributed to screening the studies. Kay Cooper and Karen Allan contributed to 10% of data extraction. All authors contributed to editing the draft manuscript and have approved the final version of the manuscript submitted for publication.

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CONFLICTS OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in the study.

TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with PRISMA guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned on OSF have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Henderson et al. 2006[17]	USA	n = 1084, DRE	To complete a meta-analysis existing studies reporting on the use of the KD	Systematic review and meta-analysis 19 studies: 10 Prospective 9 Retrospective	CKD & MCT KD	• The studies support the use of KDs in children living with DRE • The results indicate that children remaining on KDs for over three months have around a twofold chance of sustaining improved seizure control • Children living with generalised seizures have a greater chance of improved seizure control and/or ASM reduction
Li, Zou, Ding 2013[18]	Iran	n = 1790, DRE	To systematically review the success of KDs	Systematic review and meta-analysis 38 studies: 24 Prospective 14 Retrospective	CKD & MAD	• The results support the use of KDs in children living with DRE
Rezaei et al. 2019[19]	Iran	n = 3799, DRE n = 3350 CKD n = 449 MAD	To compare the short-term and long-term efficacy of KDs	Systematic review and meta-analysis 71 studies: 7 RCTs 31 Prospective 33 Retrospective	CKD & MAD	• At three and six months, the CKD does not differ from the MAD in ≥50% and ≥90% seizure reduction • The results indicate that there is no significant difference between the efficacy of the CKD and MAD

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Lyons et al. 2020[20]	UK	n = 534, Infants with DRE	To systematically review studies using KDs	Systematic review and meta-analysis 33 studies: 2 RCTs 31 Uncontrolled cohort	CKD, MAD & MCT KD	• KDs have been shown to be safe, tolerable, and effective for infants with DRE but there is a lack of high-quality research with few studies focusing on infants • To confirm efficacy, tolerability, and safety of KDs in infants, high-quality RCTs are recommended
Sourbron et al. 2020[21]	The Netherlands	n = 472, DRE	To review the evidence for the efficacy and tolerability of KDs	Systematic review and meta-analysis 5 studies: 5 RCTs	CKD, MAD & MCT KD	• There are variations between all studies included in the review, but the results show that KDs should be considered for children and adolescents living with DRE if they do not meet the criteria for epilepsy surgery
Mhanna et al. 2022[22]	USA	n = 397, DRE	To evaluate the tolerability and efficacy of the MAD compared to the CKD	Systematic review and meta-analysis 5 studies: 3 RCTs 1 Non-RCT 1 Observational	CKD & MAD	• The review and meta-analysis showed superiority of the CKD versus MAD in achieving seizure reduction >50% at six months seizure reduction >90% and seizure freedom, and tolerability, were comparable • To validate the findings large-scale RCTs are recommended

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Devi et al. 2023[23]	India	n = 907, DRE n = 664 KD n = 243CAU	To evaluate the safety and efficacy of dietary therapy	Systematic review and network meta-analysis 12 studies: 12 RCTs	CKD, MAD, MCT KD & LGIT	• CKD, MAD and LGIT result in 50% or higher seizure reduction compared to CAU in the short term • MAD had better tolerability and higher probability for >50% seizure reduction and comparable probability for >90% reduction and seizure freedom • MAD may be a better treatment option compared to CKD
Lefevre & Aronson 2000[24]	USA	n = 482, DRE	To systematically review the literature on the efficacy of KDs	Systematic review 11 studies: 2 Prospective 9 Retrospective	CKD & MCT KD	• The KD seems to be efficacious in reducing seizure frequency in children living with DRE and should be considered as a treatment option
Levy & Cooper 2003[25]	UK	n = 0, Diagnosis of epilepsy irrespective of seizure type or epilepsy syndrome	To review the evidence from RCTs regarding the effects of KDs	Systematic review 0 studies	None	• No reliable evidence was found from RCTs to support the use of KDs in DRE, but observational and prospective studies suggest that KDs have a positive effect on seizure reduction • The KD could be a treatment option in children living with difficult to control epilepsy treated with multiple ASMs

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Keene 2006[26]	Canada	n = 972, DRE	To review the evidence for the safety, efficacy and cost of KD	Systematic review 15 studies	CKD	• There is Class Two Evidence supporting the cautious use of KD in children living with DRE • Evidence of which KD is best, what type of KD to use, what length of time to use KD for, which patient benefits, who is at risk of an adverse event and whether there is a cost/benefit to the KD still requires answers which prospective studies could answer
Levy et al. 2012[27]	UK	n = 289, DRE	To review the evidence from RCTs regarding the effects of KDs and similar diets	Systematic review 15 studies: 4 RCTs, 5 publications 6 Prospective 5 Retrospective	CKD, MAD & MCT KD	• This systematic review included data from four new RCTs, some were good quality, but none were blinded • Studies suggest that KDs benefit seizure control and are comparable to ASMs • One long-term outcome study reports a high attrition rate, suggesting KD gastrointestinal side effects and dislike for the diet are concerning
Martin et al. 2016[28]	UK	n = 427, DRE	To review the evidence from RCTs for efficacy and tolerability of KDs	Systematic review 7 studies: 7 RCTs	CKD, MAD & MCT KD	• The RCTs have small sample sizes of poor quality but show promising results for the use of KDs in DRE • Attrition rates for all KDs were problematic due to lack of efficacy and tolerance • The MAD and CKD may have similar effects on seizure control, but this requires further research

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• In children with DRE or who are not suitable for surgery, KDs remain a treatment option
Prezioso et al. 2017[29]	Italy	n = 341, IS	To assess the efficacy of the KD as adjunctive therapy for IS	Systematic review 13 studies: 4 Prospective 9 Retrospective	CKD	• There is a lack of high-quality studies, but the results suggest that the CKD has a potential benefit in treating drug resistant IS
Martin-McGill et al. 2018[30]	UK	n = 778 DRE (91.5% children)	To assess the effects of KDs by reviewing the evidence from RCTs	Systematic review 11 studies: 11 RCTs	CKD, MAD & MCT KD	• The limited number of studies with small sample sizes result in a low quality of evidence, but the RCTs show promising results for the use of KDs • KDs have concerning attrition rates related to lack of efficacy and tolerance but the MAD has fewer side effects • The CKD and MAD may be similar in efficacy • KDs remain an option for children living with DRE or in those who are not suitable for surgical intervention
Rezaei et al. 2018[31]	Belgium	n = 233, DRE	To review all LGIT studies	Systematic review 8 studies: 2 Prospective	LGIT	• More high-quality studies are required to determine LGIT efficacy, but the results show that the LGIT has a beneficial effect in children living with DRE

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
				6 Retrospective		
Poelzer et al. 2019[32]	Canada	Not described, DRE	To review the evidence of the impact of KDs on children living with epilepsy and the effect on family QoL	Systematic review 18 studies: 7 RCTs & quasi-experimental 2 Observational 7 Retrospective 2 Case studies	Not discussed	• Future research should address QoL for families living with DRE and KDs, adherence and dropout rates
Martin-McGill et al. 2020[33]	UK	n = 932 DRE (76% children)	To assess the effects of KDs for people living with DRE	Systematic review 13 studies: 13 RCTs	CKD, MAD & MCT KD	• The evidence for the use of KDs is low to very low quality due to the limited number of studies, small sample sizes, associated risk of bias and imprecision • The evidence suggests that KDs could be effective in children living with DRE and in those unsuitable for epilepsy surgery • The MAD may be more palatable, have a similar effect on seizures and have fewer side effects
Christensen et al. 2021[34]	Denmark	n = 1221, CNS diseases (1131 epilepsy in adults and children)	To investigate the use and efficacy of KDs in CNS diseases	Systematic review 24 -21 RCT epilepsy	CKD, MAD & MCT KD	• The review substantiates the use of KD, MAD and MCT KD in DRE

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Zweers et al. 2021[35]	The Netherlands	n = 20, MD (not PDHD) (70% children)	To assess efficacy and safety of KDs for MD	Systematic review 16 studies: 1 controlled trial 15 case reports	CKD 11, MAD 8 & 1 uncertain	• There is limited information on the efficacy and safety of KDs for MD and DRE • KDs are a promising treatment option • An experienced team should consider KD as a treatment option, unless contraindicated • General recommendations cannot be made • Individual case study reports and side effects should be taken into consideration • Prospective studies would provide worthwhile information
Schoeler et al. 2021[36]	UK	n = 147, SRSE	To systematically review the evidence for the use of the KD	Systematic review 31 studies: 14 Retrospective 1 Prospective observational 16 Case studies	CKD	• The evidence for KD efficacy is limited and low quality but suggests positive benefits • Side effects are rare but require close monitoring • Research suggests that early KD in SRSE may be important for efficacy, but further research is required
Desli et al. 2022[37]	Greece	n = 1114, DRE	To review the efficacy and safety of KDs from RCTs	Systematic review 14 studies: 14 RCTs	CKD, MAD & LGIT	• KD is an effective treatment for DRE • RCTs researching long-term impact of KD, impact on cognition and behaviour, and cost-effectiveness are encouraged

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Dozières-Puyravel, Höhn & Auvin 2022[38]	France	Not described, SE and SRSE (73% children)	To review the safety and tolerance of KDs	Systematic review 15 studies: 2 Prospective 13 Retrospective	CKD	• There is enough preliminary data available to show that the KD is safe and feasible in refractory SE and SRSE, but further research is required to demonstrate KD efficacy
Bergqvist et al. 2005[39]	USA	n = 48, DRE	To compare KD initiation: gradual versus standard with a 24 to 48 hour fast	RCT	CKD	• A fasting initiation was not necessary for CKD efficacy • The gradual approach may simplify management and increase availability of the KD
Seo et al. 2007[40]	South Korea	n = 76, DRE n = 40 4:1 CKD (53%) n = 36 3:1 CKD (47%)	To compare the antiepileptic efficacy and diet tolerability of 3:1 and 4:1 CKD ratio	RCT	CKD	• The 4:1 CKD showed greater efficacy than the 3:1 CKD with higher seizure free outcomes • In most cases, seizure free outcome was maintained after decreasing the CKD to 3:1 • The tolerability of the 3:1 CKD was better with less frequent gastrointestinal symptoms
Kossoff et al. 2007[41]	USA	n = 20, DRE	To identify the ideal starting limit of carbohydrates to maximise efficacy, ketosis, and tolerability	RCT	MAD	• Starting the MAD diet at 10g carbohydrate per day may be ideal • An increase to 20g per day after three months could be trialled. If seizures increased, the carbohydrate could be reduced • The study provides evidence for the efficacy and safety of the MAD for

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						DRE
Neal et al. 2008[42]	UK	n = 145, DRE n = 72 control (49.7%) n = 73 KD (50.3%)	To test the efficacy of the KD	RCT	CKD & MCT KD	• The CKD and MCT KD are efficacious and should be included in the management of childhood DRE • When considering treatment options, the side effects should be taken into consideration
Freeman et al. 2009[43]	USA	n = 20, LGS	To study the efficacy of the KD	RCT	CKD	• The study design had an active control but ketosis was not eliminated as planned. There were no significant differences between the glucose or saccharin arm • A significant decrease in seizures were noted in both groups over 12 days
Neal et al. 2009[44]	UK	n = 145, DRE	To examine the efficacy and tolerability of the CKD and MCT KD	RCT	CKD & MCT KD	• This study shows that the CKD and MCT KD are comparable in efficacy and tolerability • Both KDs can be used in the treatment of DRE
Kang et al. 2011[45]	South Korea	n = 35, IS n = 16 Short-term (45.7%) n = 19 Long-term (54.3%)	To compare the prognoses between KD use at 8 months compared to >2 years	RCT	CKD	• The short-term trial of the CKD for IS is similar in relapse rate to a longer duration KD • Short-term use may improve growth and reduce other long-term adverse effects • Early discontinuation of the KD could

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						be considered at six months in spasm-free infants and the diet restarted if spasms reappear
Raju et al. 2011[46]	India	n = 38, DRE n = 19 4:1 CKD (50%) n = 19 2.5:1 CKD (50%)	To compare the efficacy and tolerability of 2.5:1 versus 4:1 KD	RCT	CKD	• The 2.5:1 CKD is possibly as effective as 4:1 CKD in controlling seizures with fewer side effects
El-Rashidy, et al. 2013[47]	Egypt	n= 40, DRE n = 15 MAD (37.5%) n = 25 CKD (62.5%)	To evaluate the efficacy, safety, and tolerability of the KD, either CKD 4:1 formula or MAD	RCT	CKD & MAD	• The 4:1 CKD and MAD are tolerable, safe, and an effective therapy for DRE • Children using the 4:1 CKD formula had better growth and significantly better seizure control compared to the MAD
Sharma et al. 2013[48]	India	n = 102, DRE n = 52 control (51%) n = 50 MAD (49%)	To evaluate the efficacy of the MAD	RCT	MAD	• The MAD was found to be tolerated and effective in children with DRE

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kim et al. 2016[49]	South Korea	n = 104, DRE n = 51 CKD (49%) n = 53 MAD (51%)	To compare the efficacy, safety, and tolerability of the MAD with the CKD	RCT	CKD & MAD	• The CKD is more suitable as a first line treatment in children younger than two years of age • The MAD might be considered as the main KD choice for the treatment of childhood DRE
Sharma et al. 2016[50]	India	n = 81, DRE n = 40 control (49%) n = 41 MAD (51%)	To evaluate a simple variation of the MAD	RCT	MAD	• A simplified MAD was found to be tolerated, feasible and efficacious in children with DRE • This simplified MAD was significantly more effective than ASMs alone and 56.1% following the MAD had >50% seizure reduction at three months
Lambrechts et al. 2017[51]	The Netherlands	n = 48, DRE n = 26 KD (54%) n = 22 CAU (46%)	To evaluate the tolerability and efficacy of the KD	RCT	CKD & MCT KD	• At four months, 13/26 (50%) children treated with the KD were responders, 3/26 (11.5%) were seizure free and 3/26 (11.5%) >90% seizure reduction • KDs are an effective treatment for children and adolescents living with DRE compared with care as usual
Dressler et al. 2019[52]	Austria	n = 32, West syndrome	To compare the efficacy and safety of the KD with standard ACTH treatment	RCT	CKD	• The CKD is as effective as ACTH in the long term, but ACTH is better tolerated • Without prior VGB treatment, ACTH remains the first choice to achieve short-term seizure remission • With prior VGB, CKD was at least as effective as ACTH in the short term and could be a second-line treatment

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						after VGB
Sondhi et al. 2020[53]	India	n = 170, DRE n = 55 CKD (32%) n = 58 MAD (34%) n = 57 LGIT (34%)	To determine whether the MAD and LGIT provide similar results to the CKD	RCT	CKD, MAD & LGIT	• The CKD, MAD and LGIT significantly reduced seizures in children with DRE • The LGIT is associated with the least number and least severe adverse events
Gupta, Dabla & Kaushik 2021[54]	India	n= 60, DRE n = 30 MAD (50%) n = 30 LGIT (50%)	To compare the efficacy of the MAD and LGIT	RCT	MAD & LGIT	• The study had a small sample size but in the LGIT group, 22/30 (73.3%) achieved >50% reduction and in the MAD 13/30 (43.4%) • Seizure freedom was noted in 2/30 (6.6%) children following the MAD and 5/30 (16.6%) in LGIT • The MAD and LGIT were comparable KD treatments
Lakshmin-arayanan et al. 2021[55]	India	n = 40, DRE n = 20 LGIT (50%) n = 20 Control (50%)	To compare the efficacy of LGIT on seizure control	RCT	LGIT	• As an add on to ongoing ASMs for three months • The LGIT is more efficacious compared to the control group where none of the patients improved

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Sharma et al. 2021[56]	India	n = 91, IS n = 45 MAD after 4 weeks (49.5%) n = 46 MAD immediately (50.5%)	To evaluate the efficacy of the MAD in children with epileptic spasms who failed hormonal therapy	RCT	MAD	• The MAD was found to be tolerated and effective in children with epileptic spasms refractory to hormonal therapy
Huang et al. 2022[57]	China	n = 33, MD with epilepsy	To confirm the efficacy of the CKD	RCT	CKD	• The CKD is safe and an effective therapy for seizure control in MD, especially in mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes and pathogenic variants of mitochondrial DNA • The KD could be considered in the management of these patients
Archna et al. 2022[58]	India	n = 101, DRE n = 51 MAD (50.5%) n = 50 Levetiracetam (49.5%)	To compare the efficacy of the MAD versus levetiracetam	RCT	MAD	• The addition of the MAD was found to be superior to Levetiracetam in achieving seizure reduction at 12-weeks • Adverse effects were higher with the MAD compared to the ASMs

