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FULL-LENGTH ORIGINAL RESEARCH

Use of ketogenic diet therapy in infants with epilepsy: A systematic review and meta-analysis

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Abstract

Objective: Ketogenic diet therapy (KDT) is a group of high-fat, low-carbohydrate diets used as an effective treatment option for children and adults with drug-resistant epilepsy. There is limited research on the efficacy of KDT in infants, where there is the highest incidence of onset of the epilepsy. We aimed to systematically review studies that have reported on response to KDT in infants with epilepsy.

Methods: An online comprehensive literature search was performed, including studies that provided seizure frequency data for at least one infant younger than 2 years of age who was treated with KDT for ≥1 month. The proportions of infants achieving ≥50% seizure reduction, seizure-freedom rates, retention rates, and reported side effects were extracted from studies. Meta-analyses were performed using a random-effects model, and subgroup analyses were performed to investigate possible between-study heterogeneity.

Results: Thirty-three studies met inclusion criteria and were included in the final analysis, with a total of 534 infants with efficacy data. Two studies were randomized-controlled trials, and the remainder were uncontrolled cohort studies. All studies were categorized as low quality. Meta-analyses of uncontrolled studies estimate 59% (95% confidence interval [CI] 53-65) of infants achieved ≥50% seizure reduction and 33% (95% CI 26-43) of infants achieved seizure freedom. Retention rates ranged from 84% at 3 months to 27% at 24 months. The most commonly reported side effects were dyslipidemia (20/171, 12%), vomiting (11/171, 6%), constipation (7/171, 4%), gastroesophageal reflux (6/171, 4%), and diarrhea (6/171, 4%).

Significance: This review indicates that KDT is safe and tolerable and that it can be an effective treatment option for infants with drug-resistant epilepsy. However, there are few studies focusing on infants treated with KDT, and high-quality evidence is lacking. High-quality randomized-controlled trials are needed to confirm the effectiveness, safety, and tolerability of dietary treatment in this vulnerable age group.

KEYWORDS

children, high-fat, low-carbohydrate

Laura Lyons and Natasha E. Schoeler are joint first authors.

1 | INTRODUCTION

Epilepsy is a neurologic disorder characterized by an enduring predisposition to generate epileptic seizures, affecting 0.5%-1% of children.[1] The incidence of epilepsy is greatest in the first 2 years of life (56-88/100 000 children/y),[2] a population that remains most at risk for neurodevelopmental compromise in the longer term.

Approximately 20%-35% of children with epilepsy are drug-resistant,[3] having failed adequate trials of two tolerated and appropriately chosen antiepileptic drug (AED) schedules to achieve seizure control.[4] Early seizure control is associated with better developmental outcome,[5] but many of the epilepsies presenting in infancy have a poor prognosis for seizure control.[6]

Ketogenic diet therapy (KDT) is a group of high-fat, low-carbohydrate diets used as a treatment option for drug-resistant epilepsy. Designed to mimic the effects of starvation on the body, fat is utilized as the principal energy source through production of ketones. KDT encompasses the classical ketogenic diet (KD), medium-chain triglyceride (MCT) KD, modified Atkin's diet (MAD), modified KD, and low glycemic index treatment (LGIT).

In the first randomized-controlled trial (RCT) of KDT for epilepsy, 38% children aged 2-16 years achieved ≥50% seizure reduction after 3 months, compared to 6% of controls ($P < .0001$).[7] Seven percent of children in the diet group had >90% seizure reduction, compared with no controls ($P = .0582$). There was no difference in effectiveness between patients who followed the classical diet or the MCT KD.[8] Further RCTs have corroborated the effectiveness of KDT, including the MAD, for epilepsy, with effects comparable to modern AEDs, in older children and adults.[9]

This review aimed to systematically assess and summarize studies with seizure efficacy data in infants age <2 years following KDT as a treatment for epilepsy. The primary aim was to determine response rates and also to assess retention and report adverse side effects in this age group.

Key Points

- Included studies were of low quality
- Approximately 60% infants were responders at 3- to 12-month follow-up
- Side effects and retention rates are similar to those reported in older children and adults
- High-quality studies are needed to assess use of ketogenic diet therapy in infants

2 | METHODS

A systematic literature search was conducted in electronic databases (MEDLINE [PubMed], Embase [Ovid], the Cochrane Database of Systematic Reviews, Cochrane CENTRAL, and the National Institutes of Health clinical trial registry) with the following keywords: infant(s) OR child(ren), AND ketogenic OR medium chain triglyceride, AND epilepsy OR spasm(s) OR seizure(s). Reference lists of publications, including reviews, were manually searched. Publications including human participants only, written in English or Spanish were included; no date restrictions were set. The search was up to date as of October 16, 2019.

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol is registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/).

2.1 | Eligibility criteria

RCTs, case-control studies, and observational cohort studies fulfilling the following criteria were included:

1. At least one participant with epilepsy who initiated ketogenic diet therapy (KDT; any type) at <24 months of age or was described as an "infant."
2. Treatment phase of at least 1 month.
3. Diet response data provided for infants, including percentage seizure reduction or absolute number of seizures, or else clear descriptions that allowed for calculation of percentage seizure reduction, such as "seizure-free" or "no change in seizures."
4. Epilepsy syndromes/diagnoses given for the study cohort (not necessarily reported specifically for infants).

Data from case reports, case series, and letters/commentaries were recorded but not included in the final analysis.

Infants initiated on KDT as treatment for glucose transporter type 1 deficiency syndrome (GLUT1-DS) or pyruvate dehydrogenase complex deficiency (PDHD), for which KDT would be the treatment of choice, were excluded.

2.2 | Study selection

Duplicate records were excluded. Titles and abstracts were screened for study eligibility, and full-text articles were

reviewed by LL and NS. Cases of disagreement were discussed until consensus was reached.

2.3 | Quality appraisal

The Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (https://merst.ca/ephpp/, accessed October 11, 2019) was used to assess quality of the evidence. This tool includes questions on selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. Each section is rated as "strong," "moderate," or "weak"; collectively, these are used to derive a global rating of "strong" (no weak ratings), "moderate" (one weak rating), or "weak" (two or more weak ratings). Global ratings are reported in this study. Quality assessment was performed for all included studies, rated independently by LL and NS, and disagreements were resolved by consensus.

2.4 | Outcomes

The primary outcome was efficacy of KDT for epilepsy in infants age <2 years, presented as the number or proportion of infants achieving ≥50% seizure reduction after ≥1 month of follow-up.

Secondary outcomes were:

1. Seizure freedom rates at ≥1 month of follow-up
2. Retention rates
3. Side effects

2.5 | Data extraction

The following data (where available), were extracted for each study:

1. Study design
2. Number of infants started on diet
3. Diet type
4. Seizure outcome at 1, 3, 6, 12, and 24 months
5. Seizure outcome at other recorded time points
6. Number of infants remaining on diet at each time point
7. Adverse side effects in infants
8. Details on diet initiation protocol for studies including infants only

2.6 | Data analysis

Descriptive analysis was conducted for the primary outcome and for seizure-freedom rates; data were summarized as aggregate rates (reported as intention-to-treat), ranges, median, and interquartile range (IQR), for numerical outcomes. Collective means were calculated from study means or individual patient data, where information was provided. Collective standard deviation could not be calculated, as these data were not available for all studies. Fisher exact or Mann-Whitney *U* tests were used to investigate associations of gender, age at seizure onset, age at diet onset, and number of failed AEDs with KDT response. Response rates were separated by epilepsy syndrome, etiology, or epilepsy/seizure type (including cohorts that included infants with only one epilepsy or seizure type) where such detail was provided. Narrative syntheses of retention rates, side effects, and diet-initiation protocols were compiled.

