Modified Atkins Diet for Drug-Resistant Epilepsy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Antonio Mutarelli , Alleh Nogueira , Nicole Felix , Amanda Godoi , Caroline Serafim Dagostin , Luiz H Castro , João Paulo Mota Telles

PII: S1059-1311(23)00242-X
DOI: https://doi.org/10.1016/j.seizure.2023.09.010
Reference: YSEIZ 4666

To appear in: *Seizure: European Journal of Epilepsy*

Received date: 30 June 2023
Revised date: 21 August 2023
Accepted date: 11 September 2023

Please cite this article as: Antonio Mutarelli , Alleh Nogueira , Nicole Felix , Amanda Godoi , Caroline Serafim Dagostin , Luiz H Castro , João Paulo Mota Telles , Modified Atkins Diet for Drug-Resistant Epilepsy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials, *Seizure: European Journal of Epilepsy* (2023), doi: https://doi.org/10.1016/j.seizure.2023.09.010

HIGHLIGHTS

- Modified Atkins diet was associated with a higher rate of 50% or greater reduction in seizure frequency compared to usual diet.
- Adults and children with drug-resistant epilepsy treated with modified Atkins diet had a 50% or greater reduction seizure frequency compared to those in usual diet.
- Modified Atkins diet was associated with a higher seizure freedom compared with usual diet.

Modified Atkins Diet for Drug-Resistant Epilepsy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Antonio Mutarelli[1], Alleh Nogueira[2], Nicole Felix[3], Amanda Godoi[4], Caroline Serafim Dagostin[5], MD, MSc, Luiz H Castro[6], MD, João Paulo Mota Telles[6], MD, PhD

[1] Federal University of Minas Gerais Medical School, Belo Horizonte, Brazil

[2] Bahiana School of Medicine and Public Health, Salvador, Brazil

[3] Federal University of Campina Grande, Campina Grande, Brazil.

[4] Cardiff University School of Medicine, Wales, United Kingdom

[5] Universidade do Extremo Sul Catarinense

[6] Department of Neurology, University of São Paulo, São Paulo, Brazil

Author's emails: antoniomutarelli@gmail.com ; nogueira.aksn@gmail.com ; nicole.santos@estudante.ufcg.edu.br ; amandacgodoi@gmail.com ; csdagostin@gmail.com ; castrolh@usp.br ; joao.telles@fm.usp.br .

Corresponding author:

João Paulo Mota Telles

Department of Neurology, University of São Paulo

Av Dr Arnaldo, 455, São Paulo, São Paulo, Brazil

Phone: +55 11 2661-0000

Email: joao.telles@fm.usp.br

ORCID:

Antonio Mutarelli – 0000-0002-5595-9433

João Paulo Mota Telles - 0000-0001-9322-0405

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.

Declarations of interest: none

Short title: Modified Atkins Diet for Epilepsy

ABSTRACT

Objective: To evaluate the effectiveness and side-effect profile of the modified Atkins diet (MAD) compared to the usual diet (UD) in reducing seizure frequency among patients with drug-resistant epilepsy (DRE).

Methods: In February 2023, we conducted an extensive search in PubMed, EMBASE, and Cochrane databases to find randomized controlled trials (RCTs) comparing MAD to UD in patients with drug-resistant epilepsy (DRE) on standard anti-seizure medication (ASM). We used random-effects meta-analyses and the Risk of Bias 2 tool to evaluate treatment effects and assess the quality of the included RCTs, respectively.

Results: Six studies were evaluated in the meta-analysis, including 575 patients, of whom 288 (50.1%) were randomized to the MAD. Average follow-up period was 12 weeks. MAD plus standard drug therapy was associated with a higher rate of 50% or greater reduction in seizure frequency compared to UD plus drug therapy (RR 6.28; 95% CI 3.52-10.50; p<0.001), both in children (RR 6.28; 95% CI 3.43-11.49; p<0.001) and adults with DRE (RR 6.14; 95% CI 1.15-32.66; p=0.033). MAD was also associated with a higher seizure freedom rate compared to UD (RR 5.94; 95% CI 1.93-18.31; p=0.002). Five studies reported adverse events with MAD; constipation was reported in 17% of patients (95% CI 5-44%), lethargy in 11% (95% CI 4-25%), and anorexia in 12% (95% CI 8-19%). Due to limited information about the ASM regimens, we were unable to further analyze the interaction between MAD and ASM.