TABLE S1 Characteristics of included studies

Author, year	**Country**	**Population**	**Study aim**	**Study design**	**Ketogenic Diet**	**Authors key findings**
Sharma et al. 2023[59]	India	n = 40, DRE n = 20, CKD (50%) n = 20, MAD (50%)	To compare the tolerability and efficacy of CKD and MAD	RCT	CKD & MAD	• The CKD and MAD were well tolerated • Constipation and vomiting were the most reported side-effect • Both diets were comparable with respect to seizure freedom • MAD is an alternative dietary option in DRE
Schoeler et al. 2023[60]	UK	n = 136, DRE, infants <2 years n = 78 CKD (57.3%) n = 58 ASM (42.6%)	To establish the efficacy of CKD compared with addition of another ASM	RCT	CKD	• The addition of the KD did not differ compared to addition of a further ASM in terms of tolerability and efficacy • The KD could be an option after two ASM in infants
El-Shafie et al. 2023[61]	Egypt	n = 40, DRE n = 20 CKD (50%) n = 20 MAD (50%)	To assess safety, tolerability, and efficacy of KD	RCT	CKD & MAD	• KD is safe and effective • Seizure freedom was present in 60% CKD and 53.3% MAD • No major side-effects were reported but six did not tolerate KD and three parents did not comply

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Freeman & Vining 1999[62]	USA	n = 17, LGS	To evaluate the change in atonic and / or myoclonic seizures during initiation of CKD	Quasi-experimental study	CKD	• Atonic or myoclonic seizures decreased by >50% immediately after CKD use • Ketosis can be achieved or eliminated in a blinded, crossover study
Freeman 2009[63]	USA	n = 20, LGS	To confirm that KD effect was not placebo effect or due to parental expectations	Quasi-experimental study	CKD	• The CKD resulted in reduced seizure activity and improved EEG despite the addition of 60g of glucose each day • The KD may not need to be as restrictive as low ketone levels appear to be sufficient to reduce seizures
Mirjavadi et al. 2010[64]	Iran	n = 66, DRE	To determine the role of the KD	Quasi-experimental study	CKD	• The CKD is more effective than many new ASMs and should be considered as an alternative therapy for children with DRE
Ghazavi et al. 2014[65]	Iran	n = 40, DRE n = 20 CKD (50%) n = 20 MAD (50%)	To compare the efficacy of the CKD and MAD	Quasi-experimental study	CKD & MAD	• There was no significant difference between seizure reduction when using CKD and MAD at the end of first, second, and third months

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Poorshiri et al. 2021[66]	Iran	n = 35, DRE n = 24 CKD (69%) n = 11 MAD (31%)	To compare the efficacy, tolerability, and compliance between the CKD and MAD	Quasi-experimental study	CKD & MAD	• At six months, there was no statistically significant difference in seizure reduction between the CKD and MAD • The MAD had fewer side effects and may be more suitable as the first line KD in children older than two years of age
Zhang et al. 2021[67]	China	n = 210, IS n = 122 CKD (58%) n = 88 control (42%)	To determine the efficacy of the CKD	Quasi-experimental study	CKD	• The efficacy of the CKD was superior to adjustment of ASMs in infants with ACTH- or corticosteroid-resistant IS
Feng et al. 2022[68]	China	n = 200, DRE	To determine the efficacy of the CKD	Quasi-experimental study	CKD	• Compared to ASMs alone the CKD reduces the frequency of seizures in children with DRE • If CKD was effective at three months, it is likely to benefit children further along their epileptic treatment journey
Kinsman et al. 1992[69]	USA	n = 58, DRE	To re-evaluate the efficacy and acceptability of the CKD	Retrospective Cohort study	CKD	• Seizure control improved in 67% and 64% of children had one or more ASMs decreased • Improved behaviour and alertness were noted • The CKD is useful in treating DRE

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Hassan et al. 1999[70]	Canada	n = 52, DRE	To report the results of treatment with the KD	Retrospective Cohort study	CKD & MCT KD	• The efficacy of KD was not related to age, sex, seizure duration, type of seizure, or EEG patterns • The CKD and MCT KD can be an effective treatment in children with DRE
Maydell et al. 2001[71]	USA	n = 143, DRE	To review the efficacy of KD for focal versus generalised seizures	Retrospective Cohort study	CKD	• There was a non-significant improvement in children with generalised seizures compared to focal seizures • Having >50% seizure reduction and the likelihood of continuing CKD after three months was less frequent in children older than 12 years compared to the younger age group • The CKD could be considered for younger patients with severe, focal DRE who are not surgical candidates
Nordli et al. 2001[72]	USA	n = 34, DRE infants <two years	To evaluate the effectiveness, tolerability, and adverse effects of the CKD	Retrospective Cohort study	CKD	• The effectiveness of CKD in infants was similar to the literature for older children • The CKD was particularly effective for children with IS and myoclonic seizures • The CKD is effective, tolerated and beneficial for infants with DRE

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Wirrell et al. 2001[73]	Canada	n = 14, DRE	To determine CKD efficacy without fasting	Retrospective Cohort study	CKD	• Children achieved prompt ketosis when CKD is started at full calories and the ratio is increased from 1:1 to 3:1 or 4:1 • Fasting prior to initiation is unnecessary, increases risk of hypoglycaemia, and probably hospital stay • KD centres can consider outpatient initiation of the CKD
DiMario & Holland 2002[74]	USA	n = 48, DRE	To review the KD experience	Retrospective Cohort study	CKD	• Approximately 1/3 or more children may experience >50% reduction in seizure frequency • Up to 22% children may become seizure free • The CKD is an effective and well tolerated treatment • Discontinuation of the CKD was due to non-compliance or perceived lack of efficacy
Kossoff et al. 2002[75]	USA	n = 23, IS	To determine whether CKD is safe, tolerated and efficacious	Retrospective Cohort study	CKD	• Three children were seizure free by three months, twelve were believed to be making developmental progress • There was a clear relationship between age at KD initiation and seizure reduction • The CKD could be considered as an early treatment in children with IS

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Mady et al. 2003[76]	USA	n = 45, DRE in adolescents	To determine the KD efficacy and compliance	Retrospective Cohort study	CKD	• The KD is as well tolerated and efficacious for adolescents with DRE as it is for the general childhood epilepsy population
Kim et al. 2004[77]	South Korea	n = 124, DRE n = 83 Initial fasting KD (67%) n = 41 Non-fasting KD (33%)	To compare non-fasting and initial fasting KD in terms of efficacy and tolerability	Retrospective Cohort study	CKD	• Initial fasting and fluid restriction are not essential when starting the CKD • Seizure freedom and seizure reduction did not differ significantly between groups at three months
Vaisleib et al. 2004[78]	USA	n = 54, DRE n = 37 outpatients (68.5%) n = 17 inpatients (31.5%)	To review the outpatient and inpatient CKD initiation	Retrospective Cohort study	CKD	• Outpatient initiation of KD can be successful without diet, fluid or caloric restriction • There were no significant differences in seizure control • A prospective, randomised trial is necessary to compare outpatient vs inpatient initiation
Caraballo et al. 2005[79]	Argentina	n = 20, DS	To evaluate CKD efficacy and tolerability	Retrospective Cohort study	CKD	• One year after initiating the CKD, 77% children had achieved a >75% reduction in seizures • Lack of effectiveness (n = 5) and severe vomiting (n = 2) was the reason for discontinuing • Children with DS should be offered the KD immediately after the failure of

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						three adequate trials of ASMs
Kang et al. 2005[80]	South Korea	n = 199, DRE	To evaluate the efficacy and safety of CKD	Retrospective Cohort study	CKD	• At three months, 123/199 (62%) of children had a reduction of seizure frequency of >50%, and 43/123 (35%) of were seizure free • The CKD was tried in 13 children with mitochondrial cytopathies. Two patients with confirmed pathologic findings had maintained CKD with a seizure reduction of >90% • The CKD is a safe and effective therapy for DRE in Korea despite the customary high carbohydrate rice diet
Lyczkowski et al. 2005[81]	USA	n = 71, DRE	To evaluate the safety and tolerability of CKD and VPA co-therapy	Retrospective Cohort study	CKD	• There were no significant differences in seizure reduction between the patients receiving VPA co-therapy and those not taking VPA • The CKD and VPA combination therapy is relatively safe and effective in DRE
Mackay et al. 2005[82]	Australia	n = 26, DRE	To report the efficacy and tolerability of the CKD	Retrospective Cohort study	CKD	• The CKD is an effective treatment for some children with DRE and is generally tolerated well • The CKD was discontinued in 64% of because of poor efficacy and in 12% due to side effects • Response is not necessarily predicted

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						by age, syndrome or aetiology
Rubenstein et al. 2005[83]	USA	n = 13, new-onset epilepsy	The hypothesis is that the CKD would have efficacy in patients with new-onset epilepsy	Retrospective Cohort study	CKD	• The KD can be effective in new-onset epilepsy, seizure reduction and side effects were similar to patients with DRE • The KD was harder to initiate and maintain than ASMs and requires a team approach for success • In motivated families early use of the CKD could be considered before seizures becomes drug resistant
Pfeifer & Thiele 2005[84]	USA	n = 11, DRE	To determine the efficacy of the LGIT	Retrospective Cohort study	LGIT	• In 8/11 (72.7%) children following the LGIT they demonstrated >50% reduction in seizure frequency, and four became seizure free • The majority that tried the CKD before the LGIT group, they maintained the seizure control previously achieved • The LGIT should be considered as an alternative to the CKD, when a KD centre is not available, KD is not tolerated, or if there is an extended wait time for CKD initiation
Eun et al. 2006[85]	South Korea	n = 43, IS	To evaluate the tolerability, efficacy and safety of KD	Retrospective Cohort study	CKD & MAD	• There were 23/43 (53.5%) infants that were seizure free and 27/43 (62.8%) had >90% reduction in seizures • KDs were efficacious in intractable IS • There was evidence that non-fasting

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						introductions are beneficial, that a short-term trial of eight months may be sufficient, a protein-rich 3:1 KD and liquid KD milk is useful
Groesbeck, Bluml, Kossoff 2006[86]	USA	n = 28, DRE	To describe the long-term effects of the KD in children who have been on the diet for over six years	Retrospective Cohort study	CKD & MKD	• In 24 children, they experienced >90% reduction in seizures and three achieved complete seizure freedom • Fifteen parents found the diet 'very easy', six found it 'easy', and two found the diet 'difficult' to maintain over the long term • Parents approved of the diet, with 22 responding that they were 'satisfied' or 'highly satisfied', and one family was 'neutral'
Freitas et al. 2007[87]	Brazil	n = 70, DRE	To analyse the efficacy, tolerability, and adverse effects of the KD	Retrospective Cohort study	CKD	• The efficacy of the CKD for generalised epilepsy was significantly higher compared to partial epilepsy • All patients experienced cognitive improvement in QoL and skills, independent of seizure control • The CKD has proven to be an effective treatment for DRE and ASMs may be reduced or withdrawn

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kossoff et al. 2007[88]	USA	n = 118, DRE	To determine the time from CKD start to seizure reduction and the time after which it was unlikely to be helpful	Retrospective Cohort study	CKD	• Starting the CKD after a fasting period may lead to a more rapid (median, five vs 14 days), but equivalent long-term seizure reduction and KD duration • When seizures are not improved after two months, the CKD can probably be discontinued
Kang et al. 2007[89]	South Korea	n = 14, DRE with mitochondrial respiratory chain defects	To evaluate the clinical efficacy and safety of the KD	Retrospective Cohort study	CKD	• There were 7/14 (50%) children that became seizure free on CKD • The CKD can control seizures in DRE associated with respiratory chain complex defects • Further studies are required to determine the safety, efficacy and the long-term prognosis
Martinez, Pyzik, Kossoff 2007[90]	USA	n = 66, DRE	To determine the incidence of recurrence after discontinuing the CKD after seizure freedom	Retrospective Cohort study	CKD	• In 13/66 (20%) children, there was seizure recurrence, at a median of 2.4 years (range, 0–5.5 year) after the CKD was discontinued • These children restarted the CKD at 4:1 ratio, but patient three did not regain seizure control • The risk of seizure recurrence after becoming seizure free on CKD appears slightly lower than after stopping ASMs, and similar post-surgery

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• Abnormal MRIs or epileptiform EEGs may indicate the possible recurrences of seizure activity
Jung, Kang, Kim 2008[91]	South Korea	n = 47, DRE with focal malformation of cortical development	To evaluate the efficacy and long-term outcome of the CKD	Retrospective Cohort study	CKD	• Long-term seizure freedom can be expected, especially if children are seizure free at three months • The CKD should be considered early in the treatment course and integrated with surgery as part of a therapeutic strategy
Karimzadeh et al. 2009[92]	Iran	n = 87, DRE	To evaluate the efficacy and tolerability of the CKD	Retrospective Cohort study	CKD	• The CKD resulted in at least 50% seizure reduction in 87% of children, in 39% they were seizure free by three months • The CKD was effective, accepted, there were low levels of side effects and improved behaviour was noted
Muzykewicz et al. 2009[93]	USA	n = 76, DRE	To report the efficacy, safety and tolerability of the LGIT	Retrospective Cohort study	LGIT	• Efficacy was correlated with lower serum glucose at times but not with b-hydroxybutyrate changes or ketosis at any time point • The LGIT was associated with decreased seizures in a large proportion of children

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Porta et al. 2009[94]	France	n = 27, DRE n = 17 CKD (63%) n = 10 MAD (37%)	To compare the efficacy of the KD	Retrospective Cohort study	CKD & MAD	• The CKD and MAD demonstrate similar efficacy in children with DRE over a six-month period • The MAD was well-tolerated and is now the primary KD option for children at this centre
Villeneuve et al. 2009[95]	France	n = 22, DRE, Symptomatic or cryptogenic focal epilepsy	To identify whether recently worsened seizures are a useful indication for the KD	Retrospective Cohort study	CKD	• CKD responders were higher in the group with a recent worsening of seizures than in those with stable seizure frequency • Seven patients were still seizure free after six months on the CKD • The CKD may be an option for children with focal epilepsy, particularly with a recent deterioration of seizures
Morrison et al. 2009[96]	USA	n = 115, DRE	To investigate if any ASMs modify the likelihood of seizure reduction when used in combination with the CKD	Retrospective Cohort study	CKD	• Children receiving phenobarbital in combination with the CKD were less likely to have a >50% seizure reduction than children combined who were receiving the other ASMs • There were no significant differences between ASMs with respect to >90% seizure reduction or seizure freedom • CKD combination with Zonisamide appears to be possibly more effective than any other ASMs

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Beniczky et al. 2010[97]	Denmark	n = 50, DRE	To identify clinical or EEG variables predicting the response to KD	Retrospective Cohort study	CKD	• More than 1/3 of children had >90% seizure reduction. There were 2/3 of patients who responded to the KD • The KD is efficacious in a wide spectrum of epileptic disorders
Cole et al. 2010[98]	USA	n = 5, DRE in infants	To describe the initiation and maintenance of breastfeeding alongside the CKD	Retrospective Cohort study	CKD	• In 2/5 (40%) infants following the CKD, mums were able to continue breast feeding, whereas 3/5 (60%) discontinued breastfeeding because of maternal discomfort, due to an underlying metabolic disorder, and the third wished to stop expressing • The initiation of the CKD in breastfed infants can result in a marked reduction in seizure frequency • Breastfeeding and CKD can be combined successfully
Dressler et al. 2010[99]	Austria	n = 50, DRE	To evaluate the long-term efficacy of the CKD	Retrospective Cohort study	CKD	• There was no significant difference between responders and non-responders with respect to specific epilepsy syndromes • The following epilepsy syndromes responded to the CKD: 44% IS, 50% LGS and 62.5% with DS • The CKD proved to be effective and safe, especially, when used early in the treatment course and did not exacerbate any specific seizure type