Meta-analyses of proportions, including uncontrolled studies only (the RCTs had different treatment arms and outcome measures), were conducted using the statistical package *meta*[10] in R (version 3.6.2).[11] Inverse-variance meta-analyses were performed using the *metaprop* function, applying a logit transformation to the outcome, and the method of DerSimonian-Laird[12] used to estimate the heterogeneity variance. Response was defined, first, as ≥50% seizure reduction and, second, as seizure freedom, at 3 months or as close as possible to 3 months or at unspecified time points, where 3-month response was not reported. Residual estimates were calculated to identify outliers (*Z*-statistic >2). The degree of heterogeneity was evaluated through visual inspection of forest plots, using the *Q*-test and I^2 statistic. An I^2 of 25%, 50%, and 75% was assumed to indicate low, medium, and large heterogeneity, respectively; a *Q*-statistic with *P*-value < .1 was considered evidence of substantial interstudy heterogeneity. Subgroup analyses were conducted to investigate potential explanatory variables of heterogeneity with the following variables: study design (retrospective or prospective), response time point (3 months or "other"), and whether the study included just infants or infants as part of a wider cohort. The R^2 statistic was also evaluated in subgroup analyses to quantify the proportion of variance explained by covariates in each model.

3 | RESULTS

In total, 2206 publications were identified. After removing 685 duplicates, 1521 studies were screened and assessed for eligibility; 37 studies met our inclusion criteria. Four studies were excluded,[13–16] as these infants were reported in other included studies.[17,18] Thirty-three studies were included in the final analysis, of which five included solely infants and 28 included infants as part of a wider cohort (Figure 1).

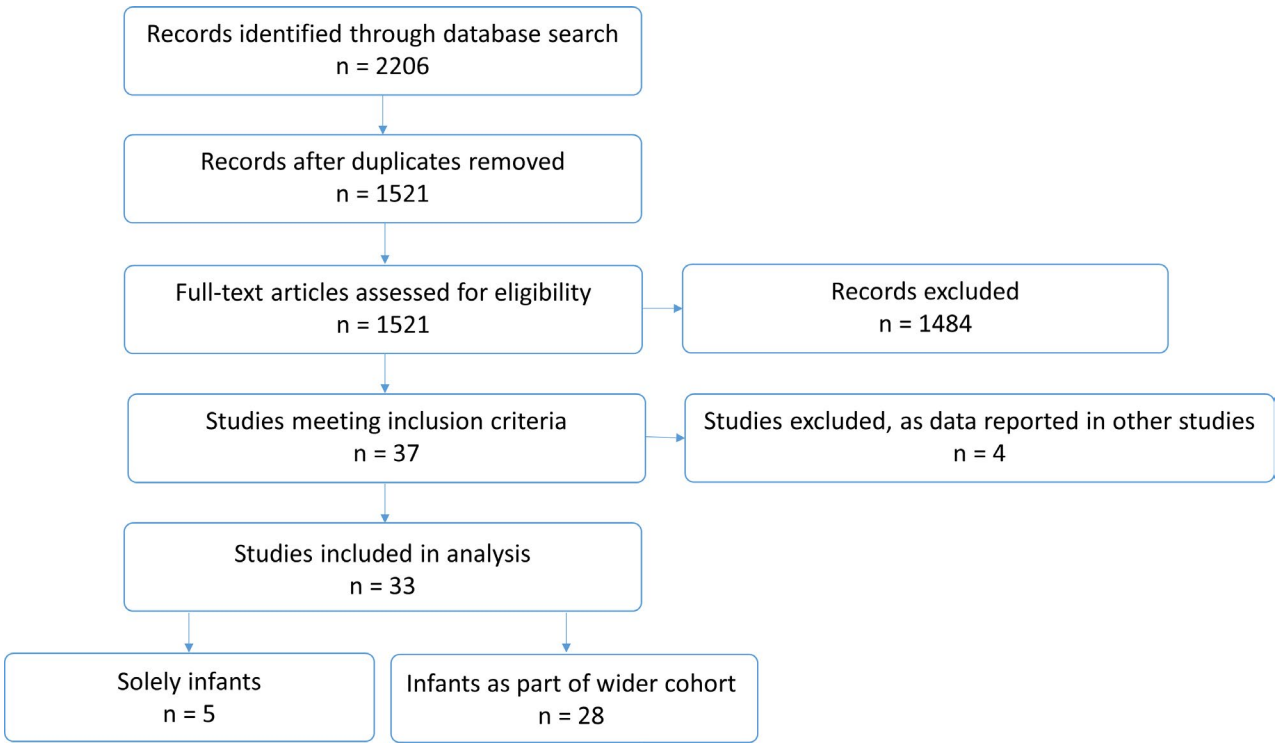

FIGURE 1 Flowchart of study selection

We also identified 32 case studies, including infants that met inclusion criteria but were not part of a cohort study (Table S1).

3.1 | Study characteristics

Eighteen studies were prospective, of which two were RCTs[19,20] (one of which also included a parallel cohort study); 15 were retrospective, single-arm cohort studies. Table 1 shows summary descriptive data for studies that included solely infants and Table 2 for studies including infants as part of a wider cohort.

A total of 534 infants who had followed a KDT for ≥1 month were included, of which 208 were from cohorts including solely infants. Eight studies only included infants with infantile spasms or West syndrome; most studies included patients with a range of epilepsy syndromes.

Fifty-eight percent (146/250) of infants were male (information given in 17 studies); mean age at seizure onset was 4.1 months (range 0-12 months, information given in 13 studies); mean age at diet onset was 13.0 months (information given in 20 studies). The youngest participant to start the diet was 11-days-old (0.03 years).[21] A total of 448 of 509 infants (88%) were following a classical KD, 29 of 509 (6%) a MAD, 3 of 509 (0.6%) an "Atkins diet" (60% fat, 30% protein, 10 g/d carbohydrate), one of 509 (0.2%) an MCT KD, and one of 509 (0.2%) an LGIT. Where specified, the classical KD ratio ranged from 2:1 to 4:1. The mean number of failed AEDs prior to starting KDT was 2.9 (range 0-10, information given in 16 studies).

3.2 | Study quality

All included studies, classified by the EPHPP method, were rated as "low" quality.

No studies were given a "strong" rating for selection bias, although all prospective studies were classed as "moderate" ("not applicable" for retrospective studies). The two RCTs[19,20] were the only studies given a "strong" rating for study design. In no studies were assessors blinded to the intervention or exposure status of participants. Most studies were single-arm or did not mention any differences between groups, so ratings for confounders were "weak." Data collection tools consisted predominantly of medical record review and were not shown to be valid or reliable. Only one study was given a "strong" rating for withdrawals and drop-outs,[23] and one a "moderate" rating[24]; the remainder were classed as "poor" ("not applicable" for retrospective studies).

3.3 | Efficacy of ketogenic diet therapy

3.3.1 | Aggregated efficacy

Data were available from 33 (controlled and uncontrolled) studies, including a total of 534 infants. The number of infants evaluated differs because efficacy rates were not reported at each time point in every study.

