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REVIEW ARTICLE

Effectiveness of medium-chain triglyceride diet and low glycemic index therapy in drug-resistant childhood epilepsy: a systematic review, meta-analysis, and meta-regression

Elbert Wiradarma[1], Herlyani Khosama[1], Finny Warouw[1], Windy M. V. Wariki[2], Seilly Y. Jehosua[1], and Junita Maja Pertiwi[1,3,4]

[1]Department of Neurology, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia
[2]Department of Community Medicine, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia
[3]Memory Clinic, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia
[4]Neurorestoration Clinic, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia

*** Correspondence Author:**
elbertwiradarma@gmail.com

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ABSTRACT

BACKGROUND

Drug-resistant epilepsy (DRE) challenges clinical management, with many patients failing to find relief. Medium-chain triglyceride diet (MCTD) and low glycemic index therapy (LGIT) are emerging variants of the ketogenic diet. MCTD and LGIT show promise but lack clear efficacy data. The purpose of this systematic review was to evaluate and compare the efficacy of MCTD and LGIT in the management of pediatric patients with DRE.

METHODS

Four databases were searched (PubMed, Embase, Scopus, and Cochrane Library) from November 2024 to February 2025. Two independent reviewers meticulously screened titles, abstracts, and full texts, ensuring adherence to predefined criteria. Data extraction encompassed study characteristics, participant demographics, intervention details, and outcomes, including seizure frequency, percentage reduction, and adverse events. Statistical analyses were performed using R 4.2.2 software, assessing heterogeneity with Cochrane Q and I^2 and utilizing random-effects and common-effects models.

RESULTS

From 1489 articles found, 487 duplicates were removed, 897 were excluded based on title and abstract screening, and of the 47 full-text articles assessed for eligibility, 31 articles were excluded, resulting in 16 articles (9 MCTD and 7 LGIT) included in this review. The pooled estimates for the proportion of children achieving seizure freedom, ≥90% seizure reduction, and ≥50% seizure reduction following the intervention were comparable between the MCTD and LGIT groups. Based on the random-effects model, the overall success proportion of MCTD in reducing seizure frequency was 0.20 [95 % Confidence Interval (CI), 0.14-0.27] ($p<0.01$). Meanwhile, in the LGIT group, the overall success proportion was 0.27 [95% CI,0.14- 0.45] ($p<0.01$).

CONCLUSION

Both MCTD and LGIT demonstrate comparable efficacy, and no definitive conclusion can be drawn regarding the superiority of one diet over the other.

Keywords: Childhood epilepsy, drug resistant epilepsy, medium-chain triglyceride diet, low glycemic index therapy, seizure freedom, seizure reduction

INTRODUCTION

Epilepsy is a brain disorder characterized by a persistent tendency to generate recurrent unprovoked seizures, with neurobiological, cognitive, psychological, and social consequences.[1-5] Epilepsy affects approximately 0.5–1% of the global population, corresponding to an estimated 50 million individuals worldwide.[6-9] Among these, 30–40% experience drug-resistant epilepsy (DRE).[10,11] The International League Against Epilepsy (ILAE) defines DRE as the failure of adequate therapy after trying two well-tolerated and appropriately dosed antiepileptic drugs (AEDs), either as monotherapy or in combination, to achieve seizure freedom.[11,12]

Drug-resistant epilepsy responds poorly to pharmacological management and often requires intervention through other modalities such as surgery,[13,14] vagus nerve stimulation,[15] deep brain stimulation,[16] and dietary therapy.[17,18] Dietary therapy for epilepsy has been reported to be effective and safe, and it is one of the non-invasive treatments that can be synergistically combined with other treatment options.[17,19,20] Dietary therapy is recommended for managing drug-resistant epilepsy at all ages, especially in children, as many pediatric epilepsy syndromes are responsive to dietary therapy.[21] Additionally, children are easier to regulate in terms of dietary patterns. Types of dietary therapy for epilepsy include the classic ketogenic diet (CKD), modified Atkins diet (MAD), low glycemic index therapy (LGIT), and medium-chain triglyceride diet (MCTD).[17,22]