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						The best CKD efficacy was seen with generalised tonic clonic seizures
Kossoff et al. 2010[100]	Denmark, Germany, USA, South Korea	n = 27, DRE	To investigate seizure control when moving from the MAD to the CKD	Retrospective Cohort study	CKD & MAD	• Only children with seizure reduction on the MAD subsequently improved with the CKD • The CKD is likely to improve seizure control in approximately 1/3 children previously treated with the MAD
Nabbout et al. 2010[101]	Argentina, France	n = 9, SE - FIRES	To report the effect of the CKD in FIRES	Retrospective Cohort study	CKD	• The CKD failed to control seizures in 2/9 (22.2%) children whilst seizures stopped in 7/9 (77.8%), within 2–4 days • Consciousness recovered within 24–48 hours after seizures stopped • Children recovered motor functions in weeks • The CKD is efficacious in SE after failure of first line ASMs • CKD treatment may be delayed in the ICU due to the risk of hypoglycaemia, carbohydrate content of fluids or medications, and feed tolerance

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Caraballo et al. 2011[102]	Argentina	n = 216, DRE	To examine the efficacy and tolerability of the CKD for different epilepsy syndromes	Retrospective Cohort study	CKD	• The CKD was efficacious in myoclonic-astatic seizures, LGS, West syndrome, DS, symptomatic focal epilepsy secondary to malformations of cortical development, and TSC • Both patients with GLUT1DS became seizure free • Fifty children (23%) remained on the CKD for over three years, 70 (32%) for 2–3 years, and 20 (9%) for 1–2 years
Chapman et al. 2011[103]	USA	n = 6, Hypothalamic hamartoma and DRE (83% children)	To report a case series	Retrospective Cohort study	CKD	• The CKD resulted in 4/6 (66.7%) achieving at least a 50% improvement in seizure frequency • Two children had a reduction in multiple seizure types including complex partial, simple partial and atonic seizures • Two individuals failed to respond
Coppola et al. 2011[104]	Italy	n = 15, DRE	To report on the first Italian experience with the LGIT in children and young adults	Retrospective Cohort study	LGIT	• The LGIT can be beneficial in children with DRE including EE with polymorphic seizures and LGS • Compliance is better with the LGIT than with the CKD, although about 25% also do not tolerate the LGIT • This experience confirms that some children living with DRE may improve on the LGIT, even if it is the first dietary option

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Nam et al. 2011[105]	South Korea	n = 5, SE (80% children)	To explore the role of CKD	Retrospective Cohort study	CKD	• In children that were not seizure free the generalised seizures stopped, and partial seizures were greatly reduced in intensity • Breakthrough seizures in patients 3 and 4 were noted when ASMs were weaned • The CKD greatly reduced the frequency and intensity of seizures in refractory SE by 75–100%. They were able to decrease ASMs and wean off mechanical ventilation
Numis et al. 2011[106]	USA	n = 26, IS	To review the efficacy of CKD	Retrospective Cohort study	CKD	• In, 11/26 (42%) children they had >90% reductions in spasm frequency at 5-7 months and 12/26 (46%) had >90% reductions at 10-13 months after CKD initiation • The CKD is an efficacious treatment for IS, demonstrating long term efficacy irrespective of prior ASM usage
Worden et al. 2011[107]	USA	n = 183, DRE	To examine how quickly the KD is discontinued and to determine which variables	Retrospective Cohort study	CKD	• Children with a longer CKD duration and lower seizure frequency were weaned slower but there was no significant difference in the incidence of seizures recurring • Children who had seizure improvement of 50—99% and were receiving more ASMs had the highest

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
			influence the weaning speed			risk of seizures returning • Discontinuing the CKD over weeks rather than months appears safe
Chen and Kossoff 2012[108]	USA	n = 87, DRE	To examine long-term benefits and side effects of the MAD	Retrospective Cohort study	MAD	• Children with myoclonic-astatic epilepsy were more likely to achieve >50% improvement than other conditions • The safety and efficacy of the MAD beyond six months was similar to previously reported short-term results, and side effects appeared minimal
Jung et al. 2012[109]	South Korea	n = 10, DRE	To evaluate the safety and role of KD PN	Retrospective Cohort study	CKD	• The mean duration of the KD PN was 4.1 (±1.5) days • In 7/10 (70%) children had >50% reduction in seizures, 2/7 (28.6%) became seizure free • All children-maintained ketosis and the efficacy of their enteral CKD during the KD PN • KD PN is a relatively safe short-term method of continuing KD to maintain seizure control when enteral feeds were not tolerated

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kim et al. 2012[110]	South Korea	n = 20, DRE	To review the experience with the MAD	Retrospective Cohort study	MAD	• In seven children who tried the MAD after the too restrictive CKD or they had serious side effects, it improved their previous achieved seizure outcomes • The MAD was well-tolerated and could successfully replace the CKD in responsive children who could not tolerate the CKD
Larson et al. 2012[111]	USA	n = 15, TSC	To evaluate the LGIT for patients with TSC	Retrospective Cohort study	LGIT	• Overall, 4/15 (27%) children had >50% reduction in seizure frequency at three months, 7/15 (47%) at six months, 6/15 (40%) at nine months, 6/15 (40%) patients at 12 months, and 4/15 (27%) at 24 months • The results of this study support the use of LGIT in TSC
Lemmon et al. 2012[112]	USA	n = 71, LGS	To determine the efficacy of the KD	Retrospective Cohort study	CKD	• The CKD is efficacious in the treatment of LGS, with approximately 1/2 of children responding at 12 months • The use of the CKD is justified in LGS
Martins et al. 2012[113]	Brazil	n = 29, DRE	To verify the nutritional impact of KD	Retrospective Cohort study	CKD	• Children following the CKD for at least 24 months gained weight, approximately 1/3 achieved significant reduction in seizure frequency, and some patients became seizure free • There was an improvement in nutritional status at 24 months and

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						there was recovery of weight-for-height
Ramm-Pettersen et al. 2013[114]	Norway	n = 10, GLUT1DS (80% children)	To evaluate the effect of the CKD and MAD	Retrospective Cohort study	CKD & MAD	• All but one child with the classic GLUT1DS phenotype became seizure free • Two patients with the mild phenotype were both treated with MAD • Two patients received an early diagnosis, followed by treatment and subsequently developed normally • The study supports early initiation of the KD which may positively affect the overall outcome in GLUT1DS
Ferraria, Mendes, Oliveira 2013[115]	Portugal	n = 16, DRE	To evaluate the efficacy and tolerability of the KD	Retrospective Cohort study	CKD	• Seizures reduced by more than 50% in 10/16 (62.5%) • No children became seizure free • KD was safe and effective in children with severe DRE
Bansal et al. 2014[116]	USA	n = 60, DRE	To determine if the initiation of KD at goal calories reduces complications while maintaining efficacy	Retrospective Cohort study	CKD	• Tolerability of the CKD was similar between the goal calorie and gradual calorie groups • Initiation of the CKD at full calorie requirements is an alternative to gradual advancement of calories and/or KD ratio

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Caraballo et al. 2014[117]	Argentina	n = 10, focal SE	To assess the efficacy and tolerability of the KD as an add on to the use of more than one ASM	Retrospective Cohort study	CKD	• Patients with a good response recovered consciousness within 48 hours following seizure cessation, or reduction, and motor function improved in the following weeks • The KD is a promising therapy for focal SE as the results showed over half of the children had a reduced seizure activity • The KD should be considered earlier in the treatment course
Dressler et al. 2015[118]	Austria	n = 10, DS	To evaluate KD effectiveness and tolerability in comparison with various ASMs	Retrospective Cohort study	CKD	• The KD was not significantly inferior to the current gold standard ASM triple combination of Stiripentol + Valproate + Clobazam (89%), Bromides (78%), Valproate alone (48%), Topiramate (35%) and VNS (37%) and was significantly more effective than Levetiracetam (30%) • The CKD should be considered as an early treatment option in infants with DS
Dressler et al. 2015[119]	Austria	n = 115, DRE in infants (<1.5 years)	To evaluate the efficacy and safety of the KD	Retrospective Cohort study	CKD	• There were significantly more infants younger than nine months (n = 42) seizure free at six and at 12 months • The CKD is highly effective, well tolerated and seizure freedom more often obtained, and maintained in infants

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• CKD should be considered early in the treatment
Hallbook et al. 2015[120]	Denmark, Norway, Sweden	n= 290, DRE	To highlight the effectiveness of the KD over two years follow-up	Retrospective Cohort study	CKD	• The association between the number of seizures at the start of treatment and seizure reduction was statistically significant at three, six and 12months • KD response might be predicted by seizure frequency prior to CKD initiation but not by age, seizure-type or aetiology • The survey showed that CKD is effective, well tolerated, and long-term efficacy was comparable or even better than reported in newer ASMs
Hirano et al. 2015[121]	Japan	n = 6, West syndrome resistant to ACTH	To report the efficacy of the KD	Retrospective Cohort study	CKD	• The CKD was effective for West syndrome resistant to ACTH therapy • Gastrointestinal side effects should be taken into consideration when starting CKD in infants
Reyes et al. 2015[122]	Argentina	n = 12, EE with SE	To assess the efficacy and tolerability of the CKD	Retrospective Cohort study	CKD	• After 18 months 1/12 (8.3%) become seizure free, 1/12 (8.3%) had a 75-99% decrease in seizures, 2/12 (16.7%) had a 50-74% decrease in seizures, and 3/12 (25%) had a <50% decrease in seizures • The CKD is a promising therapy for EE and should be considered early in the treatment options in refractory cases

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Selter et al. 2015[123]	USA	n = 200, DRE	To investigate whether adjustments to CKD and ASMs improve seizure efficacy	Retrospective Cohort study	CKD	• CKD fine tuning led to improvements for 1/5 patients, but no KD or ASM change was ideal for improving seizure control • Calorie changes were generally unhelpful • There was a trend that ASM adjustments were more successful than KD modifications, with 24% of ASM changes leading to >50% additional seizure reduction compared to 15% of KD changes
Sharma et al. 2015[124]	India	n = 25, LGS	To assess the efficacy and tolerability of the MAD	Retrospective Cohort study	MAD	• At six months, 3/11 (27%) were seizure free and 8/11 (73%) had >50% reduction in seizure frequency • The MAD was found to be effective and well tolerated in children with LGS
Simard-Tremblay et al. 2015[125]	USA	n = 9, Myoclonic Astatic Epilepsy - Doose Syndrome	To determine the efficacy of the KD	Retrospective Cohort study	CKD & MAD	• Seizure freedom was noted in, 7/9 (77.8%) within several weeks of KD • Once controlled, those fully responsive to KD could be weaned off ASMs and in many, subsequently weaned from the MAD or CKD

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
van der Louw et al. 2015[126]	Netherlands	n = 71, DRE	To investigate the relationship between efficacy of KD and ASMs	Retrospective Cohort study	CKD & MCT KD	• The KD was successful after three months in 61% of the children but efficacy was significantly reduced if children used Lamotrigine (31%), compared to other ASMs (69%) • There was no negative efficacy of KD on Valproic acid, Levetiracetam, Clobazam or Vigabatrin
Vehmeijer et al. 2015[127]	Netherlands	n = 59, DRE	To evaluate the efficacy of the KD	Retrospective Cohort study	CKD & MCT KD	• Success of the KD at three-months was significantly related to a successful response to KD treatment at 12 months • The KD can be an effective treatment in reducing seizures in children with DRE
Ville et al. 2015[128]	France	n = 42, EE	To evaluate the use of steroids and the KD	Retrospective Cohort study	CKD	• The addition of the CKD allowed the withdrawal of steroids in all responders • The combination of steroids and CKD appears to be feasible, safe, and it is possible to obtain ketosis
Wibisono et al. 2015[129]	Australia	n = 48, DRE	To evaluate the KD efficacy, tolerability, and compliance	Retrospective Cohort study	CKD, MAD & MCT KD	• KD duration or KD type did not predict the response • The MCT KD was discontinued more often, but three children stopped due to experiencing seizure freedom • The CKD, MAD and MCT KD were comparably effective and generally well-tolerated. Side effects were lower for the MAD

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Amalou et al. 2016[130]	France	n = 10, GLUT1DS	To assess the efficacy of the MAD	Retrospective Cohort study	CKD & MAD	• Seizures improved in all patients with seizures. and movement disorder was controlled in all patients experiencing this symptom • The MAD is less restrictive, more palatable and has comparable effectiveness to the CKD • The MAD is a beneficial treatment for patients with GLUT1DS
Appavu et al. 2016[131]	USA	n = 10, SRSE	To investigate the use of the KD	Retrospective Cohort study	CKD	• In 9/10 (90%) children had resolution of SRSE with CKD and 8/9 (89%) were weaned off anaesthesia within 15 days of CKD initiation • The CKD was tolerated with minimal side effects and could be effective for SRSE
Hussain et al. 2016[132]	USA	n = 22, Epileptic spasms	To describe the KD experience	Retrospective Cohort study	CKD	• In 2/22 (9%) children they experienced spasm freedom, but seizure response was more reasonably attributed to alternative therapies, suggesting limited efficacy
Khoo et al. 2016[133]	Malaysia	n = 30, DRE	To evaluate the long-term efficacy, retention rate and tolerability of the KD	Retrospective Cohort study	CKD & MAD	• The responder rates were 70%, 63%, 57%, 47% and 37%; and retention rates were 80%, 70%, 60%, 50% and 40% at 3, 6, 9, 12 and 24 months respectively • The KD is effective and tolerated well in Malaysian children

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Zhang et al. 2016[134]	China	n = 47, LGS	To evaluate the efficacy of the KD	Retrospective Cohort study	CKD	• At three months, 23/47 (48.9%) had ≥50% seizure reduction • The CKD is effective in reducing seizures and improving EEG abnormalities in LGS
Ashrafi et al. 2017[135]	Iran	n = 22, DRE in infants and young children	To evaluate the efficacy, safety, and tolerability of a 4:1 CKD using a formula-based powder	Retrospective Cohort study	CKD	• At the end of four months, 6/22 (27.3%) showed >90% reduction and 4/22 (18%) were seizure free • A CKD based on powdered feed is effective, safe, and tolerable in infants and young children living with DRE who are reluctant to eat homemade foods
Caraballo et al. 2017[136]	Argentina & Italy	n = 6, Myoclonic status in non-progressive enceph-alopathy	To assess the efficacy and tolerability of the KD	Retrospective Cohort study	CKD	• The CKD is a promising therapy with most children having more than 50% seizure reduction, improved cognitive performance and QoL • Tolerability was very good in all children and no adverse events were noted
Farias-Moeller et al. 2017[137]	USA	n = 9, SRSE	To describe the use of KD in the paediatric ICU	Retrospective Cohort study	CKD	• After one-week, seizure control was variable and ASMs did not change significantly; but most children weaned off continuous anaesthetic infusions • The CKD was well tolerated, and complications identified early through a monitoring protocol

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• It is feasible to initiate the CKD in the ICU
Grocott et al. 2017[138]	USA	n = 23, AS	To evaluate the effectiveness and tolerability of the LGIT	Retrospective Cohort study	LGIT	• Cognitive and social improvements were noted: improved speech, communication, focus, eye contact, alertness, attention, confidence, and general cognitive development • Parents noted physical improvements including improved mobility and decreased tremor • The LGIT is effective, is less restrictive and has mild side effects, could be used as a treatment for DRE in AS
Kim et al. 2017[139]	South Korea	n = 36, DRE	To determine the efficacy and tolerability of LGIT	Retrospective Cohort study	LGIT	• Children who previously responded well to the KD were more likely to be good responders to the LGIT compared to poor responders (69%, 9/13 vs. 25%, 2/8) • The LGIT reduced seizure frequency but seizure freedom was less likely to be achieved
Zhan et al. 2017[140]	USA, UK, Australia, Germany, Canada, France, and others	n = 104, Pathogenic or likely pathogenic CDKL5 variant and DRE	To review the role of the CKD	Retrospective Cohort study	CKD	• Reductions in seizure activity after commencing CKD were noted in 69/104 (66.4%) • There was a better response to CKD in CDKL5 than has been reported for ASMs • It is suggested that CKD is considered

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						early in the treatment course
Lin et al. 2017[141]	USA	n= 158, DRE	To characterise the inpatient KD initiation	Retrospective Cohort study	CKD	• At three months, 110/158 (70%) reported a reduction in seizure frequency of >50% • In 73/158 (46%) children, they experienced adverse effects which included hypoglycaemia, constipation, mood change, lethargy or fussiness. Lethargy and hypoglycaemia were correlated with fasting • Younger children and fasting were correlated with more difficulties, indicating that fasting should be avoided
Stenger et al. 2017[142]	France	n = 50, Myoclonic Astatic Epilepsy - Doose Syndrome	To identify the efficacy of the KD	Retrospective Cohort study	CKD & MAD	• Seizure freedom was noted in 27/50 (54%) of patients after six months • Earlier KD use after three failed ASMs, was correlated with a better cognitive outcome
Thompson et al. 2017[143]	USA	n = 4, DRE in neonates	To present results on CKD initiation and use in the ICU	Retrospective Cohort study	CKD	• The CKD was well tolerated, and the benefits included improved seizure control, increased alertness and decreased need for invasive respiratory support • Common side effects observed were constipation, hypoglycaemia, and weight loss