Significance: This meta-analysis, comprising 575 patients from 6 RCTs, revealed that MAD led to higher rates of seizure freedom and underscored its role in seizure frequency reduction by 50% or more in both adults and children, with no significant adverse events concerns.

Keywords: Modified Atkins Diet, Drug-Resistant Epilepsy, meta-analysis, randomized controlled trials, seizure frequency, adjunctive treatment.

ABBREVIATIONS

DRE — Drug Resistant Epilepsy

KD — Ketogenic Diet

MAD — Modified Atkins Diet

RCT — Randomized Controlled Trial

UD — Usual Diet

ASM — Anti-seizure medication

INTRODUCTION

Epilepsy is a prevalent condition characterized by chronic, recurrent, and unprovoked seizures, contributing significantly to morbidity (1). A significant number of individuals with epilepsy continue to experience insufficient control of their seizures, even when utilizing combinations of anti-seizure medications (ASM) (2). Uncontrolled seizures may lead to elevated mortality rates, arrested development, and cognitive impairment. Surgical treatment is an option for drug-resistant epilepsy (DRE), albeit limited by the invasive nature and potential complications (3,4). Hence, there is a need for alternative non-pharmacological non-surgical treatment modalities in these patients.

The ketogenic diet (KD), one of the earliest available anti-seizure treatments, has demonstrated significant efficacy in patients with DRE (5–9). Approximately one-third of patients experience a reduction of more than 50% in seizure occurrence, and one-fifth achieve freedom from seizures (5–9). Moreover, some patients reduce or discontinue their ASM, leading to improvements in alertness, behavior, and cognition. The KD likely acts by elevating ketone bodies and polyunsaturated fatty acids promoting inhibitory neurotransmitters and potassium channels, raising seizure threshold (10). The increased polyunsaturated fatty acids boost sodium-potassium pump and reduce oxidative stress reducing seizures (10). Unfortunately, the traditional KD, which consists of a 4:1 ratio of fatty acids to carbohydrates plus proteins, is poorly tolerated (11). It requires meticulous food weighing and restrictions in calories, proteins, and fluids, which can increase the risk of hypoproteinemia and growth-related disorders. Additionally, the KD often requires hospitalization for initiation, and may lead to kidney stones, constipation, acidosis, impaired growth, weight loss, and hyperlipidemia (5–9).

The modified Atkins diet (MAD) has emerged as a less restrictive and better tolerated alternative to the traditional KD, with a similar mechanism of action, for patients with DRE (12–16). Unlike KD, MAD does not require fasting and allows for unrestricted intake of protein and fat, without restricting caloric and fluid intake (12–16). MAD operates on a 1:1 ratio of fat to carbohydrates, without meal-specific restrictions, allowing a daily carbohydrate intake of approximately 25 grams (11,17). This outpatient-based approach may improve patient quality of life by reducing seizure frequency while offering enhanced tolerability compared with alternative dietary approaches (12–16). However, the available evidence of MAD effects in patients with DRE remains limited, especially in adults. Therefore, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the independent impact of MAD on seizure reduction and diet tolerability in patients with DRE, as well as explore the consistency of MAD efficacy across a broader age spectrum.

METHODS

We prospectively registered this systematic review and meta-analysis in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42023394121. The review followed the guidelines set forth by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and followed the Cochrane Handbook for Systematic Reviews of Intervention (18–20).

Eligibility Criteria

Eligible studies for this systematic review and meta-analysis were (i) RCTs published in English (ii) including patients with DRE on standard anti-seizure medication (ASM) therapy (iii) randomized to receive either MAD or usual diet (UD), that (iv) reported any of the outcomes of interest and, (v) with a follow-up period of at least two weeks. We chose this follow-up period because plasma lipids take two to three weeks to achieve highest levels, and optimal improvement of seizures may occur only after this period (21). We excluded studies published only as conference abstracts and studies not including a control group on UD.