The classic ketogenic diet has been proven effective in randomized clinical trials, and its benefits have been reported in various retrospective and prospective observational studies.[23-26] However, some patients find it difficult to adhere to CKD due to its highly restrictive nature and its considerable side effect profile.[17] Therefore, alternative diets such as MAD, LGIT, and MCTD have been studied. The modified Atkins diet is a high-fat, low-protein, and low-carbohydrate diet, but its fat-to-protein and carbohydrate ratio is lower than in CKD.[27-29] Low glycemic index therapy is a high-fat, adequate-protein, and low-carbohydrate diet with a glycemic index of less than 50, making it easier for patients to tolerate.[27,30,31] The medium-chain triglyceride diet is a more flexible diet with high fat, low protein, and low carbohydrate content, but it utilizes medium-chain triglycerides (MCT), which produce more ketones per gram compared to the long-chain triglycerides (LCT) used in CKD. Its high ketogenic potential allows for a reduced intake of fatty acids, enabling greater protein and carbohydrate consumption, making this diet more comfortable and acceptable for children compared to CKD.[27,32,33]

Results from various studies [34-36] indicate that the effectiveness of CKD and MAD in managing pediatric patients with DRE is not significantly different. A meta-analysis conducted by Sharawat et al.[37] also showed that both LGIT and MAD are equally effective in treating pediatric patients with DRE. Hence, to get a clear picture of the effect of MCTD and LGIT on DRE subjects, this systematic review and meta-analysis was conducted to compare the effectiveness of MCTD and LGIT focusing on seizure freedom outcomes and seizure frequency reduction.

METHODS

Protocol registration and reporting

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 (PRISMA 2020) guidelines.[38] Our protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO). The registration number is CRD420251007119 and the link: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251007119.

Search strategy

We searched two electronic databases, namely PubMed/ Medline and Google Scholar. The search terms used were as follows: [(medium-chain triglyceride diet OR MCTD OR medium-chain triglyceride ketogenic diet OR MCTKD) AND (low glycemic index therapy OR low glycemic index treatment OR LGIT) AND (seizure freedom OR seizure reduction)] since the start of the study until February 2025. The citation lists of all identified publications were also

manually searched to identify any additional references. Our searches did not include any restrictions on language, publication year, or country of origin.

Eligibility criteria

The inclusion criteria for this study are as follows: (1) observational studies, (2) pediatric patients with DRE aged ≤18 years who are candidates for dietary therapy, (3) studies using MCTD and LGIT dietary therapy as the intervention, and (4) outcomes of seizure freedom and seizure reduction. The exclusion criteria include symposium proceedings, unpublished dissertations, review articles, previous meta-analysis, and studies that do not meet the inclusion criteria. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart of the searching, identification, and selection of the studies is depicted in Figure 1.

Outcomes

The proportion of reduction in seizures in epileptic patients receiving the MCT and LGIT treatment was one of the outcomes of interest. Also, the relative risk reporting the relationship of reduction of seizure with MCT and LGIT treatment in RCTs was checked. Additionally, the data used to calculate these two measures (proportion and relative risk) were also considered as an outcome.