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• Education of caregivers and medical staff is paramount during KD treatment in the ICU
Wiemer-Kruel et al. 2017[144]	Germany and Switzerland	n = 30, Myoclonic Astatic Epilepsy - Doose Syndrome	To report the experience of four centres using MAD	Retrospective Cohort study	MAD	• In 25/30 (83%) children experienced ≥50% seizure reduction and 14/30 (47%) were seizure free • In 3/10 children experiencing >2 years seizure freedom the MAD was discontinued without relapse • The MAD is effective in Doose syndrome • The MAD should be considered early as an alternative to ASMs or the CKD
Ismayilova et al. 2018[145]	UK	n = 29, DRE in infants <2 years	To describe the 10-year KD experience	Retrospective Cohort study	CKD & MCT KD	• Results showed a decrease in seizure frequency or intensity in 52% of children • Benefits in alertness in 18/29 (62%), of whom 9/18 (50%) also made developmental gains in motor skills • KD can be utilised and is generally well tolerated in infants with severe epilepsies
Ko et al. 2018[146]	South Korea	n = 155, Developmental and EE n = 73 with genetic	To investigate the effects of KD	Retrospective Cohort study	CKD & MAD	• Of those with identified genetic mutations, 38/73 (52.1%) responded to KD at three months, 36/73 (49.3%) responded at six months, and 32/73 (43.8%) responded at 12 months • The KD was particularly effective in

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
		mutation (43%) n = 82 without genetic mutation (57%)				patients with SCN2A, STXBP1, KCNQ2, and SCN1A mutations and was not effective in patients with CDKL5 mutations
Kumada et al. 2018[147]	Japan	n = 42, DRE	To evaluate the efficacy and tolerability of the CKD using a Japanese KD milk	Retrospective Cohort study	CKD	• The Japanese KD milk (M817-B) used in the CKD was efficacious but lacks some trace elements and vitamins • Three children experienced alopecia which improved with biotin supplementation
Pasca et al. 2018[148]	Italy & Argentina	n = 45, DRE secondary to malformations of cortical development	To evaluate the efficacy and tolerability of the CKD	Retrospective Cohort study	CKD	• In 20/45 (44%) children they had a seizure reduction of >50%, two became seizure free • The best seizure response was observed in children with malformations of post migrational development • The CKD might be effective in seizure reduction and increasing QoL, but seizure freedom is rarely achieved • If surgery is not an option, the CKD should be considered

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Villaluz et al. 2018[149]	Australia & England	n = 9, DRE associated with acquired structural EE	To analyse the CKD responder rate	Retrospective Cohort study	CKD	• At three months, 7/9 (77.8%) children were responders, and all patients showed some improvement • Parents observed increased alertness, vocalization, improved behaviour, and small developmental gains • CKD should be considered early in the management of patients with acquired structural encephalopathies
Wirrell et al. 2018[150]	USA	n = 27, DRE in infants <12months	To evaluate the tolerability and efficacy of the CKD	Retrospective Cohort study	CKD	• The CKD responder rates at one, six and 12 months were 17/25 (68%), 14/17 (82%) and 10/11 (91%), with 5/25 (20%), 5/17 (29%) and 3/11 (27%) becoming seizure free • Inpatient initiation in infants is strongly recommended due to the risk of hypoglycaemia • The CKD is effective and tolerated in infants living with DRE
Bekker et al. 2019[151]	Netherlands	n = 7, GLUT1DS	To identify the clinical characteristics of children failing the KD	Retrospective Cohort study	CKD, MAD & MCT KD	• In 5/7 (71.4%) children tolerating KD, their compliance was good, and parents reported slight improvements in concentration, alertness and cognitive functioning • In 1/5 (20%) children a paroxysmal movement disorder improved with KD • Patients with GLUT1DS may not benefit from KD treatment due to dietary intolerance, poor ketosis, being

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						older at diagnosis or inefficacy of KD
Worden et al. 2020[152]	USA	n = 29 n = 12 SE (41%) n = 8, EE (28%) n = 9, SE and EE (31%)	To assess KD safety and feasibility in the ICU	Retrospective Cohort study	CKD	• In children with SE, ≥ 50 % reduction in seizure activity is achieved in most responders by 1–2 weeks • CKD initiation is feasible, safe, and effective for SE and EE in the ICU • There were common adverse effects which were treatable • High rates of mortality and morbidity were noted
Dressler et al. 2019[153]	Austria	n = 79, DRE in infants n = 16 Breast milk (20%) n = 63 Formula only (80%)	To describe ketosis with or without breastmilk in the KD	Retrospective Cohort study	CKD	• When breast milk was included in the CKD there was no difference between seizure freedom and adverse effects, in addition ketosis and seizure control is feasible • Recommendations are to continue breast milk when starting the CKD • Bottle-feeding ketogenic formula and feeding the remaining amount of tolerable carbohydrate at the breast is advised, similar to practices for inborn errors of metabolism such as Phenylketonuria

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Gerges et al. 2019[154]	Egypt	n = 28, DRE	To assess the feasibility of the CKD in a limited resource setting	Retrospective Cohort study	CKD	• The cost of KD, lack of health insurance and nutritional labelling are barriers to following the KD in Egypt • The CKD could be implemented in medium resources countries and should be included in the management of DRE
Zhang et al. 2019[155]	China	n = 42, DRE	To investigate the combined effects of structured exercise and a LGIT on QoL	Retrospective Cohort study	LGIT	• There was a significant improvement in seizure frequency and QoL in children following the LGIT and structured exercise programme showed promising improvement in seizures, depression and QoL
Jagadish et al. 2019[156]	USA	n = 59, DRE of genetic aetiology	To analyse the efficacy and tolerability of the CKD and MAD	Retrospective Cohort study	CKD & MAD	• There was no significant difference in KD response rates between chromosomal and non-chromosomal aetiologies • The KD is effective in DRE of genetic aetiology, it has good tolerability with relatively few sides effects • KDs should be considered early to minimise high cost ASMs, drug interactions, and side effects • KDs should be started in the hospital for children <two years as they need frequent glucose monitoring

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kim et al. 2019[157]	USA	n = 109, DRE in infants <3 years	To review 10 years of experience with the CKD	Retrospective Cohort study	CKD	• CKD use in a child living with a confirmed genetic mutation or a chromosomal abnormality showed a better response • Infants using a liquid-based KD formula with or without solids were more likely to continue following the CKD • The CKD was discontinued due to parental unhappiness with the rigid nature of CKD (7/12, 58.3%), perceived ineffectiveness (3/12, 25%) or an adverse event (2/12, 16.7%) • The CKD is effective, safe, and well-tolerated and may be enhanced by using a liquid-based KD formula in infants living with DRE
Liu et al. 2019[158]	China	n = 26, DS	To evaluate the efficacy of the CKD	Retrospective Cohort study	CKD	• After 3, 6, 12, 18, 24, and 30 months, 38.4%, 34.6%, 38.4%, 23.0%, 15.4%, and 15.4% children had >50% seizure reduction • Cognitive and other neuropsychological developmental aspects improved after CKD but there was no significant difference when compared to a non-KD group with DS

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Park & Lee 2019[159]	South Korea	n = 16, SRSE	To describe the experience of the CKD in ICU	Retrospective Cohort study	CKD	• In 9/16 (56.3%) children they achieved seizure freedom, 6/16 (37.5%) reported >50% seizure reduction, and 1/16 (6.2%) had <50% seizure improvement • The most common complication was gastrointestinal disturbance • The CKD is an effective and safe treatment option for SRSE in the ICU for reducing seizures and weaning from prolonged mechanical ventilation
Peng et al. 2019[160]	China	n = 7, FIRES with SRSE	To investigate the efficacy and safety of early CKD on the prognosis of FIRES	Retrospective Cohort study	CKD	• In 5/7 (71.4%) children the CKD was provided via the enteral route, and 2/7 (28.6%) via PN • In 7/7 (100%) children they achieved resolution of SRSE within a median of 5 days, the number of seizures reduced, seizure duration shortened, the background EEG recovered, and sleep architecture normalised • The CKD may be a safe and promising treatment for FIRES with SRSE, and that early initiation produces a favourable prognosis • KD PN can be an effective route for patients who may not tolerate enteral KD

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Riantarini et al. 2019[161]	South Korea	n = 115, DRE infants under one year n = 81 CKD (70%) n = 34 MAD (30%)	To evaluate aetiology-specific, short and long-term seizure free outcomes of the KD	Retrospective Cohort study	CKD & MAD	• There were no significant differences with respect to short-term or long-term seizure outcomes and aetiology • Early KD is beneficial in infants <one year with specific symptomatic aetiologies • The KD results in a high rate of seizure freedom, regardless of underlying aetiology
Sheng et al. 2019[162]	China	n = 109, DRE n = 57 Basic management plan (52%) n = 52 Optimised management plan (48%)	To determine efficacy and compliance of CKD	Retrospective Cohort study	CKD	• The basic CKD management plan had no established team, the CKD ratio was inflexible and only simple KD foods were included • In the basic plan >50% seizure reduction was achieved in the 1st, 3rd, 6th and 9th month in 63.2%, 45.6%, 38.6%, 21.1% of children respectively compared to the optimised management plan, 90.4%, 73.1%, 65.4%, 38.5% • Having an optimised CKD management plan can improve compliance and education
Tian et al. 2019[163]	China	n = 60, DS	To evaluate the efficacy and safety of CKD	Retrospective Cohort study	CKD	• At 24 weeks, 25/41 (61.1%) children had a >50% seizure reduction, at 48 weeks, 17/22 (77.3%) >50% reduction • CKD use in DS was tolerated and effective in more than half of children living with DS

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• CKD should be recommended as an early option for DS with DRE
van der Louw et al. 2019[164]	Netherlands	n = 105, DRE	To compare the effectiveness, safety and costs of outpatient versus inpatient initiated KD	Retrospective Cohort study	CKD & MCT KD	• The KD was effective in 61% of outpatients versus 63% of inpatients at three months, and was considered safe in 36% of outpatients compared to 29% of inpatients • Outpatient initiation was shown to be non-inferior to inpatient initiation in terms of safety • Starting KD as an outpatient seems to reduce health care costs mainly due to a reduction in the cost of hospital admissions • A multidisciplinary outpatient KD initiation is a safe option in children, who are medically stable, over one year of age
Abdelmoity et al. 2020[165]	USA	n = 33, DRE	To report the efficacy and tolerability of combining VNS and KD	Retrospective Cohort study	Not described	• This study shows that combining VNS and KD in DRE is well tolerated, reduces seizure frequency more than separate treatments, and seizure reduction increases with the length of time on KD

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Mir et al. 2020[166]	Saudi Arabia	n = 66, DRE	To examine the incidence of potential adverse events during admission for KD initiation	Retrospective Cohort study	CKD	• Adverse events occurred in 19/66 (28.7%) of patients, and included hypoglycaemia, vomiting, reduced activity and sleepiness • The incidence of adverse events during inpatient CKD initiation was low, and were managed with simple interventions if required • It may be possible to initiate the CKD at home with good communication, preparation, and monitoring
Na, Kim, Lee 2020[167]	South Korea	n = 20, LGS with mitochondrial dysfunction	To evaluate the efficacy and safety of KD	Retrospective Cohort study	CKD & MAD	• In 1/20 (5%) had 75% seizure reduction at three months, in 4/20 (20%) had 50% reduction, and 8/20 (40%) experienced 25% reduction • In 9/20 (45%) children they were treated with the KD for one year and all demonstrated improved cognition • KDs are feasible, safe, efficacious and can significantly improve the child's prognosis
Al-Baradie et al. 2021[168]	Saudi Arabia	n = 31, DRE	To study the KD	Retrospective Cohort study	CKD	• In 2/31 (6.54%) children they were seizure free at six months, 6/31 (19.4%) were seizure free at 12 months • Children with a higher baseline seizure frequency reported more favourable response to CKD at 12 months • The CKD is an effective treatment for

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						reducing the frequency of seizures in children with DRE
Breu et al. 2021[169]	Austria	n = 8, SRSE	To evaluate the use of the KD for treatment of SRSE in the ICU	Retrospective Cohort study	CKD	• Response to CKD was noted in 4/8 (50%) children with interruption of SE and burst suppression in the EEG • In 4/8 (50%) children there was clinical and EEG remission of SE within the first week, but they did not fulfil the burst-suppression (>50%) criteria of "responders" • Early CKD should be considered in children with severe underlying genetic syndromes
Lim et al. 2021[170]	South Korea	n = 67, DRE	To analyse early laboratory and clinical characteristics of children who received the KD	Retrospective Cohort study	CKD & MAD	• The beta-hydroxybutyrate at one month was positively correlated with six-month seizure outcomes • The KD was discontinued at six months due to lack of efficacy, adverse effects, compliance, or poor ketone production
Tekin et al. 2021[171]	Turkey	n = 25, DRE	To describe the experience of the CKD	Retrospective Cohort study	CKD	• Families expressed that after CKD initiation their child's perception and social behaviour improved • The CKD is effective but requires teamwork and a multidisciplinary approach • Difficulties include the time required

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						for individualised menus, cost of ketone sticks and materials, and the burden of tests and visits
Ruiz-Herrero et al. 2021[172]	Spain	n = 42, DRE in infants <two years	To describe the KD experience	Retrospective Cohort study	CKD, MAD & MKD	• In 63% of infants with West syndrome, they responded to KD, • The mean length of KD was 390 days (16 days-4.9 years) • There were early side effects noted in 40% of infants including asymptomatic hypoglycaemia and gastrointestinal symptoms • KDs are effective and a safe treatment for DRE in infancy
Sanchez et al. 2021[173]	USA	n = 15, Aicardi syndrome (93% Children)	To report the use of the KD	Retrospective Cohort study	CKD & MAD	• Several caregivers reported improved alertness and verbalisation • The KD was well tolerated, although seizure freedom was rare • The KD was a helpful treatment for DRE
Tong et al. 2022[174]	China	n=157, DRE	To describe the KD practice	Retrospective Cohort study	CKD	• Most patients adhered to CKD for three months (144/157, 92.9%) but this reduced at one year (67/157, 42.7%), and two years (32/157, 20.4%) • Lack of efficacy was the most common reason for discontinuation (39.2%), followed by patient/caregiver preference (15.2%), severe food refusal and opposition from family members

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• The CKD was effective in controlling seizures and reducing long term ASMs • Long-term adherence was difficult, but compliance may increase with improved taste and patient support
Perna et al. 2022[175]	Kingdom of Bahrain	n = 24, DRE	To assess the KD efficacy, side effects and predictors of response	Retrospective Cohort study	CKD	• In 14/24 (58.3%) children, they experienced seizure reduction in response to the CKD • At six months the CKD was discontinued in 14/24 (58.3%) and reasons were: inefficacy (8/14, 57.1%), poor compliance (n = 3, 21.4%), food refusal (n = 1, 7.1%), achieved required efficacy (n = 1, 7.1%) and death (n = 1, 7.1%) • Duration of the CKD was highly correlated with efficacy, followed by age at initiation
Nam et al. 2022[176]	South Korea	n = 12, STXBP1-related EE	To investigate the effects of CKD and MAD	Retrospective Cohort study	CKD & MAD	• In 3/12 (25%) children who were KD responders, they remained seizure free once KD was withdrawn • KDs were highly effective for some children with STXBP1-related EE, especially those with later onset

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kacker et al. 2022[177]	USA	n = 13, Genetic generalised epilepsy (92% children)	To evaluate the efficacy and tolerability of the MAD	Retrospective Cohort study	MAD	• There was 85% seizure frequency reduction in all seizure types studied • One child living with generalised tonic clonic seizures did not experience seizure reduction • The MAD is tolerated and effective in children with genetic generalised DRE and allowed ASMs to be discontinued
Yıldırım et al. 2022[178]	Turkey	n = 18, DRE	To evaluate the effect of the KD	Retrospective Cohort study	CKD & MAD	• In 10/18 (55.5%) children there was ≥50% reduction in seizures, and 1/8 (1.6%) was seizure free • There was no difference in seizure reduction between children who received the CKD or the MAD, or in children following different CKD ratios • The KD is efficacious and can significantly reduce the frequency of seizures in childhood DRE
Dou et al. 2022[179]	China	n = 23, structural DRE	To evaluate the efficacy and tolerability of the KD	Retrospective Cohort study	CKD	• Children, 6/6 (100%), with a history of hypoxic ischemic encephalopathy had the highest rate, of > 50%, seizure reduction • Subjective improvements in cognition were observed in 20/23 (87%) of children during follow-up • The CKD is effective and safe in children with DRE due to a structural aetiology