Search Strategy and Data Extraction

To ensure a comprehensive literature assessment, we systematically searched PubMed, EMBASE and the Cochrane Central Register of Controlled Trials from inception to February 2023 using a combination of medical subject headings, including "resistant epilepsy," "refractory epilepsy," "intractable epilepsy," "ketogenic diet," and "modified Atkins diet". We reviewed the reference lists of identified review articles and the final included articles to identify any additional potentially eligible studies. When the reported data was missing outcomes of interest, we contacted the authors and requested results for inclusion in the systematic review. Two investigators (AM and NF) independently reviewed the search records following predefined criteria and data extraction recommendations. They identified eligible studies and extracted key study characteristics and endpoints. Any disagreements were resolved through consensus. Specific search strategies used for each database are detailed in the **Supplementary Appendix.**

Endpoints and Subgroups

Since the majority of clinical trials and preceding meta-analyses have designated a 50% reduction in seizure frequency as their primary outcome (16,22). Our primary outcome was a 50% or greater seizure reduction. Nonetheless, in scenarios where patients endure a considerable number of daily seizures, a 50% reduction may lack clinical significance. Consequently, secondary efficacy endpoints have been extended to encompass a reduction in seizure frequency surpassing 90%, alongside an evaluation of rates of seizure freedom. We considered common adverse events — constipation, lethargy, and anorexia — as secondary endpoints. We further examined the consistency of treatment effects between adults and children.

Quality Assessment

Two investigators (AM and AG) independently appraised the quality of each full-text article using the Cochrane Risk of Bias 2 tool (RoB-2) (23). Disagreements in quality assessment were resolved through consensus between authors. RoB-2 categorizes each RCT into high, low, or some concerns risk of bias across five domains: selection, performance, detection, attrition, and reporting biases (23). Potential small study effects were explored using funnel plot analysis, examining the distribution of point estimates against their standard errors among studies with similar weights (24).

Statistical Analysis

All primary analyses were conducted following the intention-to-treat principle (25). Relative risks (RRs) were calculated to compare trial arms for all binary endpoints of efficacy. To account for potential heterogeneity between studies in terms of designs, populations, and endpoints, we utilized the DerSimonian-Laird

random-effects model with inverse variance weights to compute pooled association measures (26). The resulting estimates were accompanied by their corresponding 95% confidence intervals (CIs) and p-values. Heterogeneity was assessed according to the Cochrane Handbook for Systematic Review of Interventions, I^2 statistics and Cochran's Q test, p-values less than 0.10 and I^2 was greater than 40% were considered as elevated heterogeneity (20). We performed single-arm analyses using a random-effects generalized linear mixed model (GLMM), which is preferred in the setting of small sample sizes with heterogeneous demographics (27).

Sensitivity analyses were conducted through leave-one-out meta-analyses to assess the influence of individual studies on the overall treatment effect estimate, and Baujat plots to further investigate between-study heterogeneity (26). Exploratory subgroup analyses were performed to evaluate treatment consistency between pediatric and adult populations. All statistical analyses were conducted using R version 4.3.0 (R Foundation), and a significance level of less than 0.05 was used (26).

RESULTS

Study Selection and Characteristics

The search identified 3394 articles. After 970 duplicates were removed, 2424 articles were screened; 2413 excluded by screening of titles and abstracts. The remaining 11 full-text articles were assessed for eligibility, 6 of which met inclusion criteria (Figure 1). In total, there were 575 patients. All studies were open-label RCTs, single-center, with a 1:1 allocation ratio (15,28–32). Two studies focused on a

specific type of seizure: Kverneland et al. on focal seizure and Sharma et al. on epileptic spasm (28,32). The largest RCT included 160 patients, while the smallest had 64.The follow-up period varied between 4 and 24 weeks, with a weighted average follow-up period of 13.6 weeks, calculated based on the number of patients in each trial, and an average of 12 weeks and SD of 5.7. Baseline study characteristics are reported in Table 1. Information regarding the excluded studies is provided in the **Supplementary Appendix.**

Efficacy and Tolerability of MAD

In the pooled analysis, individuals receiving MAD exhibited higher rates of achieving >50% reduction in seizure frequency (RR 6.1; 95% CI 3.5 to 10.5; $p < 0.001$; $I^2 = 30\%$; Figure 2), >90% reduction in seizure frequency (RR 4.3; 95% CI 1.9 to 9.7; $P < 0.001$; $I^2 = 0\%$; Supplementary Figure S1), and freedom from seizures (RR 5.9; 95% CI 1.9 to 18.3; $P = 0.002$; $I^2 = 0\%$; Figure 3) compared with patients on UD.