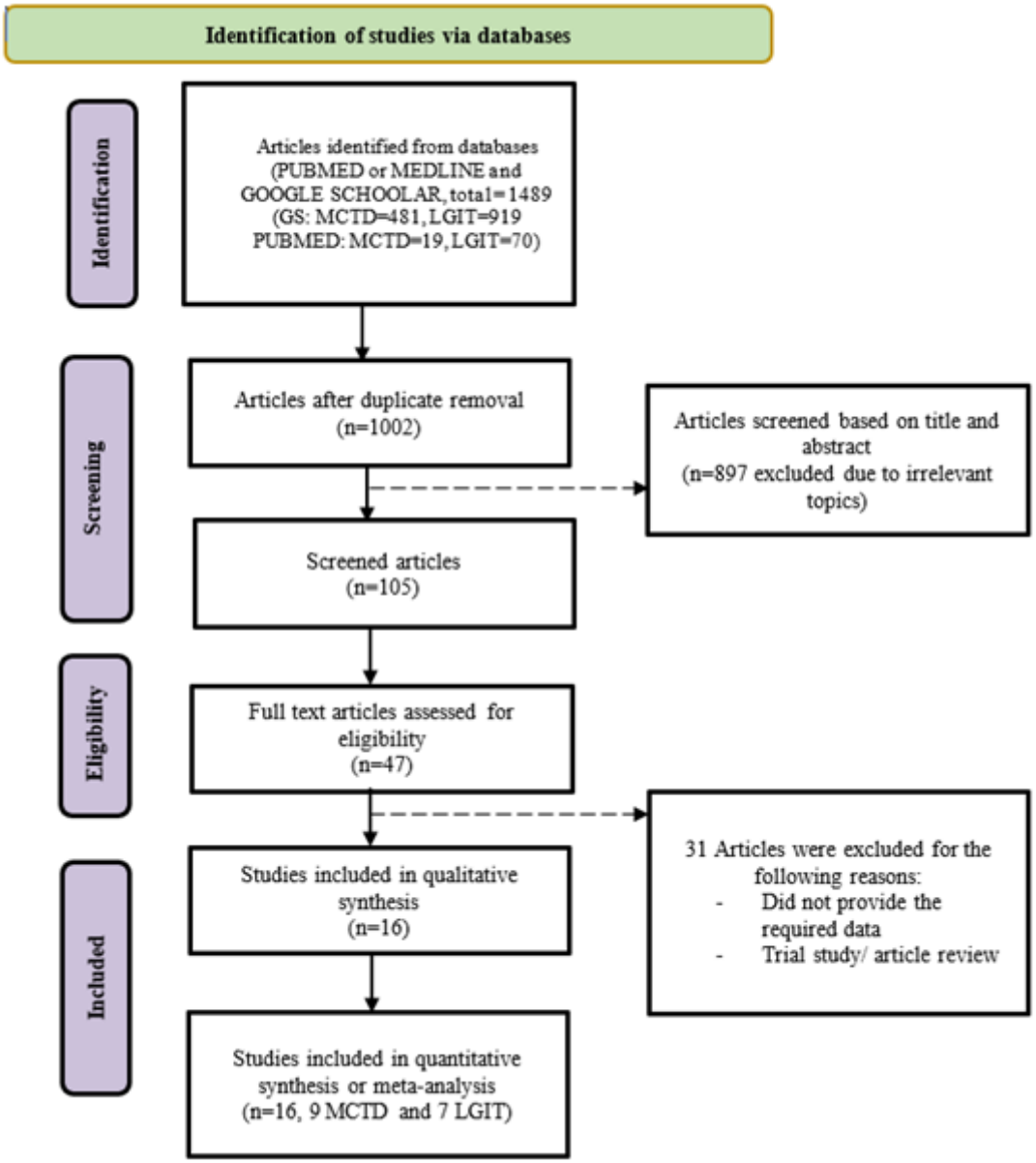

Figure 1. The PRISMA flow diagram: study selection process

Table 1. Characteristics of the studies included in the meta-analysis

Authors	Type of diet	Sample size	Mean age (years)	Follow-up (months)	Success in reducing seizure frequency		
					Free	≥50%	≥90%
Huttenlocher et al. [47]	MCTD	12	10	13	6	1	1
Trauner et al. [48]	MCTD	17	1-13	NR	5	5	NR
Sills et al. [49]	MCTD	50	4	1	9	11	4
Liu et al. [50]	MCTD	43	7.3	NR	9	NR	NR
Lambrechts et al. [51]	MCTD	48	7.8	24	1	7	2
Chomtho et al. [52]	MCTD	14	6.3	3	4	2	3
Wheeler et al. [53]	MCTD	26	6.1	3	5	NR	NR
Lowe et al. [33]	MCTD	17	5.47	6	NR	10	6
Li et al. [32]	MCTD	69	<18	6	10	NR	NR
Muzykewicz et al. [54]	LGIT	76	9.6	12	NR	50	3
Coppola et al. [55]	LGIT	15	12.4	24.1	NR	6	NR
Larson et al. [56]	LGIT	15	8.5	24	1	6	2
Karimzadeh et al. [31]	LGIT	42	5.6	2	7	33	NR
Kim et al. [30]	LGIT	36	12.6	12	2	10	7
Evangeliou et al. [57]	LGIT	8	NR	3	NR	2	NR
Boles et al. [58]	LGIT	6	8.8	3.75	2	1	NR

NR: Not reported

Data extraction

The process of screening title and abstract, followed by a detailed review of the full text articles, was carried out utilizing Covidence, an advanced web-based platform specifically designed to facilitate and streamline the steps involved in conducting systematic reviews. This platform offers a user-friendly interface and tools that simplify critical tasks such as screening, extracting data, and resolving disagreements among reviewers. Three authors (EW, WW, and SJ) independently conducted the data extraction and any disagreements were resolved through discussion with authors JMP, HK, and FW as reviewers. Data extraction included the authors' names, country of origin, year of publication, patient characteristics (age), total sample size, type of intervention, duration of intervention, and outcome results.