TABLE 1 Summary of studies of infants following ketogenic diet therapy for drug-resistant epilepsy (studies including infants only)

Study	Type of study	Epilepsy/seizure types	Number of participants starting diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%[a])	Seizure outcome (6 mo), n (%[a])	Seizure outcome (12 mo), n (%[a])	Seizure outcome (other), n (%[a])	Retention, n (%[a])
Nordli et al 2001[33]	Single-arm cohort study (retrospective)	Generalized seizures, n = 10 Partial unifocal seizures, n = 1 Partial multifocal seizures, n = 5 Generalized and partial seizures, n = 15 (n = 1 with pyruvate dehydrogenase deficiency, for whom diet efficacy data not extractable)	32 (mean 13.8 ± 5.7 mo)	Classical 3:1 or 4:1	–	–	–	At unspecified time point: 6 (19%) seizure-free 11 (34%) 50%-99% decrease 14 (44%) No worthwhile improvement One withdrawal after 8 d, response unknown	28 (88%) on diet at 3 mo 25 (78%) on diet at 6 mo 21 (66%) on diet at 12 mo
Hong et al 2010[b,17]	Single-arm cohort study (prospective)	Infantile spasms	104 (mean 1.2 y)	Classical 3:1 or 3.5:1	19 (18%) seizure-free 14 (13%) 90%-99% reduction 33 (32%) 50%-90% reduction 38 (37%) <50% reduction	29 (28%) seizure-free 12 (11%) 90%-99% reduction 26 (25%) 50%-90% reduction 37 (36%) <50% reduction	31 (30%) seizure-free 14 (13%) 90%-99% reduction 35 (34%) 50%-90% reduction 24 (23%) <50% reduction	At 9 mo: 33 (32%) seizure-free 15 (14%) 90%-99% reduction 28 (27%) 50%-90% reduction 28 (27%) <50% reduction At 24 mo: 34 (33%) seizure-free 12 (11%) 90%-99% reduction 34 (33%) 50%-90% reduction 24 (23%) <50% reduction	86 (83%) on diet at 3 mo 76 (73%) on diet at 6 mo 53 (51%) on diet at 9 mo 47 (45%) on diet at 12 mo 28 (27%) on diet at 24 mo

(Continues)

TABLE 1 (Continued)

Study	Type of study	Epilepsy/seizure types	Number of participants starting diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%[a])	Seizure outcome (6 mo), n (%[a])	Seizure outcome (12 mo), n (%[a])	Seizure outcome (other), n (%[a])	Retention, n (%[a])
Pires et al 2013[23]	Single-arm cohort study (prospective)	Infantile spasms refractory to vigabatrin and hydrocortisone	17 (4-23 mo)	Classical 3:1 or 4:1	11 (65%) seizure-free 4 (24%) 50%-99% reduction 2 (12%) <50% reduction	9 (56%) seizure-free 5 (44%) 50%-99% reduction 2 (13%) <50% reduction	–	At 1 mo: 6 (35%) seizure-free 7 (41%) 50%-99% reduction 4 (24%) <50% reduction	17 (100%) on diet at 3 mo 16 (94%) on diet at 6 mo
Ismayilova et al 2018[42]	Single-arm cohort study (retrospective)	Structural causes, n = 8 Metabolic causes, n = 2 Genetic causes, n = 2 Unknown (likely genetic) causes, n = 10 Unknown causes, n = 1	29 (2.5 wk-23 mo)	Classical 3:1; MCT KD (n = 1)	7 (24%) >50% seizure reduction 3 (10%) <50% seizure reduction (but still some decrease in seizure frequency)	–	–	At 1 mo: 7 (24%) >50% seizure reduction At unknown time point: 2 (7%) seizure-free	24 (83%) on diet at 1 mo 10 (34%) on diet at 6 mo

(Continues)

TABLE 1 (Continued)

Study	Type of study	Epilepsy/seizure types	Number of participants starting diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%[a])	Seizure outcome (6 mo), n (%[a])	Seizure outcome (12 mo), n (%[a])	Seizure outcome (other), n (%[a])	Retention, n (%[a])
Wirrell et al 2018[25]	Single-arm cohort study (retrospective)	West syndrome, n = 11 Epilepsy in infancy with migrating focal seizures, n = 5 Early myoclonic encephalopathy, n = 1 Ohtahara syndrome, n = 1 Dravet syndrome, n = 1 Undiagnosed epilepsy syndrome, n=7 Etiology: Genetic, n = 9 Genetic-structural, n = 1 Structural-malformative, n = 1 Structural-acquired, n = 6 Metabolic, n = 2 Unknown, n = 8	26[c] (median 7 mo, interquartile range 5, 11 mo)	Classical, initiated at 2:1. Median ratio at discharge: 3.0 (interquartile range 2.5, 3.25)	9 (35%) seizure-free 7 (27%) 50%-99% seizure reduction	5 (19%) seizure-free 9 (25%) 50%-99% seizure reduction	3 (12%) seizure-free 7 (27%) 50%-99% seizure reduction	At 1 mo: 5 (19%) seizure-free 12 (46%) 50%-99% seizure reduction At 24 mo: 2 (8%) seizure-free 4 (15%) 50%-99% seizure reduction	25 (96%) on diet at 1 mo 20 (77%) on diet at 3 mo 17 (65%) on diet at 6 mo 11 (42%) on diet at 12 mo 7 (27%) on diet at 24 mo

Abbreviations: d, day(s); KD, ketogenic diet; mo, month(s); MCT, medium chain triglyceride; y, year(s).

[a]Presented as a percentage of individuals starting ketogenic dietary therapy (intent-to-treat).

[b]Includes patients also reported in Kossoff et al 2002; 2008 and Rubenstein et al 2005.

[c]Excluding one patient with GLUT1-DS with no seizures.

TABLE 2 Summary of studies including infants following ketogenic diet therapy for drug-resistant epilepsy (studies including infants as part of a wider cohort)

Study	Type of study	Epilepsy/seizure types	Number of participants starting diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%[a])	Seizure outcome (6 mo), n (%[a])	Seizure outcome (12 mo), n (%[a])	Seizure outcome (other), n (%[a])	Retention, n (%[a])
Freeman et al 1998[51]	Single-arm cohort study (prospective)	Unspecified for infants	27 (1-2 y)	Classical 3:1 or 4:1	0 seizure-free 6 (22%) 90%-99% reduction 11 (41%) 50%-90% reduction 7 (26%) <50% reduction	1 (4%) seizure-free 8 (30%) 90%-99% reduction 7 (26%) 50%-90% reduction 7 (26%) <50% reduction	1 (4%) seizure-free 6 (22%) 90%-99% reduction 9 (33%) 50%-90% reduction 1 (4%) <50% reduction	–	Unknown for infants
Maydell et al 2001[38]	Single-arm cohort study (retrospective)	Unspecified for infants	15 (4 mo-2 y)	Classical 4:1	7 (46%) >50% reduction	8 (53%) >50% reduction	7 (46%) >50% reduction	–	Unknown for infants
Coppola et al 2002[41]	Single-arm cohort study (prospective)	'Clastic' aetiology	1 (<2 y)	Classical 4:1	1 (100%) seizure-free	1 (100%) seizure-free	–	At 1 mo: 1 (100%) seizure-free	1 (100%) on diet at 6 mo 0 on diet at 12 mo
Takeoka et al 2002[52]	Single-arm cohort study (retrospective)	'Cryptogenic' aetiology	1 (1 y)	Classical 4:1 (212 d of cotreatment with topiramate)	–	–	–	At unknown time point: 1 (100%) seizure-free	Unknown for infants
Hosain et al[53]	Single-arm cohort study (prospective)	Mycolonic and generalised tonic clonic seizures, n = 1 Tonic and generalised tonic clonic seizures, n = 1 Generalised tonic clonic and atypical absence seizures, n = 1 Generalised tonic clonic and gelastic seizures, n = 1	4 (7-23 mo)	Classical 3:1 or 4:1	–	–	1 (25%) >90% seizure reduction 3 (75%) 50%-90% reduction	–	Unknown