We performed age-specific subgroup analysis for the primary endpoint of a > 50% reduction in seizure frequency. There was a significantly higher rate of this outcome in both pediatric (RR 6.3; 95% CI 3.4 to 11.5; $I^2 = 12\%$; Figure 4) and adult (RR 6.1; 95% CI 1.2 to 32.7; $I^2 = 46\%$; Figure 4) patients receiving MAD. There was no statistically significant difference in treatment efficacy between the subgroups (interaction p-value=0.98).

Due to inadequate and inconsistent reporting of adverse events outcomes, a comparison of these outcomes between groups was not feasible. However, we performed a single-arm meta-analysis of safety outcomes in the MAD group. In the pooled analysis of studies that reported adverse events with MAD, constipation was reported in 17% of patients (95% CI 5-44%; $I^2=64\%$; Figure 5A), lethargy in 11% (95% CI 4-25%; $I^2=75\%$; Figure 5B), and anorexia in 12% (95% CI 8-19%; $I^2=31\%$; Figure 5C).

Sensitivity Analyses

To evaluate the impact of each study on the pooled efficacy estimate for the primary outcome, we conducted leave-one-out meta-analyses, constructed a Baujat plot to assess heterogeneity and influence, and employed the trim-and-fill method to adjust for potential publication bias. The leave-one-out sensitivity analysis was consistent (Supplementary Figure S2). Pooling the leave-one-out meta-analyses yielded an intermediate effect size (RR 8.3; 95% CI 4.9 to 14.1; Supplementary Figure S2), which was more optimistic compared to the pooled analysis of all RCTs (Figure 2).

The Baujat plot analysis revealed that the RCT conducted by Kverneland et al. exhibited the highest level of heterogeneity among the studies and had the greatest influence on the efficacy estimate for the primary outcome (Supplementary Figure S3). Even after applying the trim-and-fill method to address potential publication bias, the association between MAD and >50% reduction in seizure frequency remained significant (RR 5.2; 95% CI 3.1 to 8.8; $P < 0.001$; $I^2 = 40\%$; Supplementary Figure S4).

In addition, we conducted sensitivity analyses by excluding two studies that did not report any events (both arms with zero events) in the seizure freedom analysis. The endpoint of seizure freedom was unchanged.

Quality Assessment

All six included RCTs reported the primary endpoint. Quality assessment was performed with Cochrane's Risk of Bias 2 tool. Four studies were rated as low risk of bias (Supplementary Figure S5). The study by Kverneland et al. had low enrollment, insufficient information in the intention-to-treat analysis, and a significant loss of follow-up, resulting in

an overall assessment of some concern for bias (28). The study by Zare et al. raised concerns in multiple domains, including allocation concealment and absence of power calculation, resulting in an assessment as high risk of bias (29). Funnel plot analysis for publication bias was limited by the small number of studies in the meta-analysis, but showed no definitive evidence of publication bias. (Supplementary Figure S6).

DISCUSSION

In this systematic review and meta-analysis encompassing 575 patients across 6 RCTs, we sought to determine the efficacy and tolerability of the MAD compared with UD in reducing seizure frequency among adult and pediatric populations with DRE. The main results were as follows: (i) among those treated with MAD, there was a 6-fold and 4-fold greater incidence of the outcome of seizure frequency reduction of ≥ 50% and ≥ 90%, respectively; (ii) freedom from seizures was also nearly 5-fold more common with MAD; and (iii) the efficacy of MAD relative to UD was consistent across pediatric and adult subgroups.

Up to 20% of patients with new-onset epilepsy may develop DRE, which represents a major clinical challenge for physicians and may significantly impair quality of life of patients and their families (33). Only 14% of patients who do not respond to the initial ASM become seizure-free on a subsequent medication trial, and only 3% of patients become seizure-free after failing two ASM (34). In our study, out of 288 patients with DRE that received MAD, 26 (9%) became seizure-free, compared with 0.7% of patients on UD. The substantial proportion of patients who became seizure-free after receiving MAD, relative to the control, underscores its clinical relevance as an adjunctive therapy for DRE.

Our study addresses a gap in the literature on the efficacy of MAD in adults. Prior studies have focused predominantly on pediatric populations. A recent network meta-analysis aimed to identify the most effective diet for children with DRE, comparing MAD, KD, and low glycemic index therapy. MAD yielded comparable results to the KD in terms of reducing seizures but was better tolerated (16). These results underscore the need to explore the therapeutic role of MAD in the adults.