Risk of bias assessment

Risk of bias for each study was evaluated using the Newcastle-Ottawa Scale [41] (NOS), presented in table format. NOS helps evaluate the risk of bias and the methodological quality of observational studies to ensure that the results of a meta-analysis or systematic review have a solid foundation. There are three main domains in NOS: selection, comparability, and outcome.

Statistical analysis

The meta-analysis was conducted using the statistical software R-4.2.2 with a 95% confidence level. The outcomes of seizure freedom and seizure frequency reduction will be visualized using a forest plot, which presents the effect estimates from each study and illustrates the comparison of the average effectiveness between dietary therapies. Furthermore, meta-regression will be used to explore the comparative effectiveness of MCTD and LGIT diets on seizure freedom and seizure frequency reduction outcomes.

RESULTS

Study selection and characteristics

A total of 1,489 research articles (500 MCTD and 989 LGIT) were initially identified. After removing duplicates, 1,002 articles remained for title and abstract screening. Of these, 897 articles were excluded for not meeting the inclusion criteria, thus only 105 articles passed to the next stage. In the eligibility stage, a total of 47 full text articles were completely evaluated to determine their suitability based on the inclusion criteria. Of these, 31 articles were excluded because they did not provide the required data. In the inclusion stage, 16 studies were evaluated in the qualitative synthesis. All of these studies were also used in the meta-analysis (quantitative synthesis), consisting of 9 studies related to MCTD and 7 studies related to LGIT. The selection process is illustrated in Figure 1, which provides a clear visualization of the inclusion and exclusion flow for this meta-analysis. The characteristics of 9 studies related to

MCTD and 7 studies related to LGIT in our meta-analysis is given in Table 1.

In the present investigation, two meta-analyses were performed. First, the proportion was taken as effect size for a reduction in seizures by ≥50% in epileptic patients. Second, the (relative risk) RR was taken as the effect size for a reduction in seizure by ≥50%. For the reduction in seizure of ≥50%, only three studies provided both effect sizes (proportion and RR). Therefore, these three studies were included in the meta-analyses.

In this study, meta-regression was not conducted to examine the relationship between study-level characteristics (e.g., participant age, study setting, or specific intervention details) and the observed effect sizes (e.g., treatment effect or correlation) across studies. Instead, the purpose of the meta-regression was solely to evaluate which of the two dietary interventions—Medium Chain Triglyceride Diet (MCTD) or Low Glycemic Index Treatment (LGIT)—is more effective in managing DRE. Therefore, the analysis focused only on comparing the superiority between these two diet types, and not on the influence of other potential moderators, as the interest was in the relative difference between the diets rather than estimating an overall effect.

Risk of bias

The risk of bias was assessed using Newcastle-Ottawa Scale (NOS). The assessment was conducted based on three main aspects: selection, comparability, and outcome, with each category assigned a risk level of low ( ), moderate ( ), or high ( ). The maximum score was 4 for the selection category, 2 for comparability, and 3 for outcome, resulting in a total maximum score of 9. Studies with a total score of ≥7 are considered to have a low risk of bias, while studies with a score of 6 or lower are categorized as having a moderate risk of bias. Overall, the included studies demonstrated a low risk of bias for the selection category and a moderate risk for the comparability and outcome categories, as illustrated in Table 2.

Data extraction

The data extraction summarizes the results of various studies evaluating the effectiveness of MCTD and LGIT in reducing seizure frequency in children with DRE. The recorded data includes sample size, average participant age, follow-up duration, and outcomes in achieving seizure freedom, ≥50% seizure frequency reduction, and ≥90% seizure frequency reduction, as presented in Table 1.