(Continues)

TABLE 2 (Continued)

Study	Type of study	Epilepsy/seizure types	Number of participants starting diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%[a])	Seizure outcome (6 mo), n (%[a])	Seizure outcome (12 mo), n (%[a])	Seizure outcome (other), n (%[a])	Retention, n (%[a])
Kang et al 2005[39]	Single-arm cohort study (retrospective)	Unspecified for infants	49 (6 mo-2 y)	Classical 4:1	16 (33%) seizure-free 12 (24%) 50%-99% reduction	18 (37%) seizure-free 9 (18%) 50%-99% reduction	13 (27%) seizure-free 3 (6%) 50%-99% reduction	–	42 (86%) on diet at 3 mo 30 (61%) on diet at 6 mo 13 (27%) on diet at 12 mo
Eun et al 2006[32]	Single-arm cohort study (retrospective)	Infantile spasms	10 (≤12 mo)	Classical 3:1 or 4:1	–	–	–	At unspecified time point (diet duration in whole cohort 1-36 mo): 6 (60%) seizure-free	Unknown for infants
Dahlin et al 2007[35]	Single-arm cohort study (prospective)	Hypoxic-ischemic encephalopathy, n = 1 Cortical dysplasia, n = 1	2 (both 1.5 y)	Classical 3:1	1 (50%) >50% reduction 1 (50%) <50% reduction	1 (50%) >50% reduction 1 (50%) <50% reduction	1 (50%) >50% reduction	–	1 (50%) on diet at 12 mo
Villeneuve et al 2009[36]	Single-arm cohort study (retrospective)	Focal cortical dysplasia, n = 3 Sturge-Weber syndrome, n = 1 Polymicrogyria, n = 1	5 (5 mo-1 y 1 mo)	Classical 4:1	–	–	–	At 1 mo: 1 (20%) >90 reduction 4 (80%) <50% reduction	3 (60%) on diet at 3 mo 3 (60%) on diet at 6 mo 1 (20%) on diet at 12 mo
Coppola et al 2010[31]	Single-arm cohort study (prospective)	Generalized encephalopathy, n = 5 Myoclonic status in fixed encephalopathy, n = 1 Partial secondary generalised epilepsy, n = 1 Lennox-Gastaut Syndrome, n = 1 West syndrome, n = 1 Malignant migrating partial seizures, n = 1 Ohtahara syndrome, n = 1	11 (4-23 mo)	Classical 4:1	–	–	–	At unspecified time point: 9 (82%) ≥50% seizure reduction	Unknown for infants

(Continues)

TABLE 2 (Continued)

Study	Type of study	Epilepsy/seizure types	Number of participants starting diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%[a])	Seizure outcome (6 mo), n (%[a])	Seizure outcome (12 mo), n (%[a])	Seizure outcome (other), n (%[a])	Retention, n (%[a])
Tonekaboni et al 2010[54]	Single-arm cohort study (prospective)	Unspecified for infants	3 (<2 y)	"Atkins diet" (60% fat, 30% protein, carbohydrates initially limited to 10 g/d)	1 (33%) seizure-free 1 (33%) 50%-90% reduction 1 (33%) <50% reduction	–	–	–	Unknown
Dahlin et al[18] (also reported in Dahlin et al 2005)	Single-arm cohort study (prospective)	Ohtahara syndrome	1 (1.3 y)	Classical 3:1	1 (100%) >50% reduction	–	–	–	Unknown
Jung et al 2012[30]	Single-arm cohort study (retrospective)	Infantile spasms	2 (1 y 1 mo-1 y 3 mo)	Classical 3:1 or 4:1	–	–	–	At last follow-up (unknown time point): 1 (50%) seizure-free 1 (50%) 50%-90% seizure reduction	Unknown
Kumada et al 2012[24]	Single-arm cohort study (prospective)	Infantile spasms, n = 2 Symptomatic localization-related epilepsy, n = 1	3	MAD (10 g carbohydrate/d)	–	–	–	At 3 wk: 1 (33%) seizure-free 1 (33%) <50% reduction At last visit (unknown time point): 2 (100%) seizure-free	1 (33%) withdrew after 7 d on diet 2 (66%) on diet at 6 mo
Larson et al[37]	Single-arm cohort study (retrospective)	Tuberous sclerosis complex	2 (both 1.8 mo)	LGIT	–	–	–	Peak improvement at unspecified time point: 1 (50%) seizure-free 1 (50%) 50%-90% reduction	2 (100%) on diet at 12 mo 1 (50%) on diet at 24 mo

(Continues)

TABLE 2 (Continued)

Study	Type of study	Epilepsy/seizure types	Number of participants starting diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%[a])	Seizure outcome (6 mo), n (%[a])	Seizure outcome (12 mo), n (%[a])	Seizure outcome (other), n (%[a])	Retention, n (%[a])
Sharma et al 2012[27]	Single-arm cohort study (prospective)	Infantile spasms	6 (6.5-21 mo)	MAD (10 g carbohydrate/d)	3 (50%) seizure-free 3 (50%) <50% reduction	–	–	–	Unknown
Caraballo et al 2014[b,40]	Single-arm cohort study (retrospective)	Refractory status epilepticus	1 (0.5 y)	Classical 4:1	–		–	At 2 mo: 1 (100%) 50%-74% reduction	1 (100%) on diet for 2 mo
Dressler et al 2015[22]	Single-arm cohort study (retrospective)[c]	Unspecified for infants	58 (<1.5 y)	Classical 2.5:1 or 3:1	20 (35%) seizure-free 17 (29%) 50%-99% reduction	19 (33%) seizure-free 13 (22%) 50%-99% reduction	19 (33%) seizure-free 8 (14%) 50%-99% reduction	–	Mean treatment duration in infants 0.68 ± 0.41 y
Hirano et al 2015[26]	Single-arm cohort study (retrospective)	West syndrome	5 (9-20 mo)	Classical 3:1 or 4:1	1 (20%) seizure-free 4 (80%) ≥80% reduction	–	–	–	Unknown
van der Louw et al 2015[55]	Single-arm cohort study (retrospective)	Unspecified for infants	25 (<2 y)	Not specified for this age group (Classical, MCT KD or "Combination" in whole cohort)	14 (56%) >50% reduction	–	–	–	Unknown
Vehmeijer et al 2015[56]	Single-arm cohort study (retrospective)	Unspecified for infants	16 (<2 y)	Not specified for this age group (Classical, MCT KD or 'Combination' in whole cohort)	–	–	5 (31%) ≥50% reduction	–	Unknown

(Continues)

TABLE 2 (Continued)