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• Better seizure control was observed in infants with a history of neonatal brain injury
Chomtho et al. 2022[180]	Thailand	n = 14, SRSE n = 8 Enteral KD (57%) n = 6 KD PN (43%)	To assess the effectiveness of KD, and compare KD PN and enteral KD	Retrospective Cohort study	MCT KD	• All survivors 12/14 (85.7%) were seizure free at discharge • KD PN is as effective as the enteral KD with quicker ketosis at induction and but more metabolic side effects • KDs could be considered earlier in the SRSE treatment to avoid prolonged anaesthetic infusion
Yılmaz et al. 2022[181]	Turkey	n = 91, DRE	To investigate the effectiveness of the CKD	Retrospective Cohort study	CKD	• In 32/91 (35.2%) children they were seizure free at 12 months • The KD appears to be effective in about 2/3 of children and 1/3 children became seizure free
Ali et al. 2022[182]	Saudi Arabia	n= 16, DRE	To review the efficacy of a non-fasting KD protocol	Retrospective Cohort study	CKD	• After starting the KD, 9/16 (56%) reported >50% seizure improvement, and 6/9 (66.7%) experienced >90% improvement in seizure frequency, 3/9 (33.3%) became seizure free • A non-fasting KD protocol was safe, efficacious and associated with few side effects and might be better tolerated compared to a fasting protocol

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Winczewska -Wiktor et al. 2022[183]	Poland	n = 42, DRE n = 20, Known aetiology (48%) n = 22, Unknown aetiology (52%)	To compare the effectiveness of the KD	Retrospective Cohort study	CKD, MAD & LGIT	• KDs are safe and were effective in 29/42 (69%) of all cases • KDs were less effective in focal seizures • Children benefited more if they had simultaneous focal and generalised seizures • KDs should be recommended in all children with DRE
Fang et al. 2022[184]	China	n = 53, DRE in TSC	To analyse the efficacy and safety of KD	Retrospective Cohort study	CKD & MAD	• KD is an effective and safe treatment for TSC-related DRE • The KD can reduce seizure frequency and may potentially improve cognition and behaviour in TSC
Dou et al. 2022[185]	China	n = 55, DRE	To investigate the efficacy and tolerability of the gradual initiation of CKD	Retrospective Cohort study	CKD	• The CKD is effective and tolerable when initiated gradually • At three months 20/55 (36.4%) responded to the CKD • Predictive factors for efficacy in children may be an early age when they start and duration of over six months

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Wang et al. 2022[186]	China	n = 6, GLUT1DS	To assess the efficacy and safety of KD	Retrospective Cohort study	CKD	• Within one month of commencing CKD all patients were seizure free and when ASMs were weaned, seizures did not return • CKD is safe and effective in children living with epilepsy and GLUT1DS caused by SLC2A1 mutations • KD treatment should start as soon as possible in GLUT1DS
Hallb¨o¨ok et al. 2007[187]	Sweden	n = 18, DRE	To quantify changes of epileptiform activity during KD	Retrospective Cohort study	CKD	• There was a correlation between reduction in epileptiform activity and clinical seizures in children following the CKD • There was no correlation between reduction in seizures, epileptiform activity, and QoL improvement or attention
Paibool et al. 2023[188]	USA	n = 6, Jeavons syndrome	To report on tolerability and efficacy of MAD	Retrospective Cohort study	MAD	• All seizure types >80% reduction at six months • Absence and myoclonic seizures had 100% reduction • MAD was tolerated and effective, adverse effects were tolerable or corrected

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Yu et al. 2023[189]	China	n = 14 centres n = 114, DS	To analyse the safety and efficacy of KD over multiple centres	Retrospective Cohort study	CKD	• CKD was the first-choice treatment for three patients • CKD is effective in treating seizures in DS • In 17%, (9/52) experts reported that KD should be used 1st line in DS and 56% (29/52) felt it should be used after two failed ASMs
Zhang et al. 2023[190]	China	n = 288, DRE	To assess effectiveness and seizure recurrence in children who are seizure free on CKD	Retrospective Cohort study	CKD	• The CKD seems to be effective in improving seizure control in children living with DRE • In children achieving seizure freedom, increased seizure recurrence was noted with an abnormal EEG and short KD treatment (<12 months)
Anjum et al. 2023[191]	Pakistan	n = 55, DRE	To assess the tolerability and effectiveness of KD	Retrospective Cohort study	CKD	• Gradual initiation of KD is recommended • Children who fail two ASMs should be referred for KD immediately • Side-effects included anorexia, renal stones, diarrhoea, constipation, ketoacidosis, and hypoglycaemia
Armeno et al. 2024[192]	Argentina	n = 19, Infants with DRE	To evaluate safety, effectiveness, and survival of infants under three months on KD	Retrospective Cohort study	CKD	• There was >50% decrease in seizures in 72% at three months and 21% became seizure free • Survival rates were 76% at one year following KD • Many side-effects were manageable and infants were asymptomatic

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Shen et al. 2023[193]	China	n = 56, DRE	To evaluate the retention rate, efficacy and factors that influence KD	Retrospective Cohort Study	CKD	• CKD can be a successful optional treatment for DRE • There was a high retention rate at three months (100%) • The older the child, the longer the duration of KD More favourable KD outcomes were noted if the MRI of that child was abnormal
Falsaperla et al. 2023[194]	Italy	n = 13, Infants with DRE under two months of age	To evaluate three-month efficacy and side-effects of KD in ICU	Retrospective Cohort Study	CKD	• Three infants did not respond to CKD • CKD is efficacious and safe in infants • Adverse side-effects should be managed early and aggressively
Hopkins & Lynch, 1970[195]	Australia	n = 34, DRE	To report the efficacy of the KD	Prospective Cohort Study	CKD	• In 10/34 (29.4%) children their seizures were much improved and 4/34 (11.7%) were moderately improved • The experience of epilepsy in early infancy resulted in poorer response to CKD
Sills et al. 1986[196]	USA	n = 50, DRE	To determine the efficacy of the MCT KD	Prospective Cohort Study	MCT KD	• In 24/50 (48%) children, they tolerated 60% MCT, 18/50 (36%) tolerated 50-58% MCT, 2/50 (4%) tolerated 45% MCT, and 6/50 (12%) were unable to tolerate MCT KD • In 8/44 (18.2%) children they achieved seizure freedom, 4/44 (9%) experienced excellent control, and

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						10/44 (22.7%) achieved good control • Sixteen children remained on the MCT KD, eight with astatic myoclonic epilepsy, three with absence epilepsy, three with generalised tonic-clonic seizures, and two with complex partial seizures
Woody et al. 1988[197]	USA	n = 6, DRE	To report the substitution of corn oil for MCT oil	Prospective Cohort Study	CKD	• The corn oil KD was safe, effective, well-tolerated, inexpensive, and practical • Reductions of ASMs were possible in 5/6 (83%), with three patients having all ASMs stopped • Tolerance was better in 3/6 (50%) children using with corn oil compared to MCT oil, as they experienced fewer episodes of vomiting, cramps, and diarrhoea
Schwartz et al. 1989[198]	UK	n = 59, DRE (93% children)	To report the effects of the KD	Prospective Cohort Study	CKD & MCT KD	• Older patients had less encouraging results • All KDs were effective but impose dietary restrictions and must be followed accurately • Large volumes of MCT oil were unpalatable

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Edelstein & Chisholm, 1996[199]	USA	n = 20, DRE	To determine whether initiation of the non-MCT KD would continue to reduce seizures	Prospective Cohort Study	CKD	• Seizure reduction occurred in 16/20 (80%) children. In 10/20 (50%) were seizure free for the two-week trial • The CKD was effective in seizure control and is worthwhile to trial in children living with DRE
Wexler et al. 1997[200]	USA	n = 7, PDHD	To evaluate the effects of either the standard CKD or nearly carbohydrate-free diets	Prospective Cohort Study	CKD	• A nearly carbohydrate-free diet may improve neurological outcome and longevity of patients with PDHD and should be started as soon as possible after the diagnosis is confirmed • The metabolic efficacy should be monitored via serum lactate, pyruvate (or alanine), and ketone bodies • It is likely that the benefits of KD would be greatest in those who are least severely affected
Freeman et al. 1998[201]	USA	n = 150, DRE	To determine the efficacy and tolerability of CKD	Prospective Cohort Study	CKD	• At three months, 125/150 (83%) remained on CKD and 34% had >90% decrease in seizures • Most families discontinuing the CKD reported it was in-effective or too restrictive
Vining et al. 1998[202]	USA	n = 51, DRE	To determine the efficacy of the CKD in seven centres	Prospective Cohort Study	CKD	• At three months, 28/45 (54%) had >50% decrease in seizures • Age, sex, principal seizure type, and EEG were not statistically related to the outcome

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• The KD is effective in substantially decreasing difficult to control seizures
Coppola et al. 2001[203]	Italy	n = 56, DRE (96% children)	To evaluate the efficacy and safety of the 4:1 CKD as an add-on treatment	Prospective Cohort Study	CKD	• At three months, 6/42 (11%) were seizure free and 15/42 (27%) had a 50–90% reduction in seizures • There was no significant relationship between CKD efficacy and seizures or epilepsy diagnosis, age or sex • In 64% of patients with neuronal migration disorders improved on CKD • The KD was effective in difficult to treat patients with partial and generalised epilepsies, but efficacy dropped significantly by nine – 12 months
Hemingway et al. 2001[204]	USA	n = 143, DRE (at least 79% children	To examine CKD seizure outcome comparing focal and generalized seizures	Prospective Cohort Study	CKD	• A reduction in seizures (>50%) was less frequent in patients older than 12 years compared to the younger age group • The likelihood of continuing the diet after three, six, or 12 months was lower in patients older than 12 years • There were improved outcomes in patients living with generalised epilepsy compared to focal seizures, but this was not statistically significant

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kankira-watana et al. 2001[205]	Thailand	n= 35, DRE	To assess CKD feasibility and efficacy	Prospective Cohort Study	CKD	• At three months 5/22 (22.7%) children were seizure free and 10/22 (45.5%) had over 90% reduction in seizures • ASMs in each patient were reduced • The KD requires a team effort to commence and manage
Lightstone et al. 2001[206]	USA	n = 46, DRE	To examine the reasons why children discontinue the CKD	Prospective Cohort Study	CKD	• In, 19/46 (41%) patients discontinued CKD due to medical concerns. In 10/19 (52.6%) - lack of efficacy, complications, unrelated acute admissions or non-medical reasons in 9/19 (47.4%) - regimented, anxiety provoking, perception of too little food, perception of caregiver. In 5/9 caregiver had concerns and 4/9 child refused KD or cheated • In neurologically normal children 2/8 discontinued almost immediately as they wanted to be accepted like their peers • A better understanding of psychosocial issues may help identify suitable candidates for the KD which would aid compliance

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Hosain et al. 2005[207]	USA	n = 12, DRE	To evaluate efficacy, tolerability, and safety of the CKD in gastrostomy feeding	Prospective Cohort Study	CKD	• In, 6/12 (50%) children had >90% seizure reduction, 1/12 (8.3%) at least 75% reduction, 3/12 (25%) >50% reduction • Seizure control did not correlate with degree of ketosis • No meaningful QoL improvement was observed but caregivers of five children reported increased alertness • Results suggest that provision of the KD via gastrostomy tube is safe, well tolerated and effective in DRE demonstrated with 100% compliance at one year
Klepper et al. 2005[208]	Germany & The Netherlands	n = 15, GLUT1DS	To provide data on the effects of KD use in GLUT1DS	Prospective Cohort Study	CKD	• In, 12/15 (80%) patients they became seizure free and ASMs stopped, 10/12 (83.3%) remained seizure free on monotherapy for the follow-up period • In 3/15 (20%) did not achieve complete seizure control or KD was discontinued • Caregivers reported improved alertness, demeanour, physical and mental endurance but effects on neurodevelopment, and movement disorder appeared less prominent • The KD is the treatment of choice in GLUT1DS

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Caraballo et al. 2006[209]	Argentina	n = 11, Myoclonic Astatic Epilepsy - Doose Syndrome	To assess the efficacy and tolerability of the CKD	Prospective Cohort Study	CKD	• The CKD is a promising therapy for Doose, with over half of children showing a >50% reduction in seizures, and 18% achieving seizure freedom • Responders did not show further neurological deterioration • The CKD should be considered early in the course of the syndrome, and not as a last resort
Farasat et al. 2006[210]	USA	n = 100, Parents of children with DRE	To obtain the expectations of parents for their children starting the KD	Prospective Cohort Study	Not the focus of the study	• In mothers their first goal of KD treatment was: seizure reduction 66/92 (69%), 12/92 (13%) ASM reduction, and the remaining 18% cognition, happiness, injury, alertness, or other • The second goal was ASM reduction 42/92(42%), the third, cognitive improvement 20/69 (29%) • In 50/75 fathers (67%) cited seizure reduction as the first goal, 31/68 (46%) named ASM reduction as a second goal, and 18/40 (45%) cited cognition improvement as a third goal • Parents may have differing goals and expectations • Improvement in cognition and alertness was more important than seizure and ASM reduction in predicting the duration of KD

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						treatment
Kossoff et al. 2006[211]	USA	n = 20, DRE	To evaluate the efficacy and tolerability of MAD	Prospective Cohort Study	MAD	• The average seizure frequency reduced from 163 to 40 per week at six months • Five children with absence epilepsy had a good response • Eighteen families chose to increase carbohydrates from 10g to 15 g/day and one to 20 g/day. One child had increased seizures, and carbohydrates were reduced to 10 g/day with seizure improvement • In 5/18 (27.8%) families, children used low-carbohydrate prepared foods and reported an increase in seizures • The MAD appears to be an effective and well-tolerated therapy for children with DRE
Kang et al. 2007[212]	South Korea	n = 14, DRE	To evaluate the efficacy, safety, and tolerability of the MAD	Prospective Cohort Study	MAD	• In 6/14 (42.9%) children they had >90% reduction in seizure frequency, whereas 8/14 (57.1%) experienced a <50% reduction • Consistently strong ketosis (>3 mmol/L) seems important to obtain favourable seizure outcomes • The MAD was tolerated suggesting it can replace the CKD • Serious complications were rare, but long-term complications require

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						further review
Rizzutti et al. 2007[213]	Brazil	n = 46, DRE n = 23, KD pre-diet (50%) n = 23 KD hospital regime (50%)	To compare the efficacy and tolerability of the introduction of a 2:1 CKD prior to admission	Prospective Cohort Study	CKD	• At 12 months, 8/46 (17.4%) children became seizure free, 7/46 (15.2%) >90% seizure reduction, 16/46 (34.8%) had a 50%-90% decrease, and 15/46 (32.6 %) had a <50% decrease • There were no significant differences in the treatment efficacy between the two groups, but the CKD 2:1 pre-diet were better adapted to the CKD
Nathan et al. 2008[214]	India	n = 105, DRE	To evaluate the efficacy of the CKD	Prospective Cohort Study	CKD	• In 39/105 (37%) children they became seizure free, 23/105 (22%) achieved between 90-99% seizure freedom, 23/105 (22%) achieved between 50-90% control • The CKD is well tolerated and efficacious in controlling DRE in children. Benefits in development and ASM reduction were noted
Evangeliou et al. 2009[215]	Greece	n = 17, DRE	To study the role of the BCAA as additional therapy to the CKD	Prospective Cohort Study	CKD	• In 3/17 (17.6%) who experienced reduction of seizures when following the CKD, they became seizure free with addition of BCAA • In, 4/17 (23.5%) they did not benefit from the addition of BCAA and CKD was unsuccessful • Parental reports noted improvement in