Table 2. Risk of bias using NOS

Author	Type of diet	Selection	Comparability	Outcome	Overall risk of bias assessment
Huttenlocher et al. [47]	MCTD	Low	Low	Moderate	Low
Trauner et al. [48]	MCTD	Low	Moderate	Moderate	Moderate
Sills et al. [49]	MCTD	Moderate	Moderate	Moderate	Moderate
Liu et al. [50]	MCTD	Moderate	Moderate	Moderate	Moderate
Lambrechts et al. [51]	MCTD	Moderate	Moderate	Moderate	Moderate
Chomto et al. [52]	MCTD	Low	Moderate	Moderate	Moderate
Wheeler et al. [53]	MCTD	Low	Moderate	Moderate	Moderate
Lowe et al. [33]	MCTD	Low	Moderate	Moderate	Moderate
Li et al. [32]	MCTD	Low	Low	Moderate	Low
Muzykewicz et al. [54]	LGIT	Low	Moderate	Moderate	Moderate
Coppola et al. [55]	LGIT	Moderate	Moderate	Moderate	Moderate
Larson et al. [56]	LGIT	Low	Moderate	Moderate	Moderate
Karimzadeh et al. [31]	LGIT	Low	Moderate	Moderate	Moderate
Kim et al. [30]	LGIT	Low	Low	Moderate	Low
Evangeliou et al. [57]	LGIT	Low	Moderate	Moderate	Moderate
Boles et al. [58]	LGIT	Low	Moderate	Moderate	Moderate

Note : NOS : Newcastle-Ottawa scale

Meta-analysis of proportion for a reduction in seizure of ≥50%

This study compares the effectiveness of MCTD and LGIT in DRE children, categorized into three outcome subgroups: seizure freedom, ≥50% seizure reduction, and ≥90% seizure reduction. In the MCTD group, the proportion of success in achieving seizure freedom ranged from 0.02 to 0.50, with a combined effect estimate of 0.21 [95% CI, 0.15- 0.29] in a random-effects model (I^2=52%, p=0.04). For the outcome of ≥50% seizure reduction, the success proportion ranged from 0.08 to 0.59, with a combined effect estimate of 0.24 [95% CI,0.1-; 0.39] in a random-effects model (I^2=65%, p=0.01). For the outcome of ≥90% seizure reduction, the success proportion ranged from 0.04 to 0.25, with a combined effect estimate of 0.13 [95% CI, 0.06- 0.28] in a random-effects model (I^2=65%, p=0.02). The overall average success proportion of MCTD in reducing seizure frequency was 0.20 [95% CI,0.14- 0.27] in a random-effects model (I^2= 59%, p<0.01). The forest plot from the MCTD group can be seen in Figure 2.

In the LGIT group, the proportion of success in achieving seizure freedom ranged from 0.07 to 0.17, with a combined effect estimate of 0.13 [95% CI,0.06- 0.26] in a random-effects model (I^2=34%, p=0.21). For the outcome of ≥50% seizure reduction, the success proportion ranged from 0.10 to 1.00, with a combined effect estimate of 0.50 [95% CI, 0.23-0.77] in a random-effects model (I^2=82%, p<0.01). For the outcome of ≥90% seizure reduction, the success proportion ranged from 0.06 to 0.16, with a combined effect estimate of 0.12 [0.06; 0.25] in a random-effects model (I^2=40%, p=0.19). The overall average success proportion of LGIT in reducing seizure frequency was 0.27 [95% CI, 0.14 - 0.45] in a random-effects model (I^2=83%, p<0.01). The forest plot from the LGIT group can be seen in Figure 3.