A prior review from the Cochrane Collaboration on ketogenic diets for DRE included four studies on children and two studies on adults, with two studies on children specifically investigating MAD and other two examining the classical KD (22). In the subgroup of adult patients in that meta-analysis, there was no significant improvement in seizure reduction among patients treated with KD. In contrast to the Cochrane review, our study focused exclusively on MAD and demonstrated its efficacy in both children and adults, possibly due to improved power in the context of a larger sample size. Our results also showed that patients with DRE treated with MAD were more likely to achieve freedom from recurrent seizures compared with those on UD, which was not reported previously (22).

Despite our efforts to compare common diet-related adverse events between both groups, there was limited reporting of safety outcomes in the control groups of the included studies. Nevertheless, we conducted a meta-analysis of proportions (single-arm) to investigate potential adverse effects of MAD in the study population. The most frequently reported potential adverse events associated with MAD were constipation (17%), anorexia (12%), and lethargy (11%). Although less common side effects, including diarrhea, vomiting, and weight loss, were mentioned in various studies included in our analysis, the lack of consistent reporting across these studies precluded us from conducting a comprehensive statistical analysis on these effects. Traditional ketogenic diets have been reported to cause gastrointestinal side-effects in over 35% of cases (14,35). Potential mechanisms for constipation in the ketogenic

diets such as MAD include the lower intake of dietary fiber, as most fiber-rich foods are carbohydrate-based, such as fruits (14). Studies have demonstrated that this issue can be addressed by increasing fiber intake or prescribing laxatives, such as polyethylene glycol, which can help alleviate constipation (14,36).

Our study has limitations. First, all included studies relied on outcomes reported by patients or family members, which raises the concern for observer and measurement bias. Second, the absence of patient-level data precluded a more definitive assessment of potential factors associated with a better response to the MAD relative to UD. Unfortunately, we could not perform meta-regression analysis due to the small number of studies in the meta-analysis (< 10). Finally, there was moderate heterogeneity between studies for the primary outcome in the adult population (I^2 = 46%). Nevertheless, we explored causes for heterogeneity, and results were consistent after removing studies contributing to elevated heterogeneity (28,29).

CONCLUSION

In this meta-analysis of RCTs, patients with DRE treated with MAD more frequently achieved a ≥50% reduction in seizure frequency and freedom from recurrent seizures, compared with UD, over a follow-up of up to 24 weeks. These results indicate that MAD should be considered in patients with DRE, particularly if the diet is well-tolerated.

Acknowledgement: None

Authors contribution: Conception, design of the research: Mutarelli A, Nogueira A; Acquisition of data: Mutarelli A, Felix N, Godoi A; Analysis and interpretation of the data: Mutarelli A, Nogueira A, Felix N, Telles JPM; Writing of the manuscript: Mutarelli A Felix N, Nogueira A, Serafim C; Critical revision of the manuscript for intellectual content: Telles JPM, Castro LH; Orientation: Telles JPM.

Conflict of interest disclosure: All authors report no conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

REFERENCES

1. Devinsky O, Vezzani A, O'Brien TJ, Jette N, Scheffer IE, de Curtis M, et al. Epilepsy. Nat Rev Dis Primers. 2018 May 3;4(1):1–24.

2. Löscher W, Potschka H, Sisodiya SM, Vezzani A. Drug Resistance in Epilepsy: Clinical Impact, Potential Mechanisms, and New Innovative Treatment Options. Pharmacol Rev. 2020 Jul;72(3):606–38.

3. Treatment-of-epilepsy-4th-edition-Historical-Introduction.pdf [Internet]. [cited 2023 Jun 6]. Available from: https://simonshorvon.uk/wp-content/uploads/2017/07/Treatment-of-epilepsy-4th-edition-Historical-Introduction.pdf

4. Joudi Mashhad M, Harati H, Parooie F, Salarzaei M. Epilepsy surgery for refractory seizures: a systematic review and meta-analysis in different complications. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2020 Mar 12;56(1):35.

5. A Multicenter Study of the Efficacy of the Ketogenic Diet | Epilepsy and Seizures | JAMA Neurology | JAMA Network [Internet]. [cited 2023 Jun 6]. Available from: https://jamanetwork.com/journals/jamaneurology/fullarticle/774424

6. Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. Pediatrics. 1998 Dec;102(6):1358–63.