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						behaviour and concentration, learning ability, and communication skills in 9/17 (52.9%) • BCAA may increase the effectiveness of the CKD
Nikanorova et al. 2009[216]	Denmark	n = 5, DRE in enceph-alopathy with CSWS	To evaluate the effect of the CKD	Prospective Cohort Study	CKD	• In one child they responded with CSWS disappearance • In 1/5 (20%) the effect of the CKD was partial and intermittent, whereas in 3/5 (60%) no response was observed • The CKD did not appear to influence the neuropsychological outcome but in two patients an improvement in attention and behaviour was demonstrated
Sharma et al. 2009[217]	India	n = 27, DRE	To evaluate the efficacy and tolerability of the CKD	Prospective Cohort Study	CKD	• At six months 13/27 (48%) children had >50% reduction in seizures, and 4/27 (15 %) were seizure free • CKD is an effective and well-tolerated treatment option in young Indian children with DRE
Weber et al. 2009[218]	Denmark	n = 15, DRE	To evaluate the tolerability and efficacy of the MAD	Prospective Cohort study	MAD	• At three months, 6/15 (40%) of children had a seizure reduction of >50%, which was noted in different epileptic syndromes and age groups • Parents reported no correlation between degree of ketosis and seizure

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						reduction
Barzegar, Irandoust, Mameghani 2010[219]	Iran	n = 21, DRE	To evaluate the efficacy and tolerability of the MAD	Prospective Cohort Study	MAD	• The MAD was more effective in children living with cryptogenic epilepsy at three months, but this was not significant at six months • MAD is safe and effective as an alternative to the CKD
Coppola et al. 2010[220]	Italy	n = 38, EE in children <five years	To assess the efficacy and tolerability of CKD	Prospective Cohort Study	CKD	• In 11/35 (23.7%) children they experienced seizure freedom at three months • In 16/35 (46%) of children had 50-90% seizure improvement at three months • The CKD is efficacious and tolerable as an add-on treatment in children, under five years, with catastrophic epileptic syndrome
Hong et al. 2010[221]	USA	n = 104, IS	To assess the efficacy of the CKD	Prospective Cohort Study	CKD	• In 38/104 (37%) infants they achieved at least six months of spasm freedom and 30/38 (79%) did not relapse • The CKD was shown to be efficacious in IS and should be considered when vigabatrin and steroid treatment fails

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kossoff, Borsage, Comi 2020[222]	USA	n = 5, Sturge-Weber syndrome	Hypothesis, the MAD would be effective in Sturge-Weber syndrome	Prospective Cohort Study	MAD	• At three months, 3/5 (60%) children had >50% seizure improvement and 2/5 (40%) had 25% seizure reduction • At six months, seizure freedom was noted in two children for a two to three-month period • MAD can be successful in children with Sturge-Weber syndrome
Lee et al. 2010[223]	South Korea	n = 28, DRE n= 9 CKD 3:1 (32%) n = 19 CKD 4:1 (68%)	To evaluate the usefulness of a liquid ketogenic milk	Prospective Cohort Study	CKD	• Overall, seizures reduced by >90% in 16/28(57.1%), including 9/28 (32.1%) who became seizure free after three months • In, 24/28 (85.7%) the liquid ketogenic milk was well tolerated and convenient • There were no serious complications • The liquid ketogenic milk increased CKD tolerability
Tonekaboni et al. 2010[224]	Iran	n = 24, DRE	To evaluate the efficacy of the MAD	Prospective Cohort Study	MAD	• The mean seizure frequency after the first, second and third months of MAD were significantly lower than at baseline • The MAD can be considered safe, effective, and a well-tolerated alternative therapy for DRE • The MAD seems to be as effective as CKD in reducing seizures, and it is easier to initiate, maintain and has no restriction on protein, calories, or fluids

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Caraballo 2011[225]	Argentina	n = 24, DS	To provide an experience of the KD	Prospective Cohort Study	CKD	• All five patients with SE responded well to CKD, experiencing no further episodes • The authors suggest that children with DS should be offered the KD immediately after failing three or four adequate trials of ASMs
Kossoff et al. 2011[226]	USA	n = 30, DRE	To investigate the use of a daily liquid ketogenic supplement in addition to the MAD	Prospective Cohort Study	MAD	• The addition of a liquid ketogenic supplement to the MAD during its initial month appears to improve efficacy • In 6/30 (20%) parents, they reported an increase in their children's seizures immediately after this was stopped • The high fat content of the KD could be an important aspect of seizure control, but it may only be necessary for an initial time period
Nabbout et al. 2011[227]	France	n = 15, DS	To test the efficacy of the CKD	Prospective Cohort Study	CKD	• There were 10/15 (66.7%) responders • In 1/15 (6.7%) children, they were seizure free at three and six months • Parents (10/15, 66.7%) reported a major decrease in atypical absences and myoclonic seizures • The results support the consideration of the KD as an additional treatment, in DRE or when there are major behavioural disturbances in DS

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kumada et al. 2012[228]	Japan	n = 10, DRE	To study the efficacy of the MAD	Prospective Cohort Study	MAD	• At three weeks following the MAD with a restriction of 10g carbohydrate per day, 3/7 (42.9%) children had decreased seizure frequency, and 2/3 (66.7%) became seizure free • SE (n = 2) could be successfully controlled by the MAD • The MAD was acceptable to a high proportion of Japanese children
Sharma et al. 2012[229]	India	n = 15, IS	To evaluate the efficacy and tolerability of the MAD	Prospective Cohort Study	MAD	• At three months, 6/15 (40%) infants were spasm free, 3/15 (20%) had >50% reductions in spasm clusters • At six months follow up, 6/9 (66.7%) were spasm free, 3/9 (33.3%) experienced >90% reduction in spasms • Parents reported improved alertness and interaction • The MAD was shown to be an effective, feasible, and well tolerated treatment in children with refractory IS
Thammon-gkol et al. 2012[230]	Australia	n = 61, DRE (93% children)	To report the efficacy of the KD	Prospective Cohort Study	CKD	• In 29/61 (48%) of patients there was >50% reduction in seizures at three months • One child with focal epilepsy of unknown aetiology and another with childhood absence DRE became seizure free • Children living with lissencephaly and hypoxic ischemic encephalopathy had

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						a good response, in addition to DS, migrating partial epilepsy of infancy, childhood absence epilepsy, focal epilepsy and myoclonic-atonic seizures • The CKD is an effective treatment for children living with DRE
Pires et al. 2013[231]	France	n = 17, IS	To evaluate the effect of the CKD as a third-line treatment, after VGB and steroids	Prospective Cohort Study	CKD	• At the third month, 11/17 (65%) infants were seizure free but after one month, felbamate (n = 7), and topiramate (n = 4) were added. The efficacy of CKD with the additional ASMs remains stable at three to six months • The CKD is a useful treatment in cases of refractory IS and is tolerated well in children under one year of age • Felbamate seems to increase the rate of spasm-free patients refractory to KD
Suo et al. 2013[232]	China	n = 317, DRE	To evaluate the efficacy and safety of the CKD and determine which children are more likely to respond in Chinese children	Prospective Cohort Study	CKD	• The CKD was effective in IS, LGS and TSC • The treatment efficacy is better among children younger than 10 years • The CKD is a safe and efficacious therapy for DRE in Chinese children • KD food refusal was experienced due to the low carbohydrate intake compared to the high carbohydrate, low fat Chinese diet

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Caraballo et al. 2014[233]	Argentina	n = 20, LGS	To assess the efficacy and tolerability of the CKD as an add-on to ASMs	Prospective Cohort Study	CKD	• All three seizure free patients had cryptogenic LGS • The CKD was mostly effective in tonic, atonic, myoclonic-atonic seizures, and epileptic spasms • The CKD also worked in atypical absences, generalized tonic–clonic seizures, but less frequently in focal seizures • Fifteen patients who remained on the CKD for more than one year did not develop severe complications • The KD should be considered early in the course of the syndrome, and not as a last resort
Karimzadeh et al. 2014[234]	Iran	n = 42, DRE	To determine the efficacy and tolerability of LGIT	Prospective Cohort Study	LGIT	• Seizure reduction was observed in 73.8% of children at the end of one month and in 77.8% at the end of the second month • The LGIT was easier to prepare, better tolerated, and a more palatable dietary option but there was still discontinuation due to restrictiveness, lack of satiation and excessive meat intake • The low-cost outpatient implementation and fewer psychosocial issues are an advantage

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kayyali et al. 2014[235]	USA	n = 20, IS	To determine the efficacy of the CKD in controlling epileptic spasms after failing traditional ASMs	Prospective Cohort Study	CKD	• At three months, > 50% seizure reduction was reported in 70% infants and >90% seizure reduction was reported in 20% • Three infants (15%) achieved at least six months of spasm freedom during treatment with CKD • The KD is safe and a potentially effective method of treatment for IS
Amari et al. 2015[236]	USA	n = 30, DRE n = 15 CKD n = 15 MAD	To examine the relationship between fat preference and efficacy of KD	Prospective Cohort Study	CKD & MAD	• There was no difference in KD efficacy between the CKD and MAD • There is a positive correlation between fat preference and efficacy of CKD and MAD • Assessment of fat preferences could be a useful screening tool for KDs
Lambrechts et al. 2015[237]	The Netherlands	n = 48, DRE	To assess the long-term efficacy of the KD as an additional treatment	Prospective Cohort Study	CKD & MCT KD	• There was a statistically significant decrease in the mean seizure frequency at all time points, except for at 12 months • There was reduction in seizure frequency, seizure clustering and seizure severity

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Chomtho, Suteerojntr-akool, Chomtho 2016[238]	Thailand	n = 16, DRE	To determine the efficacy, side effects and feasibility of MCT KD	Prospective Cohort Study	MCT KD	• At three months, 9/14 (64%) had >50% seizure reduction and 7/14 (50%) had >90% reduction • There were no concerns regarding palatability, diet refusal or difficulty in dietary preparation • The MCT KD is effective, tolerable and feasible despite a previous high carbohydrate intake
Kossoff et al. 2016[239]	USA	n = 26, DRE in children Re-attempt KD (73% children)	To investigate the re-attempt of dietary therapy after the CKD was previously tried	Prospective Cohort Study	CKD & MAD	• There was no difference in seizure freedom between the CKD and MAD (15% vs 19%), but seizure reduction was less with the MAD • Using MAD as second time was feasible, well tolerated and largely similar to the first KD attempt • The CKD and MAD were equal in efficacy
Mehta et al. 2016[240]	India	n = 31, DRE	To evaluate the efficacy and tolerability of the MAD	Prospective Cohort Study	MAD	• In 17/31 (54.8%) children, they achieved >50% seizure reduction at three months and 9/31 (29%) at six months • Parents reported improvement in alertness (85%), activity level (42.8%), understanding (33.3%), social interaction (66.6%), communication (33.3%), sleep pattern (85%) and behaviour (38%)

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• The MAD was found to be feasible, effective, and tolerated in young children with DRE
Wu et al. 2016[241]	China	n = 87, DRE	To evaluate the efficacy of the KD	Prospective Cohort Study	CKD	• CKD efficacy was not correlated with age, gender, aetiology, glucose or ketone levels, or seizure frequency pre-KD • There was a positive correlation between increased cognition and the efficacy of CKD after three months
Wang et al. 2016[242]	Taiwan	n = 53, DRE (79% children)	To determine the efficacy of a MCT KD in Taiwan	Prospective Cohort study	MCT KD	• In 12/53 (22.6%) patients, they experienced >50% reduction in seizures and 9/53 (16.9%) became seizure free • The MCT KD was a safe and effective therapy • The MCT KD has a higher carbohydrate content and increased palatability compared to the CKD which may make it more suitable for Asian families used to high carbohydrate diets

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
De Brito Sampaio, Takakura, De Manreza 2017[243]	Brazil	n = 10, DRE	To evaluate the acceptability, tolerance, and efficacy of a formula-based CKD	Prospective Cohort Study	CKD	• After three months, 6/10 (60%) children had >50% seizure reduction and 1/10 (10%) children were seizure free • Formula-based KD was accepted and tolerated except for one child who disliked the taste. The formula was easy to use, facilitated the introduction of CKD and improved adherence • The CKD was effective in reducing seizures, improving cognition and QoL
van Egmond et al. 2017[244]	The Netherlands	n = 4 North Sea Progressive Myoclonus Epilepsy (50% children)	To evaluate the efficacy of the MAD	Prospective Cohort Study	MAD	• The 12-year-old boy had a significant (40%) improvement in health related QoL and continued the MAD due to reduced fatigue, less jerking in the evening, less nocturnal shaking, and increased participation in activities • In the youngest child, parents reported a deterioration in health related QoL but conversely the child reported considerable improvement • This illustrates that the burden of KDs is different for parents and children, and this influenced their decision to continue the MAD • Children living with North Sea Progressive Myoclonus Epilepsy may benefit from the MAD

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Dressler et al. 2017[245]	Austria	n = 17, DRE	To evaluate the efficacy and safety of KD PN	Prospective Cohort Study	CKD	• Of the four children with de novo KD PN, 2/4 (50%) were responders • Children who were following an enteral CKD and had previously shown seizure reductions of ≥50% maintained this improvement throughout KD PN despite lower ketosis • KD PN was safe and effective with fat intakes of 3.5–4.0 g/kg/day
El Rashidy et al. 2017[246]	Egypt	n = 7, DRE	To evaluate the impact of nine months on the MAD after failing the CKD	Prospective Cohort Study	MAD	• Children who failed the CKD completed a successful nine months of the MAD • The MAD was described as affordable, less tedious than the CKD, and rewarding • Growth, seizure control and their mothers` QoL improved • The MAD is recommended as a flexible, less restrictive alternative to the CKD
Sofou et al. 2017[247]	Sweden	n = 19, PDHD n = 7 CKD (36.8%) n = 12 MKD (63.2%)	To study KD and PDHD	Prospective Cohort study	CKD & MKD	• KDs had a positive effect on epilepsy, ataxia, sleep disturbance, language development, social functioning, and hospital stays • One child discontinued due to acute pancreatitis • Poor dietary compliance was associated with relapsing ataxia and

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						halted development • The KD should be introduced as early as possible in PDHD to prevent further brain damage
Arya et al. 2018[248]	USA	n = 14, SE	To describe the safety and efficacy of the CKD	Prospective Cohort Study	CKD	• At three months, four children were seizure free and three had decreased seizure frequency • Seizure resolution on EEG was achieved within seven days of CKD initiation in 10/14 (71.4%) children and 11/14 (78.6%) weaned off their continuous infusions within 14 days • This study suggests efficacy & safety of CKD for paediatric refractory SE
Baby et al. 2018[249]	India	n = 74, DRE	To report on the experience of the CKD in South India	Prospective Cohort Study	CKD	• There were 1/10 (8.4%) children who became seizure free, while 6/10 (61.4%) reported a seizure reduction of >50%. • CKD and GLUT1DS, DS, Doose and LGS showed a good response to the CKD • The CKD can be maintained long term, even in Indian children used to a high carbohydrate diet

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Lee, Chi, Liao 2018[250]	Taiwan	n = 63, DRE	To assess the long-term effectiveness and tolerability of the 2:1 CKD	Prospective Cohort Study	CKD	• Learning was positively affected in children but seizure reduction was varied • The CKD at a 2:1 ratio was effective, safe and could be applied in Asian countries that are highly dependent on a higher carbohydrate containing diet
Wu et al. 2018[251]	China	n = 52, DRE in EE	To evaluate the clinical impact of the CKD	Prospective Cohort Study	CKD	• There were improvements in cognition (n = 23), language (n = 12), and motor function (n = 10) • The CKD showed the best effect in children living with Doose and West syndrome
Yan et al. 2018[252]	China	n = 20, DS	To evaluate the efficacy and tolerability of CKD in children living with generalised convulsions and SE	Prospective Cohort Study	CKD	• The CKD reduced the frequency of general convulsions and decreased the risk of nerve injury due to SE • There were ten patients (50%) who became seizure free • The CKD improved cognition in children • The CKD is tolerable and an effective therapy for DS

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Weijenberg et al. 2018[253]	The Netherlands	n = 16, DRE	To evaluate whether the introduction of an all-liquid CKD in an outpatient setting is feasible	Prospective Cohort Study	CKD	• In 4/16 children seizure frequency reduced, the retention rate at 26 weeks was 50% • Introduction of CKD with a liquid formulation in orally fed children was successful • An all-liquid CKD resulted in fast and stable ketosis
Guzel, Uysal, Arslan 2019[254]	Turkey	n = 389, DRE	To investigate the efficacy and tolerability of an olive oil-based CKD	Prospective Cohort Study	CKD	• Reports from 87 parents (18.2%) reported CKD to be too restrictive and they had difficulties in finding time for meal preparation • Previous ACTH use and constipation at baseline or during KD reduced the efficacy
Karimzadeh ,Moosavian, Moosavian 2019[255]	Iran	n = 45, DRE in children aged one to three years n=21 CKD food (47%) n = 24 CKD formula (53%)	To investigate the efficacy and tolerability of the CKD compared with a formula-based CKD	Prospective Cohort Study	CKD	• Most children in the food only group were reluctant to eat high-fat homemade foods and children younger than two years of age discontinued the CKD • Around 33% of under two-year-olds and 41.6% of the total children aged one-three years old in the formula-based CKD group completed the trial • Using formula increased the chance of KD response seven-fold • The CKD in conjunction with a powdered formula is effective, safe, and tolerable, and can be an alternative