Study	Type of study	Epilepsy/seizure types	Number of participants starting diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%[a])	Seizure outcome (6 mo), n (%[a])	Seizure outcome (12 mo), n (%[a])	Seizure outcome (other), n (%[a])	Retention, n (%[a])
Kim et al 2016[20]	Randomised controlled trial (prospective)	Unspecified for infants	37 (17 on classical KD, 20 on MAD) (1-<2 y)	Classical 4:1 and MAD	Classical:[b] 9 (53%) seizure-free 1 (6%) 50%-90% reduction MAD: 4 (20%) seizure-free 1 (5%) >90% reduction 3 (6%) 50%-90% reduction	Classical:[b] 9 (53%) seizure-free 1 (6%) 50%-90% reduction MAD: 5 (25%) seizure-free 2 (10%) >90 reduction 2 (10%) 50%-90% reduction	–	–	Unknown
Wu et al 2016[57]	Single-arm cohort study (prospective)	Unspecified for infants	6 (<1 y)	Classical 4:1	1 (17%) seizure-free 1 (17%) 50%-90% reduction 4 (67%) <50% reduction	1 (17%) seizure-free 1 (17%) 50%-90% reduction 4 (67%) <50% reduction	–	At 1 wk: 0 (0%) seizure-free 1 (17%) 50%-90% reduction 5 (83%) <50% reduction At 1 mo: 2 (33%) seizure-free 1 (17%) 50%-90% reduction 3 (50%) <50% reduction	Unknown
Sampaio et al[28]	Single-arm cohort study (prospective)	West syndrome	1 (1.5 y)	Classical 4:1	1 (100%) 75% reduction	–	–	–	Unknown
Yan et al 2018[34]	Single-arm cohort study (prospective)	Dravet syndrome	6 (9-23 mo)	Classical 4:1	6 (100%) ≥50% reduction	–	–	–	Unknown

(Continues)

TABLE 2 (Continued)

Study	Type of study	Epilepsy/seizure types	Number of participants starting diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%[a])	Seizure outcome (6 mo), n (%[a])	Seizure outcome (12 mo), n (%[a])	Seizure outcome (other), n (%[a])	Retention, n (%[a])
Zhang et al 2018[29]	Single-arm cohort study (prospective)	West syndrome, n = 1 Dravet syndrome, n = 1	2 (1.2 and 1.8 y)	Classical 4:1	–	1 (50%) 50%-90% reduction 1 (50%) <50% reduction	–	–	Unknown
Dressler et al 2018[21]	Single-arm cohort study (prospective)	West syndrome, n = 7 Ohtahara syndrome, n = 3 Focal epilepsy, n = 2 Partial migrating seizures, n = 1	11 (0.03-1.38 y)[d]	Classical (parenteral nutrition preceded/followed by enteral nutrition)	3 (27%) seizure-free[e] 5 (55%) 50%-90% reduction[e] 3 (27%) <50% reduction[e]	–	–	–	Duration of parenteral KD: range 1-19 d For those on enteral KD prior to parental KD, time on diet ranged from 2 wk to 3.5 y
Dressler et al 2019[f,19]	parallel-cohort and randomised controlled trial (prospective)	West syndrome	16 Median (minimum-maximum) age at epilepsy onset 4.9 mo (0-12) Median (minimum-maximum) time from epilepsy onset to trial treatment 4.9 d (0-12)	Classical 3:1	–	–	–	At 1 mo: 10/16 (62%) seizure-free	Unknown

Abbreviations: KD, ketogenic diet; LGIT, Low Glycaemic Index Treatment; mo, month(s); MAD, Modified Atkins Diet; y, year(s).

[a]Presented as a percentage of individuals starting ketogenic dietary therapy (intent-to-treat).

[b]Inconsistent age data presented in article: Table 1 states Patient 3 was age 0.5 y at diet initiation, in text, stated 'age of the patients ranged from 2 to 9 y'.

[c]Study includes comparative component but all cases exposed to KD treatment.

[d]For patients who had already been treated with an enteral KD, age was calculated as 'age at initiation of parenteral KD minus 3 mo or, for patients who had followed an enteral KD for <3 mo, minus the number of months for which enteral KD had been followed.

[e]When parenteral KD was used in children who had been already treated with an enteral KD, treatment response was defined as maintenance of the previously achieved ≥ 50% reduction compared to baseline, defined as the 3 mo before initiation of parenteral KD. In cases where parenteral KD was the initial treatment, response was defined as the absolute reduction in seizure frequency ≥ 50% after 3 mo of KD treatment.

[f]Results presented for individuals randomised to KDT. Age at epilepsy onset and Time from epilepsy onset to trial treatment (median, minimum and maximum) indicates that some individuals in the parallel cohort were aged > 2 y at diet start (no age-specific diet efficacy data given).

A total of 52 of 100 infants (52%) achieved ≥50% seizure reduction after 1 month (range 20%-100%; median 63%; IQR 34%), 24 of which (24% of the whole group) were seizure-free (range 0%-100%; median 33%; IQR 39%).

A total of 256 of 430 infants (60%) achieved ≥50% seizure reduction after 2-3 months (range 24%-100%; median 63%; IQR 41%), 98 of which (23% of the whole group) were seizure-free (range 0%-100%; median 19%; IQR 35%).

A total of 202 of 344 infants (59%) achieved ≥50% seizure reduction after 6 months (range 33%-100%; median 54%; IQR 10%), 97 of which (28% of the whole group) were seizure-free (range 0%-100%; median 24%; IQR 34%).

A total of 166 of 301 infants (55%) achieved ≥50% seizure reduction after 12 months (range 31%-100%; median 47%; IQR 21%), 67 of which (22% of the whole group) were seizure-free (range 0%-33%; median 4%; IQR 27%).

Two studies reported efficacy data for longer periods than 12 months[17,25]: 86 of 130 infants (66%) achieved ≥50% seizure reduction after 24-month follow-up (range 23%-770%; median 50%; IQR 27%), 36 of which (28% of the whole group) were seizure-free (range 8%-33%; median 20%; IQR 13%).

For studies giving efficacy rates at unspecified time points, 37 of 87 infants (43%) achieved ≥50% seizure reduction, 17 of which (20% of the whole group) were seizure-free.

When only prospective studies (n = 18) were included, 140 of 221 (63%) achieved ≥50% reduction at 3 months, 52 of which (24% of the whole group) were seizure-free; 140 of 233 (60%) achieved ≥50% reduction at 6 months, 69 of which (30% of the whole group) were seizure-free; and 101 of 137 (74%) achieved ≥50% reduction at 12 months, 32 of which (23% of the whole group) were seizure-free.

From case studies, 35 of 46 (76%) achieved ≥50% reduction, 23 of which (50% of 46) were seizure-free.

3.3.2 | Randomized-controlled trials

One RCT compared classical KD to MAD in children 1-18 years of age,[20] including 37 infants aged 1 to <2 years. At 3 months, 9 of 17 (53%) receiving classical KD were seizure-free and 10 of 17 (59%) achieved >50% seizure reduction, compared to 4 of 20 (20%) seizure-free and 8 of 20 (40%) with >50% seizure reduction on MAD. At 6 months, 9 of 17 (53%) on classical KD were seizure-free and 10 of 17 (59%) achieved >50% seizure reduction, compared to 5 of 20 (25%) seizure-free and 9 of 20 (45%) with >50% seizure reduction on MAD.

The other RCT compared classical KD to standard adrenocorticotropic hormone (ACTH) treatment in infants with West syndrome.[19] Ten of 16 (62%) in the KD group and 11 of 16 (69%) in the ACTH group achieved the primary end point of electroclinical seizure remission at 28 days. Six of 16 (38%) in the KD group and 7 of 16 (44%) in the ACTH group remained seizure-free at last follow-up.

3.3.3 | Predictors of efficacy

Response (≥50% seizure reduction or seizure freedom) at 3 months (n = 33 from eight studies) and at unspecified time points (n = 49 from six studies) was not associated with gender, age at diet onset, or number of failed AEDs; age at seizure onset was higher in infants who achieved seizure freedom at 3 months ($Z = -2.162$, $P = .036$) (Tables S2-S5). Association with response at other time points was not evaluated as data were available for <7 infants.

Response rates separated by epilepsy syndrome are detailed in Supporting Information. Response rates were not separated into epilepsy or seizure type, as these were grouped inconsistently.