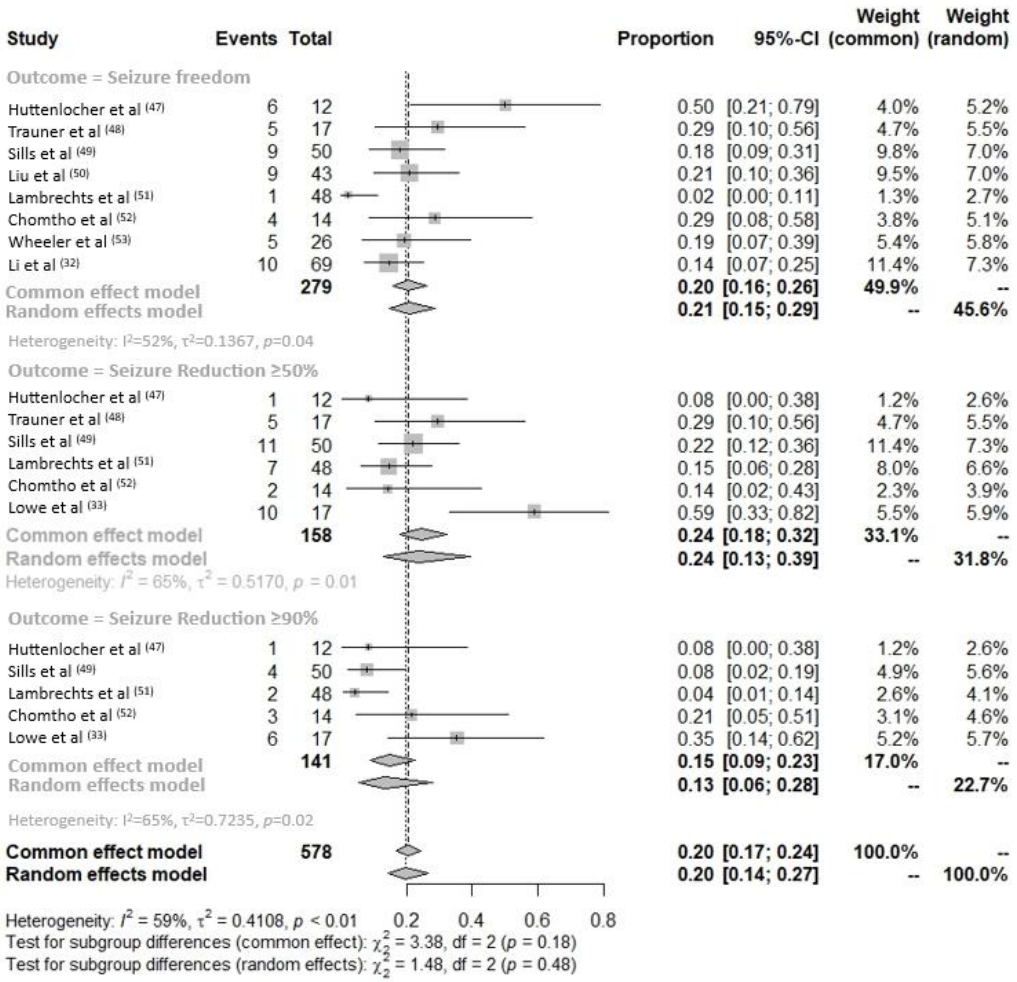

Figure 2. Forest plot of MCTD with each study effect size (proportion) and summary effect size ≥50% and 90% reduction in seizure. CI, confidence interval

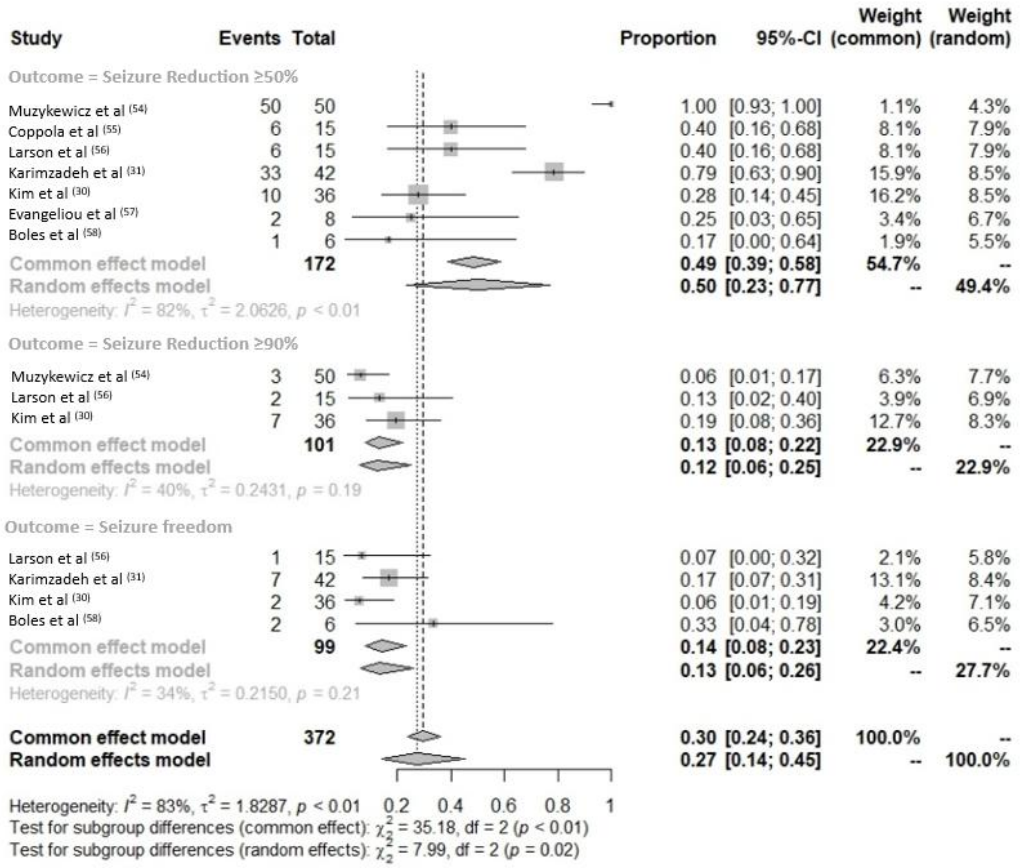

Figure 3. Forest plot of LGIT with each study effect size (proportion) and summary effect size ≥50% and 90% reduction in seizure. CI, confidence interval