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						for those reluctant to eat homemade food
Wang et al. 2020[256]	China	n = 10, SRSE in FIRES	To investigate the effectiveness and safety of the KD	Prospective Cohort Study	CKD	• All 10 children achieved ketosis within 24–72 hours and SE was suppressed in 8/10 patients within two to 19 days after CKD initiation • In 7/10 patients there was a relapse in seizures after the KD was discontinued which developed into DRE • The CKD was a safe, effective treatment which should be considered early in the treatment course
Thibert et al. 2012[257]	USA	n = 6, AS	To assess the efficacy and tolerability of the LGIT	Prospective Cohort Study	LGIT	• All AS children had a decrease in seizure frequency on the LGIT, with 5/6 (83.3%) exhibiting >80% seizure frequency reduction • All EEG studies showed improvement and developmental gains were reported • The LGIT was well tolerated • The results indicate a potentially higher degree of efficacy in AS and LGIT use than is observed in the general epilepsy population
Lowe et al. 2021[258]	Canada	n = 45, DRE n = 28 CKD (62%) n = 17 MCT KD (38%)	Hypothesis, that MCT KD exhibits similar seizure reduction compared to	Prospective Cohort Study	CKD & MCT KD	• In this cohort of DRE, there was no significant difference in the proportion of children achieving ≥50% and ≥90% seizure reduction between CKD and MCT KD despite lower ketonuria

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
			the CKD			
Armeno et al. 2021[259]	Argentina	n = 56, DRE in infants <two years	To describe the effectiveness and tolerability of the CKD	Prospective Cohort Study	CKD	• The CKD was found to be effective and well-tolerated in infants • Adverse effects were common, and observed in infants younger than one year of age but this was not a reason to discontinue the CKD
Ye et al. 2022[260]	China	n = 481, IS	To evaluate the effect and safety of the CKD	Prospective Cohort Study	CKD	• Seizure freedom after CKD use was reported in 6.9% infants at one month, 11.6% at three months, 16% at six months and 16.8% at 12 months • The KD efficacy was not affected by age, ASMs, and previous steroid use • CKD is one of the effective treatments for IS
Hsieh et al. 2023[261]	Taiwan	n = 13, Infants <2years with DRE	To investigate the safety, efficacy, tolerability, and achievability of using the CKD	Prospective Cohort Study	CKD	• In 11/13 (84.6%), they responded to the CKD • Infants with an underlying genetic aetiology became seizure free • Authors recommended that the CKD ratio be lower and KD initiation longer due to their young age
Nguyen et al. 2023[262]	Vietnam	n = 45, DRE	To assess tolerability and feasibility of the CKD	Prospective Cohort Study	CKD	• KD use in Vietnam is safe and feasible, despite it being a low-income country with a high reliance on rice • Close follow up with the KD team

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						leads to success • Use of technology was essential, especially as KD initiation was during the COVID-19 pandemic
Rafli et al. 2023[263]	Indonesia	n = 31, DRE	To evaluate MAD use in Indonesia in children with severe epilepsy	Prospective Cohort Study	MAD	• At six months, there was a significant reduction in seizures • MAD is effective and well tolerated, but is still a restricted diet and compliance remains a concern • Gastrointestinal side-effects were the most common
Operto et al. 2023[264]	Italy	n = 36, DRE	To evaluate parental stress after KD use for six and 12 months	Prospective Cohort Study	CKD	• After six and 12 months of KD, parental distress and total stress scores significantly increased • Reasons reported, included: difficulties managing KD (72%), time (64%), child compliance (55%), side-effects (42%), increased cost (22%), restrictions in social activities (19%), no difficulties (17%) and lack of clinical support (8%)
Falk et al. 1976[(265)]	USA	n = 2, PDHD	To report two PDHD brothers and the use of the KD	Case series	Not described	• Both brothers improved clinically and biochemically when consuming a high fat diet which resulted in ketosis

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Haas et al. 1986[266]	USA	n = 7, Girls with Rett syndrome and DRE	To describe Rett syndrome and MCT KD	Case series	MCT KD	• There was clinical and EEG improvement in EEG in 3/5 girls • All patients had difficulties with tolerating the MCT KD • It was thought that enthusiasm and hope for improvement led to bias
Bergqvist et al. 1999[267]	USA	n = 3, Acquired epileptic aphasia	To report on the CKD use	Case series	CKD	• All children had a significant reduction in seizures and had lasting improvement in their language • The KD should be considered in the treatment of acquired epileptic aphasia
Klepper et al. 2002[268]	Germany	n = 4, Infants	To report CKD use in four young infants with suspected GLUT1DS	Case series	CKD	• The CKD can safely be used in infants with a long-chain triglycerides and low carbohydrate infant formula • All infants tolerated the ketogenic formula well • The KD effectively controls seizures and might prevent neurological impairment in infants with GLUT1DS
Kossoff et al. 2003[269]	USA	n = 6, DRE (two children)	To investigate the efficacy of the MAD	Case series	MAD	• At the time of this publication patient one was seizure free on the MAD and Zonisamide was weaned • Patient two was previously following the CKD for two years and six months but found it too restricted and weaned, then the MAD was started when seizures returned resulting in improvement in behaviour and seizure freedom

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						• The MAD may have a role as a treatment option in DRE
Kossoff et al. 2005[270]	USA	n = 12, TSC	To describe the efficacy of the CKD	Case series	CKD	• In, 11/12 (92%) children, they had a >50% reduction in seizures at six-months and eight (67%) had a >90% response. Five had at least a five-month seizure free period • KD was generally effective for DRE seen in children with TSC and may be a useful option as ASMs can be ineffective, and surgery may not be an option
Coppola et al. 2006[271]	Italy & Germany	n = 3, refractory partial seizures with TSC	To describe the efficacy of the CKD	Case series	CKD	• CKD should be considered as an early treatment option in children waiting for surgery, if surgery fails or is not indicated
Harris et al. 2008[272]	USA	n = 2, GLUT1DS	To describe the CKD use	Case series	CKD	• Both children were seizure free and showed developmental progression • Early diagnosis and the initiation of CKD is important
Kumada et al. 2010[273]	Japan	n = 2, non-convulsive SE	To report the use of MAD	Case series	MAD	• SE was controlled by the MAD after five and ten days • Experience suggest that MAD is potentially useful for patients with medically intractable non-convulsive SE

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Ito et al. 2011[274]	Japan	n = 6, GLUT1DS	To review the effectiveness of the MAD	Case series	MAD	• Epileptic seizures and paroxysmal events decreased in all children • MAD is palatable, less restrictive, and easier to maintain compared to the CKD but its effectiveness was similar • MAD is a promising treatment for children living with GLUT1DS
Peuscher et al. 2011[275]	The Netherlands	n = 2, DRE with arginino-succinate lyase deficiency	To present the CKD use	Case series	CKD	• Urea cycle function and ammonia levels were stable • Patient 1 had >50% reduction in seizures and patient 2 saw no effect • CKD does not cause metabolic derangement, is well tolerated, and can be effective in patients with Arginosuccinate Lyase deficiency treated with a protein restriction
Zupec-Kania et al. 2011[276]	USA	n = 5, DRE	To describe enteral KD and KD PN	Case series	CKD	• Children living with enteral feeding tubes are excellent candidates for KDs due to ease of compliance and no need for food preparation • KDs are effective, improve QoL and reduce the medical costs associated with DRE • A team approach is crucial to the KDs success

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Sort et al. 2013[277]	Denmark	n = 3, SE	To report on the CKD experience	Case series	CKD	• In two cases the children responded to CKD and termination of SE occurred • Research on KD efficacy, optimal KD timing and contraindications for KD in SE, and which cases need to continue to prevent relapse was suggested
O'Connor et al. 2014[278]	USA	n = 5, SE	To report a case series on the use of the CKD	Case series	CKD	• Experience suggests that the CKD can be useful in managing refractory SE in children • Starting KD earlier in the treatment course may prove beneficial for children
Vaccarezza et al. 2014[279]	Argentina	n = 9, DRE (67% children)	To present case series of the MAD	Case series	MAD	• There was a >90% reduction in seizures in 2/6 (33.3%) children and 3/6 (50%) children experienced a reduction of 50-90% and 1/6 (16.7%) <50% reduction • The MAD should be considered an option, especially in adolescents with DRE
Singh et al. 2014[280]	USA	n = 2, FIRES	To report two cases of CKD use	Case series	CKD	• CKD was started in the acute SE phase and they continued for several months to one year • Children returned to school with mild impairment in cognition but did not return to their baseline level • Outcomes were more positive than reported in previous literature • Early consideration of KD may be

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						important in the acute management of children with FIRES
Caraballo et al. 2015[281]	Argentina	n = 2, refractory myoclonic SE	To describe the use of the CKD	Case series	CKD	• CKD is a promising therapy for refractory myoclonic SE and should be tried earlier during treatment and considered as an option regardless of the aetiology • If seizure control is achieved, then cognitive deterioration and behavioural disturbances may be avoided
Caraballo et al. 2015[282]	Argentina	n = 3, Migrating focal seizures in infancy	To present the use of the CKD	Case series	CKD	• One infant became seizure free and the remainder had 75-99% reduction in seizures • Early CKD treatment should be considered to avoid progressive cognitive impairment
Cobo et al. 2015[283]	USA	n = 4, SRSE	To describe the experience of using the CKD in the ICU	Case series	CKD	• Seizure cessation was not seen in this cohort but after CKD was started, all infants in the ICU successfully weaned off anaesthesia without recurrence of SE • This case series supports early consideration of KD in the management of SRSE • Further studies are needed to determine a protocol for KD initiation

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						and management in the ICU
Fenton et al. 2015[284]	USA	n = 4, Infants	To report the experience of using expressed breast milk alongside the CKD	Case series	CKD	• All patients had improvements in seizure activity within the first two months • The use of breast milk, in a controlled manner, alongside CKD is possible • Breast milk is recommended to be the carbohydrate source for infants
Fung et al. 2015[285]	China	n = 4, SRSE	To report the clinical characteristics, treatment, and outcome of four children treated with the KD in ICU	Case series	CKD	• The experience suggests that CKD is a safe and feasible option in the ICU • KDs can be considered as a treatment option for SRSE • Standardised guidelines for KD use in ICU for SRSE may help
Gumus et al. 2015[286]	Turkey	n = 6, GLUT1DS	To assess the efficacy of the KD	Case series	CKD & MAD	• Five children became seizure free and KD use resulted in improvement in cognitive functions • If the CKD is not tolerated, a less restrictive KD may be helpful • Early KD may offer protection from the potentially effects of hypoglycorrhachia on neurodevelopment

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Joshi et al. 2016[287]	USA	n = 2, DRE with early EE due to PIGA protein deficiency	To describe the KD in two brothers	Case series	Not described	• Both boys remained on the KD indefinitely due to the perceived benefits in seizure activity • Using KD for the treatment of DRE in children with PIGA deficiencies has been highlighted as a treatment option
Armeno et al. 2019[288]	Argentina	n = 3, Epilepsy of Infancy with migrating focal seizures	To report the use of KD PN in infants	Case series	CKD	• KD PN was safe and tolerated when enteral feeds were not feasible and should be considered in this scenario • Seizure activity may still improve and children respond well to KD PN despite lower ratios • Care should be taken to maintain ketosis and avoid undesirable additional carbohydrates
Nkole et al. 2020[289]	Zambia	n = 3, DRE	To describe KD use in Zambia	Case series	CKD	• There are limited treatment choices and ASM accessibility in Zambia • This research demonstrates the feasibility of CKD as an option for DRE in Zambia
Paketci et al. 2020[290]	Turkey	n = 2, DRE in ALG3-CDG	To report the use of the CKD	Case series	CKD	• In one sibling, after the first week of CKD seizures stopped and alertness improved • The other sibling had a significant decrease in seizures within week one • CKD can be considered as a treatment option for DRE in ALG3-CDG

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Hamada et al. 2021[291]	Japan	n = 3, DRE in Infantile Alexander Disease	To describe the use of the CKD	Case series	CKD	• Seizures stopped within a month in all cases • KD doesn't prevent disease progression but earlier KD use may lead to a better clinical prognosis
Yıldırım et al. 2021[292]	Turkey	n = 3, Glut1DS	To describe the treatment with the CKD	Case series	CKD	• The CKD was most effective on treatment of seizures and less effective on ataxia, language skills, and behaviour • Further GLUT1DS case series to determine the long-term effect of KD and outcomes would be welcome
Maiorana et al. 2021[293]	Italy	n = 3, DRE in hyperinsulinaemic hypoglycaemia caused by glucokinase mutations	To describe the CKD use	Case series	CKD	• After days on KD all patients became asymptomatic, seizures improved, and they no longer required a near-total pancreatectomy • The CKD was efficacious and safe in the short and long-term • Families reported physical, psychosocial and QoL improvements
Hu et al. 2021[294]	China	n = 3, girls with DRE in nonsense mutations of SMC1A gene	To explore the use of the CKD as an add-on therapy	Case series	CKD	• All patients had cluster seizures and KD use resulted in seizure freedom within 3 to 4 weeks

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Anand et al. 2021[295]	India	n = 4 SRSE (one child)	To describe the experience with CKD	Case series	CKD	• Case 4 was started on 4:1 CKD and ketosis was achieved on day 5 and seizures stopped on day 7. Treatment included CKD, Oxcarbazepine, and Clobazam for 10 months • KD is effective in controlling SRSE
Inui et al. 2022[296]	Japan	n = 2, PDHD	To describe two cases of PDHD treated with KD PN	Case series	CKD	• Early KD PN improved short and long-term prognoses • KDs are a treatment option for neonatal-onset PDHD
Phitsanu-wong et al. 2023[297]	USA	n = 2, DRE in SCN2A-related EE	To share the experience of KD in premature neonates	Case series	CKD	• KD was well-tolerated, safe and effective • Seizure frequency was >90% in both neonates • Side effects included hypoglycaemia and weight loss. Both were correctable
Winczewska-Wiktor et al. 2024[298]	UK and Poland	n = 4, DRE in DEPDC5 gene mutation	To evaluate the effectiveness of KD in DEPDC5-related epilepsy	Case series	CKD & MAD	• KD was safe and effective in treating DEPDC5-related epilepsy • Seizure freedom was noted in ¾ patients • The authors recommend early consideration of KD in DEPDC5-related epilepsy

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Mac-Cracken & Scalisi 1999[299]	USA	n = 11, DRE	To assess the effectiveness and compatibility of the CKD	Descriptive surveys	CKD	• KD satisfaction was high but compliance was a concern • The three-year experience showed benefits to seizure activity and improved QoL • Support groups, KD treatment at an earlier age and access to a computer program for recipes was suggested as areas for improvement
Katyal et al. 2000[300]	USA	n = 48, DRE	To review the CKD experience at the Children's Hospital of Pittsburgh since 1994	Descriptive surveys	CKD	• Fourteen (33%) had a 50-90% reduction in seizures and 16 (38%) had a >90% reduction in seizures after 45 days • The KD seems to be an effective treatment for children with DRE
Magrath, MacDonald, Whitehouse 2000[301]	UK	n = 127, Paediatric dietitians caring for children living with DRE and KD via a questionnaire	To audit current practice of the use of the KD in the UK	Descriptive surveys	CKD & MCT KD	• There were 101 patients treated with the KD, CKD = 57 and MCT KD = 44 • Reasons for stopping the KD include failure to improve seizures, difficulty following the KD and poor compliance • Further research is needed on the KDs nutritional safety and application