3.3.4 | Meta-analysis of uncontrolled studies

Including all 33 studies, the pooled response proportion was 0.58 (95% CI 0.52-0.64), with moderate heterogeneity ($I^2 = 23\%$; $\tau^2 = 0.0879$; $\chi^2 = 41.58$, $df = 32$, $P = .1196$). Near-significant heterogeneity was explained by study design ($I^2 = 17.54\%$, $R^2 = 23.56\%$, $Q(df = 1) = 3.5459$, $P = .0597$), but not by whether response was taken at 3 months or at other time points ($R^2 = 0.00\%$, $I^2 = 25.20\%$, $Q(df = 1) = 0.0069$, $P = .9340$), or if the study included solely infants or infants as part of a wider cohort ($R^2 = 0.00\%$, $I^2 = 25.44\%$, $Q(df = 1) = 0.1407$, $P = .7076$). Removal of two outliers and accounting for subgroups by study design reduced heterogeneity ($I^2 = 0\%$; $\tau^2 = 0.07$; $\chi^2 = 28.75$, $df = 30$, $P = .53$), with a pooled response proportion of 0.59 (95% CI 0.53-0.65; Figure 2).

When response was classified as seizure freedom, no outliers were identified and there were no significant effects of study design ($R^2 = 0.00\%$, $I^2 = 54.57\%$, $Q(df = 1) = 0.3228$, $P = .5699$), response time ($R^2 = 3.96\%$, $I^2 = 50.96\%$, $Q(df = 1) = 2.2266$, $P = .1356$), or whether the study included solely infants ($R^2 = 15.33\%$, $I^2 = 45.97\%$, $Q(df = 1) = 2.1673$, $P = .1410$). The overall proportion of responders was 0.34 (95% CI 0.26-0.43; Figure 3); moderate heterogeneity remained ($I^2 = 52\%$; $\tau^2 = 0.3395$; $P < .01$).

3.4 | Diet initiation protocols

Of the five studies that included solely infants, two of five o (40%) adopted a fasting protocol for KDT initiation,[17,33] and three of four (75%) admitted all, or almost all, infants.[23,25,33]

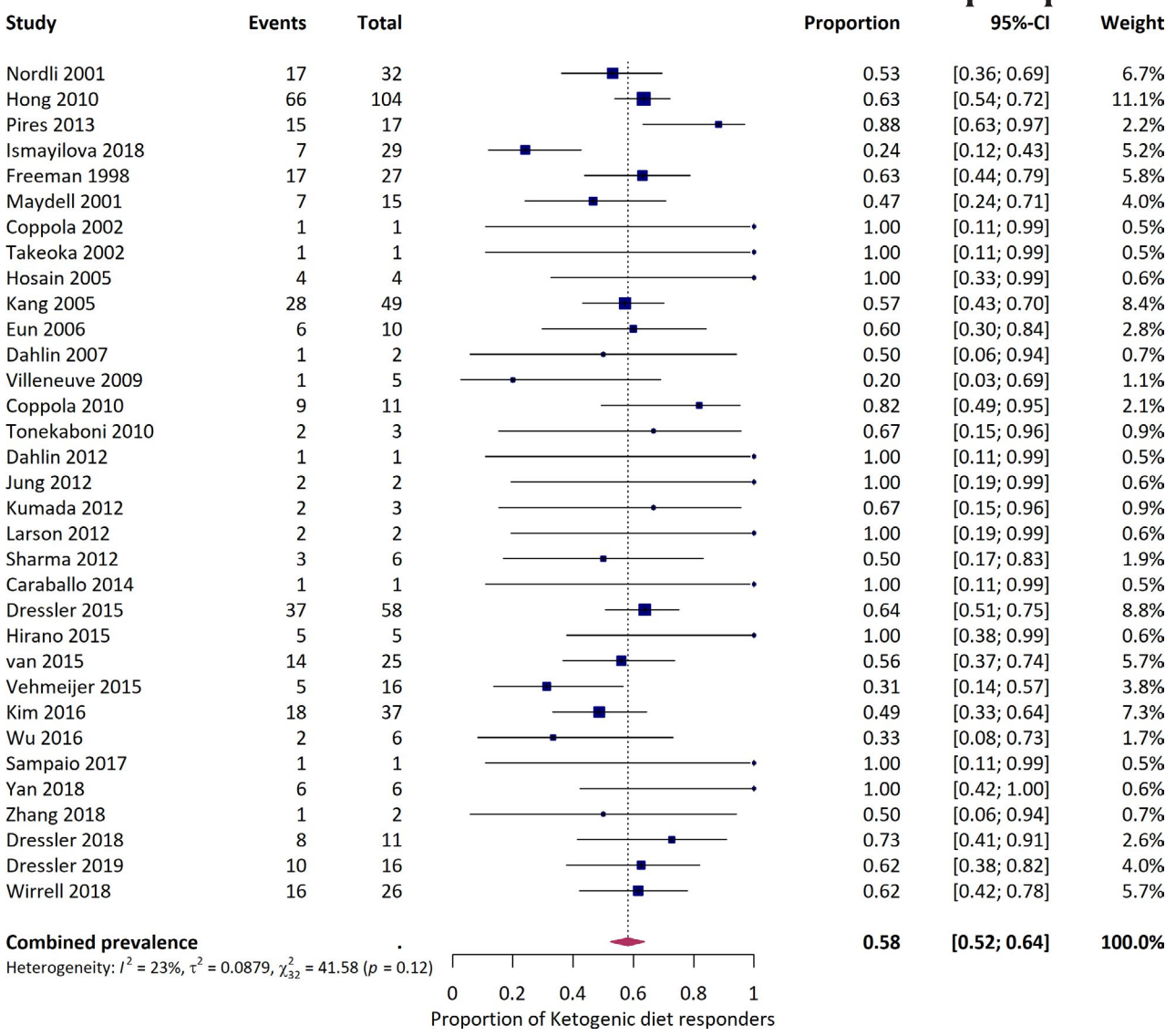

FIGURE 2 Proportion of responders to ketogenic diet therapy, defined as ≥50% seizure reduction at 3 mo follow-up (or at an unspecified time point where 3 mo data are not available). The vertical dotted line is placed at the point estimate of the summary proportion, with the horizontal tips of the diamond representing the 95% confidence interval of the summary proportion using a random-effects model. The squares represent the point estimate of each study, with the horizontal lines representing the 95% confidence interval around the point estimate. The size of each square is proportional to the weight of the study in the pooled estimate. Estimates are separated into prospective (prosp) and retrospective (retro) studies, and pooled proportions including all studies

Three studies[17,25,33] reported that they monitored blood glucose, either "periodically," with "any episode of emesis or reduced oral intake" or, for specific patients, regular checks every 6-12 hours. Two studies reported that full caloric requirements were prescribed.[25,33]

3.5 | Retention rates

Minimum duration of dietary treatment was 1 month (due to our review criteria), and longest duration was 58 months.[38]

Retention rates at 3, 6, 12, and 24 months were given in 12 studies. Aggregated rates were 197 of 235 (84%) at 3 months,[17,23,25,33,36,39–41] 180 of 266 (68%) at 6 months[17,23–25,33,36,39,41,42] (10 month retention data used from Ismayilova et al[42]), 96 of 211 (43%) at 12 months,[17,25,33,35–37,39,41] and 36 of 132 (27%) at 24 months.[17,25,37]

All individuals in the above studies were following a classical KD, with the exception of n = 1 on an MCT KD[42] (unknown diet duration), n = 3 on a MAD[24] (one on diet for 7 days; one still on diet at 6 months; and another still on diet