7. Hassan AM, Keene DL, Whiting SE, Jacob PJ, Champagne JR, Humphreys P. Ketogenic diet in the treatment of refractory epilepsy in childhood. Pediatr Neurol. 1999 Aug;21(2):548–52.

8. Katyal NG, Koehler AN, McGhee B, Foley CM, Crumrine PK. The ketogenic diet in refractory epilepsy: the experience of Children's Hospital of Pittsburgh. Clin Pediatr (Phila). 2000 Mar;39(3):153–9.

9. Kankirawatana P, Jirapinyo P, Kankirawatana S, Wongarn R, Thamanasiri N. Ketogenic diet: an alternative treatment for refractory epilepsy in children. J Med Assoc Thai. 2001 Jul;84(7):1027–32.

10. Barzegar M, Afghan M, Tarmahi V, Behtari M, Rahimi Khamaneh S, Raeisi S. Ketogenic diet: overview, types, and possible anti-seizure mechanisms. Nutr Neurosci. 2021 Apr;24(4):307–16.

11. Payne NE, Cross JH, Sander JW, Sisodiya SM. The ketogenic and related diets in adolescents and adults—A review. Epilepsia. 2011;52(11):1941–8.

12. Kossoff EH, Krauss GL, McGrogan JR, Freeman JM. Efficacy of the Atkins diet as therapy for intractable epilepsy. Neurology. 2003 Dec 23;61(12):1789–91.

13. Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. Epilepsia. 2006 Feb;47(2):421–4.

14. Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia. 2004 Sep;45(9):1116–23.

15. Manral M, Dwivedi R, Gulati S, Kaur K, Nehra A, Pandey RM, et al. Safety, Efficacy, and Tolerability of Modified Atkins Diet in Persons With Drug-Resistant Epilepsy: A Randomized Controlled Trial. Neurology. 2023 Mar 28;100(13):e1376–85.

16. Devi N, Madaan P, Kandoth N, Bansal D, Sahu JK. Efficacy and Safety of Dietary Therapies for Childhood Drug-Resistant Epilepsy: A Systematic Review and Network Meta-analysis. JAMA Pediatr. 2023 Mar 1;177(3):258–66.

17. Kossoff EH, Dorward JL. The Modified Atkins Diet. Epilepsia. 2008;49(s8):37–41.

18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009 Jul 21;339:b2535.

19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.

20. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [cited 2023 Jun 12]. Available from: https://training.cochrane.org/handbook

21. Dekaban AS. Plasma lipids in epileptic children treated with the high fat diet. Arch Neurol. 1966 Aug;15(2):177–84.

22. Ketogenic diets for drug- resistant epilepsy - Martin-McGill, KJ - 2020 | Cochrane Library [Internet]. [cited 2023 Jun 24]. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001903.pub5/full

23. RoB 2: a revised tool for assessing risk of bias in randomised trials | The BMJ [Internet]. [cited 2023 Jun 6]. Available from: https://www.bmj.com/content/366/bmj.l4898

24. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011 Jul 22;343:d4002.

25. Detry MA, Lewis RJ. The Intention-to-Treat Principle: How to Assess the True Effect of Choosing a Medical Treatment. JAMA. 2014 Jul 2;312(1):85–6.

26. Schwarzer G, Carpenter JR, Rücker G. Meta-Analysis with R [Internet]. Cham: Springer

International Publishing; 2015 [cited 2023 Jun 6]. (Use R!). Available from: https://link.springer.com/10.1007/978-3-319-21416-0

27. Lin L, Chu H. Meta-analysis of Proportions Using Generalized Linear Mixed Models. Epidemiology. 2020 Sep;31(5):713–7.

28. Kverneland M, Molteberg E, Iversen PO, Veierød MB, Taubøll E, Selmer KK, et al. Effect of modified Atkins diet in adults with drug-resistant focal epilepsy: A randomized clinical trial. Epilepsia. 2018 Aug 1;59(8):1567–76.

29. Zare M, Okhovat AA, Esmaillzadeh A, Mehvari J, Najafi MR, Saadatnia M. Modified Atkins diet in adult with refractory epilepsy: A controlled randomized clinical trial. Iran J Neurol. 2017 Apr 4;16(2):72–7.

30. Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: A randomized controlled trial. Epilepsia. 2013;54(3):481–6.