Meta-regression

The meta-regression analysis revealed that the highly significant p-value (p<0.001) of the intercept indicates a statistically significant overall baseline success proportion, irrespective of diet type.[42] However, when assessing the diet type variable comparing the MCTD and LGIT, the p-value of 0.1599 suggests that the difference in effectiveness between the two dietary interventions is not statistically significant. Consequently, no definitive conclusion can be drawn regarding the superiority of one diet over the other. The meta-regression results can be seen in Table 3.

Publication bias

The funnel plot of the meta-analysis for MCTD and LGIT studies can be seen in Figure 4. There is no strong evidence of asymmetry in the funnel plot for either MCTD or LGIT studies, suggesting a low likelihood of publication bias in this meta-analysis.

DISCUSSION

The meta-analysis findings suggest that both MCTD and LGIT are significantly effective in achieving seizure freedom and reducing seizure frequency in pediatric patients with DRE. Based on the random-effects model, the overall success proportion of MCTD in reducing seizure frequency was 0.20 [95% CI, 0.14-0.27] (p<0.01), indicating a 20% reduction in seizure frequency. Similarly, for LGIT, the overall success proportion was 0.27 [95% CI, 0.14-0.45] (p<0.01), demonstrating a 27% reduction in seizure frequency.

Table 3. Meta-regression of the relationship between diet types

Parameter	Estimate	SE	95% CI	p value
Intercept	0.213	0.050	0.11:0.31	<0.001
Type of diet	0.110	0.078	-0.04:0.26	0.159

Note : CI : confidence interval

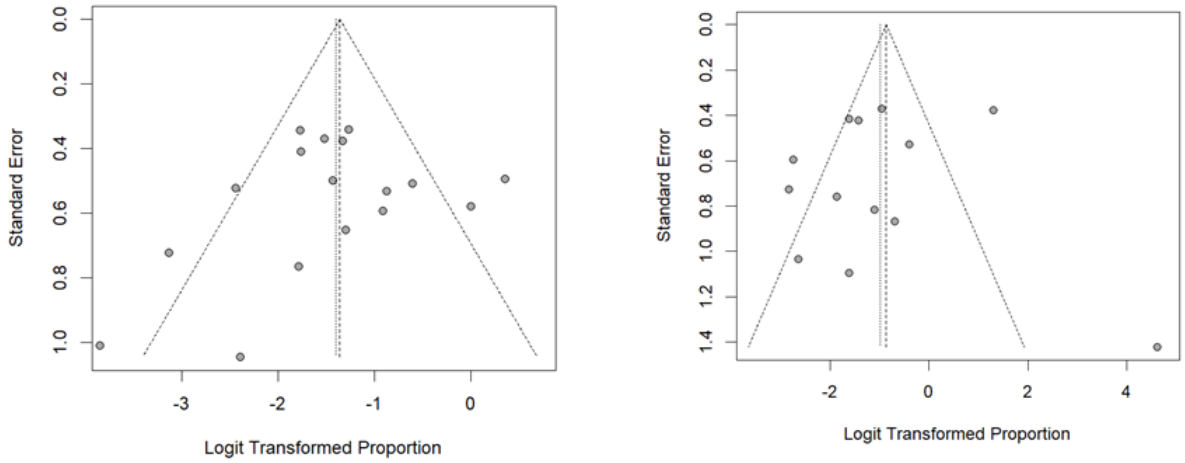

Figure 4. Funnel plot of MCTD and LGIT

Analysis of three outcome subgroups—seizure freedom, ≥50% seizure reduction, and ≥90% seizure reduction—revealed varying effectiveness of both MCTD and LGIT across different outcomes. However, no statistically significant difference was observed between the two dietary interventions. The variations in effectiveness may be attributed to the distinct mechanisms of action of each diet. MCTD primarily facilitates ketone body production and increases polyunsaturated fatty acids (PUFA), which contribute to ketosis and exert anticonvulsant effects.[43,44] Conversely, LGIT primarily functions by lowering insulin levels and reducing blood glucose concentrations, thereby decreasing neuronal excitability and seizure susceptibility.[45,46]