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kossoff & McGrogan 2005[302]	USA	n = 73, academic centres in 41 countries	To evaluate the worldwide use of the KD	Descriptive surveys	Not the focus of the study	• KDs are being used worldwide and international collaborative groups are active. Difficulties were noted in populations with limited resources, when avoiding rice, fat tolerance and nutrition labelling
Lord & Magrath 2010[303]	UK	n = 135 Paediatric dietitians caring for children living with DRE and KD via a questionnaire	To determine whether there had been an increase in the use of the KD	Descriptive surveys	CKD & MCT KD	• There was a 50% increase in KD use for DRE between 2000 and 2007, this was an additional 51 patients • To further increase the use of KDs, more trained dietitians via an education programme and funds are needed. In addition, KD guidelines and a database to benchmark the time and cost per patient is suggested • A national database to record patient numbers treated with the KD and clinical outcomes would be welcome
McNamara, Carbone, Shellhaas 2012[304]	USA	n = 25, Parents of children living with DRE and the KD	Hypothesis, there are other factors involved in KD adherence	Descriptive surveys	CKD	• Families wished they had known the impact that KDs would have on the family, the side effects, the supplies needed, and the time required before implementation • Increased KD support including being able to call the KD team, a parent mentor network, improved food selection, and education classes were requested

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Schoeler et al. 2014[305]	UK	n = 92, Parents of children living with DRE and the KD	To assess and quantify parental beliefs regarding KDs & determine whether these were related to the KD response	Descriptive surveys	CKD, MCT KD & MKD	• There was a significant relationship between parents' KD beliefs and seizure response to KD. Negative perception of KD was seen in non-responders • There was a great belief in the necessity of KDs (79%), but over half (58%) of parents expressed strong concerns about long-term KD effects
Jung, Joshi, Berg 2015[306]	North America	n = 56, KD centres looking after children living with DRE and the KD	To review North American KD practices	Descriptive surveys	Not the focus of the study	• KDs were considered as a first- or second-line treatment (0%), third/ fourth (67%), fifth/sixth (29%), and as a last resort (4%) by centres • KDs were first or second treatment for GLUT1DS (86%) and third/fourth for DS (63%), West syndrome (71%), and Doose syndrome (65%)
Fujii et al. 2016[307]	Japan	n = 499 (49% response rate) paediatric neurologists n = 46 GLUT1DS	To evaluate the outcome of KDs in patients with GLUT1DS in Japan	Descriptive surveys	CKD, MAD & MCT KD	• KDs were effective for seizure control (80%), aggravation after fasting (79%), and ataxia (79%). Ataxia was as responsive to KD as seizures were • The MAD was as effective as the CKD, more palatable and used more frequently

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Kass et al. 2016[308]	USA	n = 90, parents at a GLUT1DS conference	To learn more about KD and GLUT1DS	Descriptive surveys	CKD, MAD, MCT KD & LGIT	• Nearly all parents surveyed had children following a KD for long durations and reported excellent seizure control, often with no ASMs • There was an equal percentage of seizure free children with the CKD and MCT KD compared to the MAD and LGIT indicating similar efficacy
Dozières-Puyravel et al. 2018[309]	France	n = 25, centres that provide KDs for children living with DRE and the KD	Evaluation of the use of KDs in France in 2018	Descriptive surveys	CKD & MAD	• Twenty-two (88%) centres reported an increased annual number of children starting KDs in 2018 compared to 2008 • KD use in France has increased alongside the increase in knowledge
Oguni et al. 2018[310]	Japan	n = 34, GLUT1DS (76% children) n = 18 MAD (53%) n = 9 MCT KD (26%) n = 5 CKD (15%) n = 1 LGIT (3%)	To investigate the efficacy and side effects of KDs in Japan	Descriptive surveys	CKD, MAD, MCT KD & LGIT	• KDs markedly improved seizures and non-epileptic neurological symptoms • Satisfaction was high level but improved dietary tolerability would be welcomed by families if KD was a long-term treatment option

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Martin-McGill et al. 2019[311]	UK	n = 18 centres that provide KDs for children living with DRE and the KD (13 paediatric, 3 adult, 2 combined)	To understand the MKD practice in the UK	Descriptive surveys	MKD	• MKD 'prescription' was based on estimated total energy requirements, with the average fat content (75%), carbohydrate (5%), with protein to appetite • To make KDs simpler and accessible, dietitians in the UK and Ireland developed a hybrid KD which adopts principles from established protocols and adds new elements unique to the MKD
Varesio et al. 2019[312]	Italy	n = 17, GLUT1DS (71% children)	To assess Health Related QoL in children living with GLUT1DS and the KD	Descriptive surveys	CKD	• Global scores for QoL were impaired both in parents' and children living with GLUT1DS and CKD which is comparable to other patients with chronic disease • The presence of a movement disorder in GLUT1DS is a factor when discussing QoL and 53% still experienced this despite KD use
Whiteley et al. 2019[313]	UK	n = 26, KD centres in UK and Ireland looking after children living with DRE and the KD	To assess the impact of a change in NICE guidance on the use of KDs	Descriptive surveys	CKD, MCT KD, LGIT & MKD	• Over seven years, the number of patients living with DRE and the KD in the UK and Ireland increased by 647%. The centres offering KDs increased by 77%, from 22 in 2000, to 39 in 2017 • CKD was used in 324/580 (55.9%) patients, MKD in 187/580 (32.2%),

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						MCT KD in 56/580 (9.7%) and LGIT in 13/580 (2.2%) • KDs are in high demand and there is a need for an expansion of services
Sarlo & Holton 2021[314]	USA	n = 192, caregivers of children living with DRE and the KD	To identify caregiver perspectives on KDs	Descriptive surveys	CKD, MAD, MCT KD & LGIT	• Clinically significant seizure reduction was associated with higher QoL • Family stress and food refusal was associated with younger children • Caregivers felt supported and observed improved QoL but they would benefit from increased support and educational resources
Serdaroğlu & Arhan 2021[315]	Turkey	n = 27, Paediatric neurologists, providing KDs for children living with DRE	To determine the KD input in Turkey	Descriptive surveys	Not the focus of the study	• KD services were hindered by lack of personnel (53.8%), including dietitians (52%), poor parental education (24%), and inadequate experience of healthcare staff (23.1%) • Negative KD factors, included: non-appealing taste (76.9%), need for supervision (76.9%), and low patient motivation (73.1%) • Reasons for KD failure included: imprecise KDs (94%), limited family support (92.3%), reduced oral intake (73%), incorrect indication for KD (53.9%), and lack of efficacy of KD (42.3%)
Weber, Antognetti,	USA	n = 7, PDHD	To assess the use of diets	Ambispective cohort study	Not described	• The percentage of dietary fat and carbohydrate varied considerably

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Stacpoole 2001[316]			high in fat and low in carbohydrate			between patients and response varied considerably • A controlled, prospective study of the benefits and risks of KDs in the long-term treatment of PDHD is needed before nutritional guidelines can be developed
Miranda et al. 2011[317]	Denmark	n = 83, DRE n = 33 MAD (40%) n = 50 CKD (60%)	To compare the effect of the MAD to CKD	Ambispective cohort study	CKD & MAD	• There was a strong trend for higher incidence of responders in the CKD group (MAD 39% vs. CKD 60%) • Increased alertness during the day and more quiet nights were reported with less seizure activity • There was no difference between the responder-rates of the children following the CKD and MAD suggesting that the MAD was effective as the CKD
Kossoff, Henry, Cervenka 2013[318]	USA	n = 8 JME (25% adolescents)	To describe the use of the MAD	Ambispective cohort study	MAD	• The MAD was an efficacious adjunctive therapy for young adults with very drug resistant JME • It was found that the MAD was difficult to adhere to in several patients

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Le Pichon et al. 2019[319]	USA	n = 9, Infants with DRE	To evaluate the safety and efficacy of the CKD whilst maintaining the use of breast milk	Ambispective cohort study	CKD	• The infants tolerated CKD and breast milk well, except one who developed gastrointestinal side effects • Four infants were seizure free with no ASMs when breast milk was discontinued • This study supports the use of breastfeeding and CKD in infants living with DRE
Herrero et al. 2020[320]	Spain	n = 26 n = 25 DRE (96%) n = 1 GLUT1DS (4%)	To assess the effectiveness and side effects of a KD when used for more than two years	Ambispective cohort study	CKD & MAD	• The KD is an efficient and safe childhood treatment • It is possible to transition to less restrictive KDs if treatment duration is prolonged
Youn et al. 2020[321]	South Korea	n = 31, DRE in TSC	To investigate the long-term outcomes of KDs	Ambispective cohort study	CKD & MAD	• The KD appeared to be an effective treatment for DRE in TSC, but long-term efficacy wasn't guaranteed • Future studies should investigate the role of KDs in mTOR inhibition
Herrero et al. 2021[322]	Spain	n = 18, GLUT1DS n = 6 3:1 CKD (33.3%) n = 12 MAD (66.7%	To evaluate the effectiveness of the KD	Ambispective cohort study	CKD & MAD	• There were no significant differences between KDs • The MAD was as effective and safe as the CKD • Movement disorders improved (4/5), and >50% reduction in seizures compared to baseline was achieved in more than half of the children living

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
						with seizures • KD should be used life-long in confirmed GLUT1DS diagnosis
Ko et al. 2022[323]	South Korea	n = 25, DRE due to presence of detectable somatic mTOR pathway mutations n = 18, 4:1 CKD (72%) n = 4, 3:1 CKD (16%) n = 3, MAD (12%)	To determine the efficacy of the KD in focal cortical dysplasia	Ambispective cohort study	CKD & MAD	• The efficacy of the KD after 3 months was superior (not-significant) in children with detectable mTOR pathway mutations compared to without detectable mTOR pathway mutations
Than et al. 2005[324]	USA	n = 107, DRE n = 18 dramatic responder (16.8%) n = 89 control KD (83.2%)	Hypothesis, CKD responders may have some commonality	Case-control study	CKD	• An early, dramatic response to CKD is more likely in patients with IS or predominant seizure types compared to children with complex partial seizures which appeared to be a negative prognostic factor

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Stainman et al. 2007[325]	USA	n = 69, DRE n = 45 non-surgical candidates on KD (65%) n = 24 treated with KD and surgery (35%)	To investigate the efficacy of the CKD	Case-control study	CKD	• Non-surgical candidates were more likely to become seizure free (29% versus 13%) compared to the surgical group. Of 24 children who received CKD and surgery, at six months there was a higher likelihood of >90% seizure reduction and seizure freedom after surgery • Children with surgically approachable epilepsy respond to CKD, but are more likely to be seizure free following surgery
Kossoff et al. 2008[326]	USA	n = 33, IS n = 13 CKD (39%) n = 20 ACTH (61%)	Hypothesis, CKD would have similar efficacy but better tolerability than ACTH when used first-line	Case-control study	CKD	• Eight infants became spasm-free with the CKD. The recurrence rate was low over six months, with only one infant (12.5%) having a relapse at three months • The six-month treatment duration could possibly be shortened by several months based on EEG normalization, in a similar manner to ACTH administration • Combination therapy with KD and ASMs may further increase the efficacy of the KD

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Yang et al. 2022[327]	China	n = 634, DRE n = 317 control (50%) n = 317 CKD (50%)	To evaluate the efficacy and safety of KD compared to a previous cohort	Case-control study	CKD	• The CKD was effective in 55.5% children at three months • Goal setting and long-term management are effective for KDs • The retention rate significantly increased over time and response rate significantly improved
Armeno et al. 2022[328]	Argentina	n = 37, DRE n = 18 Telemedicine (49%) n = 19 outpatient (51%)	To explore the feasibility, effectiveness, and safety of online KD initiation and follow-up	Case-control study	CKD	• There were no statistical differences regarding efficacy and safety of CKD if started in an outpatient setting or by telemedicine • Positive aspects: reduced travel, reduced waiting time, efficiency, individualised approach and good coordination • Negative aspects: technology, inadequate anthropology, and clinical information • Face-to-face KD services remains the main choice
Dou et al. 2023[329]	China	n = 56, Infantile epileptic spasm syndrome	To compare the safety, tolerability and efficacy of CKD and MAD	Case-control study	CKD & MAD	• There was no difference between KD groups with regards to spasm freedom • Patients following MAD had lower rates of poor compliance and remained on diet longer compared to CKD • Authors mentioned that commencing the KD earlier may be advantageous

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Boles et al. 2020[330]	Canada	n = 6, DRE	To explore the QoL in children living with the KD	Cross-sectional	LGIT	• The LGIT led to improved seizure control in some patients but their QoL did not improve • Positive themes after KD initiation included introducing new foods, benefits to health, and collaborative meal preparation • Negative themes included restrictions, loss of independence, social impact, isolation, and preparation difficulties
El-Rashidy et al. 2023[331]	Egypt	n = 143, DRE	To highlight the benefits of KD	Cross-sectional	CKD	• CKD is effective, safe and tolerable • There was no significant negative impact on growth or lipid profile • Positive effects on adaptive behaviour was noted
Webster & Gabe 2016[332]	UK	n = 12, 10 mothers and two fathers of children living with DRE and the KD	To examine the meanings that parents attach to KD foods	Qualitative	CKD, MAD & MCT KD	• Parents viewed food as medicine and reversed the negative meanings attached to fat. The enjoyment of KD food and larger KD portion sizes were prioritised • Food symbolised inclusion and love, whilst fat was viewed as good. • The KD was medicalised, and the good parent identity maintained if KD is successful in controlling seizures
Alqahtani & Mahmoud 2016[333]	Saudi Arabia	n = 30, Parents of children living with DRE and the	To examine the attitudes and experience of parents after	Qualitative	Not the focus of the study	• Cultural beliefs are amenable to change and after KD initiation there was a change to a positive attitude towards scientific epilepsy treatment

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
		KD	KD intervention			and KDs • Improved cognition, walking, mood, vocabulary, sleep, and medication reduction were the major improvements described by parents
Samia et al. 2021[334]	Kenya	n = 17, 14 caregivers, three adolescents living with DRE and KD	To assess feasibility and acceptability of MAD in Kenya	Qualitative	MAD	• Important factors to the caregivers were support (dietetic, family, and social), food availability and the child's acceptance of the MAD. Cultural factors did not influence feasibility or acceptability • Adolescents avoided foods they disliked, carrying snacks or having a meal delivered to school was an inconvenience • Caregivers reported shopping changes, cost-related challenges, and increased time for meal preparation. They avoided social situations, had to inform friends and family of the child's needs and provide packed food for the child

TABLE S1 Characteristics of included studies

Author, year	Country	Population	Study aim	Study design	Ketogenic Diet	Authors key findings
Orr et al. 2024[335]	USA	n = 17, 10 mothers and 7 fathers of children living with DRE and the KD	To explore parents' experiences and expectations on the efficacy and the use of KD	Qualitative	CKD	• One overarching theme was that parents "do what you have to do" despite potential social, financial, physical, and mental/emotional impacts to benefit the health and well-being of a child • KD can both positively and negatively impact emotional and social well-being, especially in children with normal cognition • Important factors to parents were close follow-up, support from the KD team, and family centred care
Carroll et al. 2024[336]	UK	n = 21, 19 individual parents or carers, one couple of a child or children with DRE	To explore how families experience epilepsy and KD as told by parents	Qualitative	CKD, MCT KD & MKD	• KD brings challenges but parents believe that the benefits to seizure activity outweigh the challenges • Parent reported themes include: 'Epilepsy in all consuming', 'Opening the window to new opportunities', 'The reality of KD therapy' and 'Looking to the future' • Parents welcome enhanced variety of KD foods, improved access to KD, transition to adult services, access to education and support, regular social education, and peer mentoring

Abbreviations: ACTH, adenocorticotropic hormone; AS, Angelman syndrome; ASM, anti-seizure medication; BCAA, branched-chain amino acids; CKD, classical ketogenic diet; CNS, central nervous system; CSWS, continuous spikes and waves during sleep; DRE, drug resistant epilepsy; DS, Dravet syndrome; EE, epileptic encephalopathy; EEG, electroencephalography; FIRES, febrile infection-related epilepsy syndrome; GLUT1DS, glucose transporter 1 deficiency syndrome ICU, intensive care unit; IS, infantile spasms; JME, Juvenile myoclonic

TABLE S1 Characteristics of included studies

epilepsy; KD, ketogenic diet; LGIT, low glycaemic index treatment; LGS, Lennoux Gastaut syndrome; MAD, modified Atkins diet; MCT, medium-chain triglyceride; MD, mitochondrial disease; MKD, modified ketogenic diet; MRI, magnetic resonance imaging; NICE, National Institute for Health and Social Excellence; PDHD, Pyruvate dehydrogenase deficiency; PN, parenteral nutrition; QoL, quality of life; RCT, randomised controlled trials; SE, status epilepticus; SRSE, super-refractory status epilepticus; TSC, Tuberous Sclerosis Complex; UK, United Kingdom; USA, United States of America; VGB, Vigabatrin; VNS, Vagus nerve stimulator; VPA, Valproic Acid.