31. Sharma S, Goel S, Jain P, Agarwala A, Aneja S. Evaluation of a simplified modified Atkins diet for use by parents with low levels of literacy in children with refractory epilepsy: A randomized controlled trial. Epilepsy Res. 2016 Nov;127:152–9.

32. Sharma S, Goel S, Kapoor D, Garg D, Panda I, Elwadhi A, et al. Evaluation of the Modified Atkins Diet for the Treatment of Epileptic Spasms Refractory to Hormonal Therapy: A Randomized Controlled Trial. J Child Neurol. 2021 Jul;36(8):686–91.

33. Sultana B, Panzini MA, Veilleux Carpentier A, Comtois J, Rioux B, Gore G, et al. Incidence and Prevalence of Drug-Resistant Epilepsy: A Systematic Review and Meta-analysis. Neurology. 2021 Apr 27;96(17):805–17.

34. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000 Feb 3;342(5):314–9.

35. Wells J, Swaminathan A, Paseka J, Hanson C. Efficacy and Safety of a Ketogenic Diet in Children and Adolescents with Refractory Epilepsy—A Review. Nutrients. 2020 Jun;12(6):1809.

36. Lin A, Turner Z, Doerrer SC, Stanfield A, Kossoff EH. Complications During Ketogenic Diet Initiation: Prevalence, Treatment, and Influence on Seizure Outcomes. Pediatr Neurol. 2017 Mar;68:35–9.

37. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005 Apr 20;5:13.

Study	Follow up (weeks)	Group	Definition of DRE	Total (n) MAD / UD	Male (%) MAD / UD	Mean age (y) MAD / UD	Mean age of epilepsy onset	Most prevalent type of seizure	Seizure reduction ≥ 50%, MAD / UD
Sharma, 2013	12	Children	Daily seizure + ≥ 3 ASM	50 / 52	82 / 71	4.7 / 5.2	1.4 / 2	Tonic Myoclonic	26 / 6
Sharma, 2016	12	Children	Daily seizure + ≥ 2 ASM	41 / 40	81 / 77	5.6 / 4.8	1.4 / 1.1	Epileptic Spasm Tonic	23 / 3
Zare, 2017	8	Adults	≥ 2 seizure monthly + ≥ 2 ASM	34 / 32	71 / 66	29.4 / 27.2	NA	Tonic-clonic Focal	12 / 0
Kverneland, 2018	12	Adults	≥ 3 seizure monthly + ≥ 3 ASM	37 / 38	32 / 52	36 / 37	14 / 11	Only Focal	3 / 2
Manral, 2023	24	Children and Adults	≥ 2 seizure monthly + ≥ 3 ASM	80 / 80	80 / 60	19.5 / 19.4*	5.3 / 6.5*	Tonic-clonic Focal	21 / 2
Sharma, 2021	4	Children	Daily seizure + using corticosteroids + 1 ASM	46 / 45	80 / 69	1.83 / 1.55	0.4 / 0.46	Only Epileptic Spasm	30 / 0

Table 1 – Baseline characteristics of included studies.

DRE = Drug resistant epilepsy. MAD = Modified Atkins Diet. UD = Usual diet. ASM = Anti-seizure medication. *To estimate the mean and variance from median, range and the sample size we used the formula provided from the paper of Hozo, S.P, 2005. (37)