The high level of heterogeneity observed in our meta-analysis results, with I^2 values of 59% for MCTD and 83% for LGIT, indicates that most of the variability among the study outcomes is unlikely to be due to random fluctuations alone. Instead, it is likely attributable to methodological differences and variations in population characteristics across the included studies. This substantial heterogeneity suggests that the results of each study may have been influenced by different factors, making it challenging to generalize the findings comprehensively. Several potential factors may contribute to this heterogeneity, including variations in the duration of dietary therapy and follow-up periods, the year in which the study was conducted, the type of epilepsy diagnosed, the use of antiepileptic drugs, and specific patient characteristics. Additionally, differences in study design may also play a critical role in contributing to heterogeneity. To address and account for this variability, a random-effects model was employed in this meta-analysis. This model assumes that the true effect size may vary between studies due to differences in study populations, methodologies, and other underlying factors, thereby providing a more conservative and generalized estimate of the overall effect.

This study possesses several notable strengths, including comprehensive literature coverage and the application of meta-analysis, which facilitates the integration of data from multiple studies to provide a more robust assessment of the effectiveness of MCTD and LGIT in pediatric patients with DRE. Moreover, the use of meta-regression analysis enables the evaluation of potential differences in effectiveness between these two dietary approaches. Another key strength lies in the selection of studies that focus on newer ketogenic diet variants, such as MCTD and LGIT, which have not yet been widely adopted. This perspective extends beyond the more traditional ketogenic dietary therapies, such as CKD and MAD, which have been in use for a longer period. Additionally, the funnel plot analysis suggests a low probability of publication bias in this meta-analysis, further supporting the reliability of the findings.

However, this study also has certain limitations. One notable limitation is the high degree of heterogeneity, particularly among studies on LGIT, which may impact the reliability of the results and limit the generalizability of the findings. This variability could stem from differences in patient characteristics, epilepsy subtypes, or treatment durations, all of which may influence the observed outcomes across studies. Furthermore, the studies included are

observational in nature, which increases the risk of selection bias and confounding factors, thereby contributing to the heterogeneity observed in the analysis.

Clinical implication of the study

The findings of this meta-analysis have significant clinical implications, particularly in guiding the selection of dietary therapy for pediatric patients with DRE, especially those who are unable to tolerate the CKD due to its restrictive nature and complex implementation. The MCTD and LGIT represent more flexible ketogenic diet variants, offering improved adherence and tolerability compared to CKD. Consequently, these dietary approaches serve as viable alternatives to conventional ketogenic therapy.

Although MCTD and LGIT differ in their mechanisms of action and associated side effects, the analysis indicates no significant difference in their effectiveness in reducing seizure frequency among pediatric patients with DRE. Therefore, both dietary therapies can be considered effective treatment options. The choice of dietary intervention should be individualized based on the patient's clinical condition as well as the preferences of both the patient and their caregivers.

The findings of this meta-analysis provide valuable guidance for selecting non-invasive therapeutic approaches, such as MCTD and LGIT, while also serving as a reference for future research directions. To enhance the robustness of evidence, future studies should prioritize the inclusion of randomized controlled trials (RCTs), as this study design offers stronger methodological rigor and greater control over potential confounding factors. Implementing this approach may also facilitate the identification of statistically significant differences in the effectiveness of MCTD and LGIT in pediatric patients with drug-resistant epilepsy.

CONCLUSIONS

Both MCTD and LGIT demonstrate significant effectiveness in achieving seizure freedom and reducing seizure frequency in pediatric patients with drug-resistant epilepsy. However, the absence of a statistically significant difference between these two dietary approaches indicates that neither can be definitively regarded as superior in terms of efficacy.

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Conflict of Interest

All the authors of this article declared no conflict of interest.

Author Contributions

EW, WW, and SJ participated in data collection, library searches and assembling relevant literature, writing the paper, and critical review of the paper. JMP, HK, and FW participated in the conception and design of the study, supervising the writing of the paper, and database management. All authors have read and approved the final version of the manuscript.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

Declaration the Use of AI in Scientific Writing

No AI tools were used in the writing, editing, data analysis, or any part of the preparation of this manuscript. All work was conducted and completed solely by the authors.

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