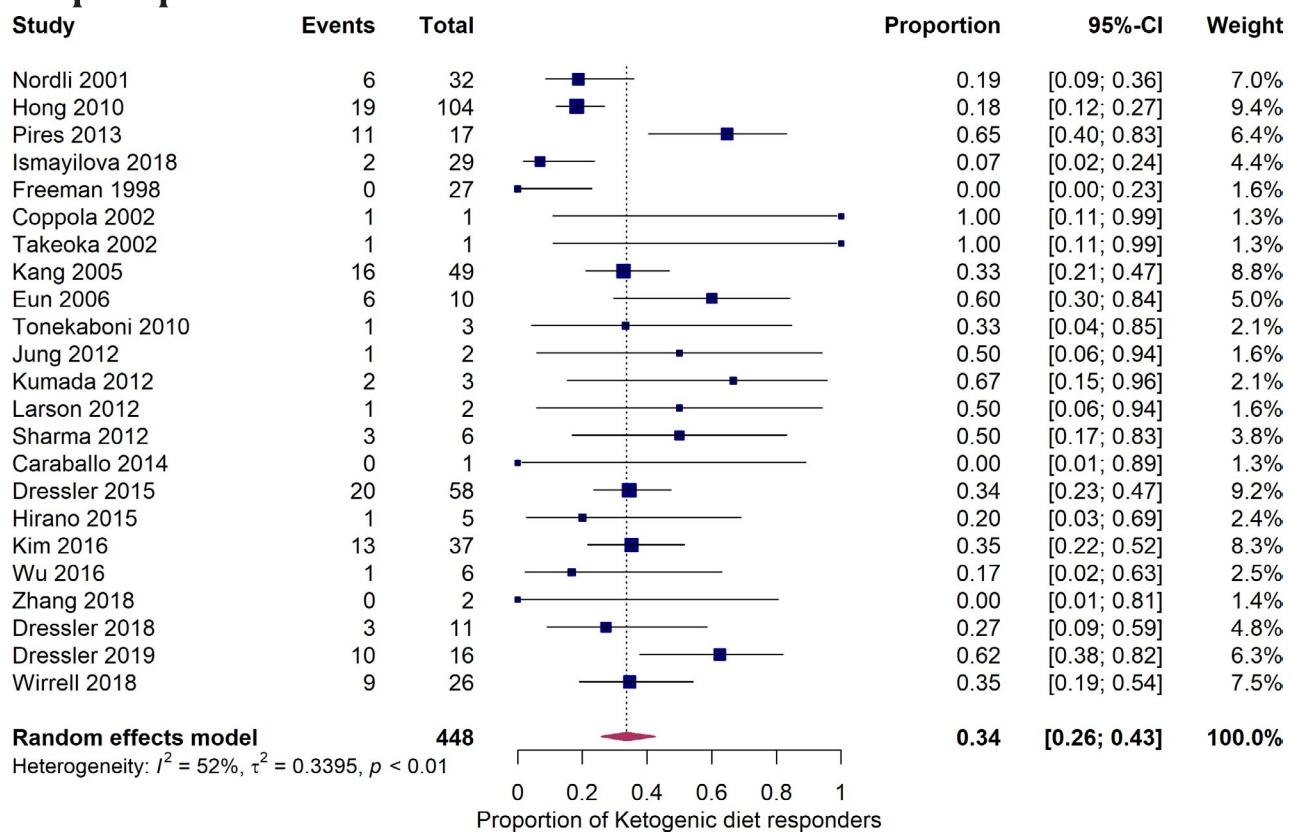

FIGURE 3 Proportion of responders to ketogenic diet therapy, defined as seizure freedom at 3 mo follow-up (or at an unspecified time point where 3 mo data are not available). The vertical dotted line is placed at the point estimate of the summary proportion, with the horizontal tips of the diamond representing the 95% confidence interval of the summary proportion, using a random-effects model. The squares represent the point estimate of each study, with the horizontal lines representing the 95% confidence interval around the point estimate. The size of each square is proportional to the weight of the study in the pooled estimate

at 8 months at the time of publication), and n = 2 on LGIT[37] (one on diet for 16 months and one on diet for 24 months).

Reasons given for diet discontinuation are summarized below (percentages are calculated from the total number of infants who had reasons reported for KDT discontinuation in each study):

1. Inefficacy, n = 61/105 (58%).[17,25,42]
2. Adverse effects, n = 6/22 (27%): n = 1 comatose with hypoglycemia and acidosis[33]; n = 1 with "generalised fatigue with severe metabolic acidosis" (this patient subsequently restarted the diet with no difficulties)[24]; n = 2 "poor tolerability"[42]; n = 1 "markedly elevated triglyceride level"; n = 1 dehydration and ketoacidosis.[25]
3. Intercurrent rotavirus enterocolitis, n = 1/2 (50%).[24]
4. Seizure-free, n = 1/9 (11%).[25]

Kossoff et al[13] also detailed reasons for diet discontinuation, which included perceived ineffectiveness (n = 9), seizure freedom (n = 4), intercurrent viral illness (n = 3), and feelings of restrictiveness (n = 2). Diet duration from case studies ranged from 2 months to 8 years.

3.6 | Adverse side effects

Adverse side effects were reported in 83 infants, across six studies including a total of 171 infants (Table 3). The most commonly reported side effects were dyslipidemia (20/171, 12%), vomiting (11/171, 6%), constipation (7/171, 4%), gastroesophageal reflux (6/171, 4%), and diarrhea (6/171, 4%). The time points at which side effects occurred was mostly unspecified (Table 3). Vomiting was more frequently reported within the first 3 months of KDT.

Dyslipidemia was reported in 17 of 104 infants (16%) in one study,[17] although only one child required dietary intervention to resolve this. Another study reported a mild elevation in serum triglycerides in one infant, who continued the diet, and "markedly elevated triglyceride level concerning for lipoprotein lipase deficiency" in another[25]; one infant had type I hyperlipidemia after following KDT for 23 months.[33]

Seventeen deaths were reported in infants either during or after KDT, of which 14 were believed to be due to the underlying disease or intercurrent illness, rather than the diet per se.[25,33,42] For the three deaths reported by Hong et al,[17] it was not stated whether they were thought to be related to KDT or not.

TABLE 3 Reported adverse side effects in infants following ketogenic diet therapy

Adverse side effect	Nordli et al[33] (n = 32)	Hong et al[17] (n = 104)	Takeoka et al[52] (n = 1)	Jung et al[30] (n = 2)	Hirano et al[26] (n = 5)	Wirrel et al[25] (n = 26)	Total (n = 171 (%))	Adverse effect reported within first 3 mo on diet?
Dyslipidaemia	1	17	–	–	–	2	20 (12%)	Yes, n = 2 No = 1 Unknown, n = 17
Vomiting	1	–	1	2	3	4	11 (6%)	Yes, n = 6 No, n = 2 Unknown, n = 3
Constipation	–	7	–	–	–	–	7 (4%)	Unknown n = 7
Gastroesophageal reflux	–	6	–	–	–	–	6 (4%)	Unknown, n = 6
Diarrhoea	–	3	–	1	1	1	6 (4%)	No, n = 1 Unknown, n = 5
Refusal to eat and/or drink	–	–	–	–	2	3	5 (3%)	Yes, n = 2 No, n = 1 Unknown, n = 2
Renal stones	1	3	–	–	1	–	5 (3%)	Yes, n = 1 No, n = 1 Unknown, n = 3
Acidosis	–	3	–	–	–	1	4 (2%)	Yes, n = 1 Unknown, n = 3
Behavioural problems	–	3	–	–	–	–	3 (2%)	Unknown, n = 3
Haematuria	–	3	–	–	–	–	3 (2%)	Unknown, n = 3
Hair thinning	–	2	–	–	–	–	2 (1%)	Unknown, n = 2
Hypercalcemia	–	2	–	–	–	–	2 (1%)	Unknown, n = 2
Hypoglycaemia	–	–	–	–	–	2	2 (1%)	
Gastrointestinal bleeding	1	–	–	–	–	–	1 (1%)	No, n = 1
Ulcerative colitis	1	–	–	–	–	–	1 (1%)	No, n = 1
Coma with hypoglycaemia and acidosis	1	–	–	–	–	–	1 (1%)	Yes n = 1
Weight gain	–	–	–	–	1	–	1 (1%)	Unknown, n = 1
Weight loss	–	–	–	–	–	1	1 (1%)	Yes, n = 1
Dry skin	–	1	–	–	–	–	1 (1%)	Unknown, n = 1
Pica	–	1	–	–	–	–	1 (1%)	Unknown, n = 1
Hypokalaemia	–	–	–	–	1	–	1 (1%)	Yes, n = 1
Poor water intake	–	–	–	–	1	–	1 (1%)	Unknown, n = 1
Dehydration	–	–	–	–	–	1	1 (1%)	Yes, n = 1

Note: The following studies are not included in the table, as they provided limited details about adverse side effects: Pires et al[23] reported 'None of our patients had major side effects'; Ismayilova et al reported 'Seventy-five percent patients experienced no side-effects or had only mild vomiting or constipation. Adverse biochemical events (for example: hypervitaminosis E, hypercholesterolaemia, or zinc level disturbances) were found in 38% patients, but in no case was of sufficient severity alone to discontinue KD'[42].

4 | DISCUSSION

This review suggests that KDT can be an effective treatment for reducing seizure frequency in infants with epilepsy. Approximately 60% infants achieved ≥50% seizure reduction, with 33% becoming seizure-free. Results from RCTs were similar or higher than pooled results from uncontrolled studies. Caution must be exercised when interpreting overall

response rates due to interstudy heterogeneity and low-quality data.

Our findings are consistent with a recent review of observational studies, in which 57.4% infants with infantile spasms achieved >50% seizure reduction and 33.63% became seizure-free within 6 months of KDT.[43] Response rates in infants seem comparable to rates in older children, if not more promising. A systematic review looking at the KDT efficacy in children younger than 18 years of age (one study also included adults), in uncontrolled studies only, estimated 56% participants to achieve ≥50% seizure reduction and 16% becoming seizure-free.[44] There have since been three RCTs comparing KDT to a control group in children 2 years of age or older[7,45,46]; 38%-56% participants achieved ≥50% seizure reduction and 1%-15% became seizure-free.

Potential higher response rates in infants compared to older individuals may be due to increased compliance or biological factors. The suggestion that higher age at seizure onset is associated with increased likelihood of seizure freedom at 3 months is consistent with findings from individual studies in our review, but conflicts with others: Older age at spasm onset has been associated with increased likelihood of >90% improvement in spasm frequency at 6 months,[17] but higher seizure freedom rates have been reported in children age <1.5 years compared to >1.5 years,[22] and children <12 months of age have been reported to have a "tendency for a better response" compared to those aged >12 months.[42] Response rates in patients with Dravet syndrome, Ohtahara syndrome, tuberous sclerosis complex, and generalized encephalopathy may be particularly high, although numbers included in our review are small. Response rates for those with infantile spasms or West syndrome were in keeping with the wider cohort, although it should be noted that, in these patients, seizure freedom tends to be the desired clinical outcome.

Benefits of KDT in addition to seizure control were also reported, although inconsistently, in our included studies, such as cognitive and behavioral improvements[33] and developmental gains.[13,17,26,42] Authors of a systematic review commented that KDT seemed to have cognitive benefits in a lower proportion of infants compared to older children and adults, but evidence was available from only two infant studies.[47]

Retention rates in infants were comparable to those reported in RCTs, including infants and older children: 74%-90% retention (presented as 10%-26% dropout) at 3-4 months, 66% by 6 months, and 58% at 16 months in individuals following a classical KD.[9] One may expect retention to be higher in infants younger than 2 years, as parents/guardians are, in theory, able to exert a greater degree of control over the infant's diet. However, due to the clinical vulnerability of this age group, the trial period for dietary treatment may be shorter than in older children and adults, leading to more rapid diet discontinuation in the case of ineffectiveness.

Reported adverse side effects in infants were inconsistently reported and thus likely unreported. As in studies of older children, they were commonly gastrointestinal and rarely led to diet discontinuation.[7,48] Dyslipidemia was reported in 12% of infants in our review, similar to older children: 12.8% for hyperlipidemia, including prospective and retrospective studies.[48] Hypoglycemia and renal stones were also reported in a similar proportion of infants (2% and 3% in our review) compared to older children (1.8% and 1.4%, including prospective studies only).[48] The time points at which side effects occurred were inconsistently reported—it would be useful in future studies to guide health care professions and families regarding risk of specific side effects when KDT is initiated and in the longer term. As with all individuals initiating KDT, monitoring for hypoglycemia and excess ketosis is recommended for infants as well as gastrointestinal symptoms.[49] The report of an infant becoming comatose with hypoglycemia and acidosis was in a study where a fasting protocol was adopted,[33] although hypoglycemia also occurred in infants initiated without fasting[25]; both occurred when admitted to start KDT, which is recommended for infants younger than 1 year of age.[49]

There are several limitations of this review. All studies included were rated as "low" quality, including two RCTs, due to lack of blinding (understandably problematic with any "real food" dietary intervention) and the lack of overt validity or reliability of data-collection methods. No studies including age-specific diet efficacy data for infants compared a KDT to placebo or no change in treatment, although, in reality, clinicians are faced with the question of starting KDT or trying another AED, and high-quality evidence comparing these two treatment options may be more appropriate. Other treatment changes, including additional medications, dose reductions, and discontinuation, were not detailed consistently for infants, which may have affected diet-efficacy rates. More infants have been treated with KDT and are published in the literature, but without age-specific diet efficacy data, and so have not been included in this review. Alongside this data-collection bias, publication bias against negative results must also be considered.

Study design explained a significant amount but not all heterogeneity between ≥50% reduction outcomes; our subgroup variables could not explain heterogeneity for seizure-freedom outcomes. Clinical heterogeneity both within and between studies, for example, in terms of epilepsy syndrome, seizure type, concomitant AEDs, and type of KDT, may alter clinical outcome and likely contributed to heterogeneity. Higher quality, more homogenous data may allow

meta-analysis of effect-size metrics that are indicative of a relationship between a treatment and a control group, as well as investigation of whether specific clinical factors are associated with KDT response.

In conclusion, KDT appears to be a promising treatment for epilepsy in infancy, with (mostly mild and transient) adverse side effects and retention rates similar to those in older children. However, a well-conducted RCT is needed including age-specific diet efficacy data for infants. Further investigation is warranted into the long-term efficacy and potential adverse effects of KDT, particularly in this vulnerable age group. In response to these findings, our team is conducting a multicentre RCT to determine the efficacy of the classical KD in infants with epilepsy.[50]

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CONFLICT OF INTERESTS

NS has received honoraria from Nutricia and Vitaflo. JHC has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo, and Marinius. She has been a speaker and on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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