Figure 1. Flow chart of study selection

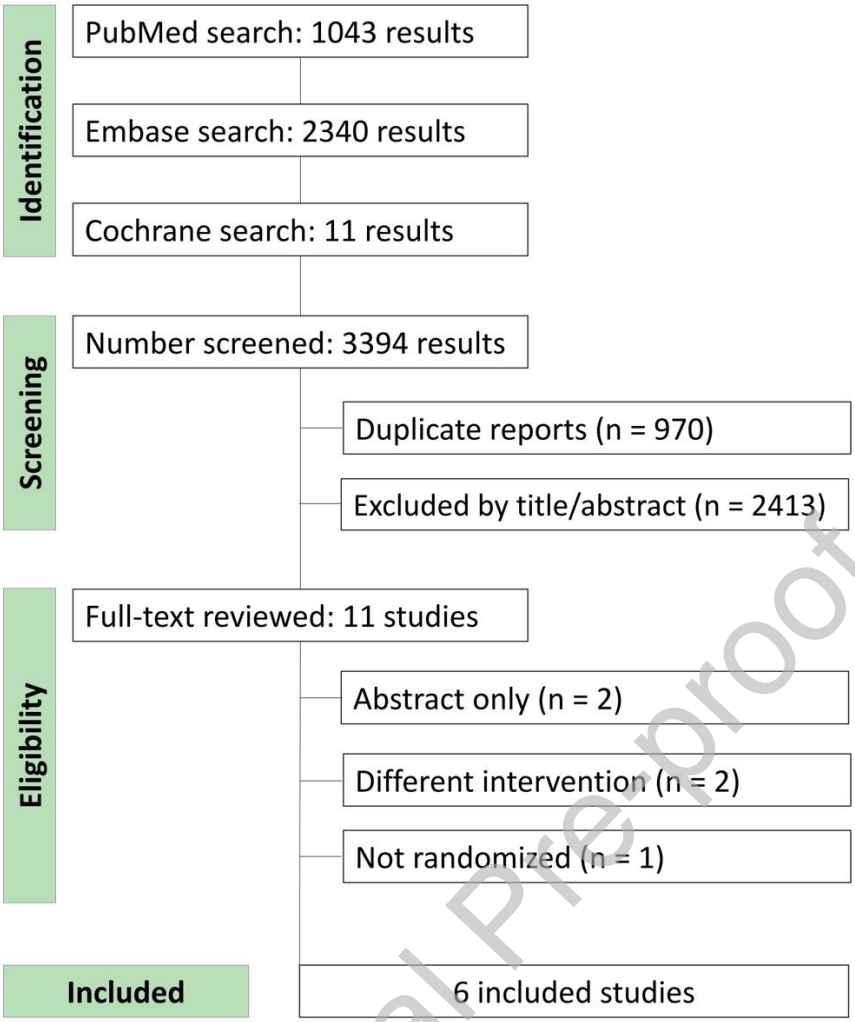

Figure 2. A 50% or greater reduction in seizure frequency was more common in the Modified Atkins Diet (MAD) group compared with usual diet (UD).

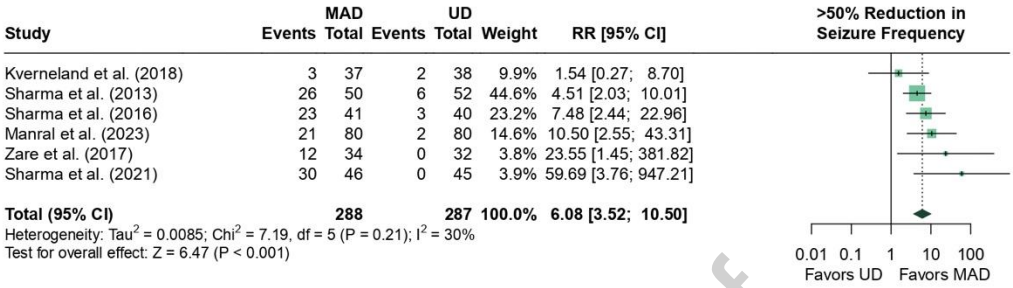

Figure 3. Seizure freedom was more common in the Modified Atkins Diet (MAD) group compared with usual diet (UD).

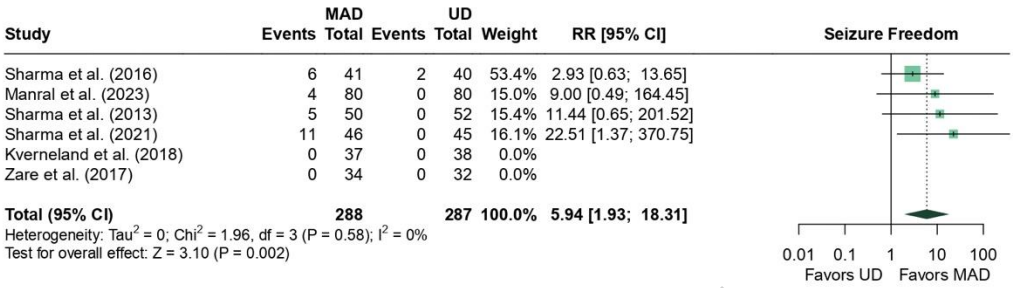

Figure 4. In both adults and children, a 50% or greater reduction in seizure frequency was more common in the Modified Atkins Diet (MAD) group compared with usual diet (UD).

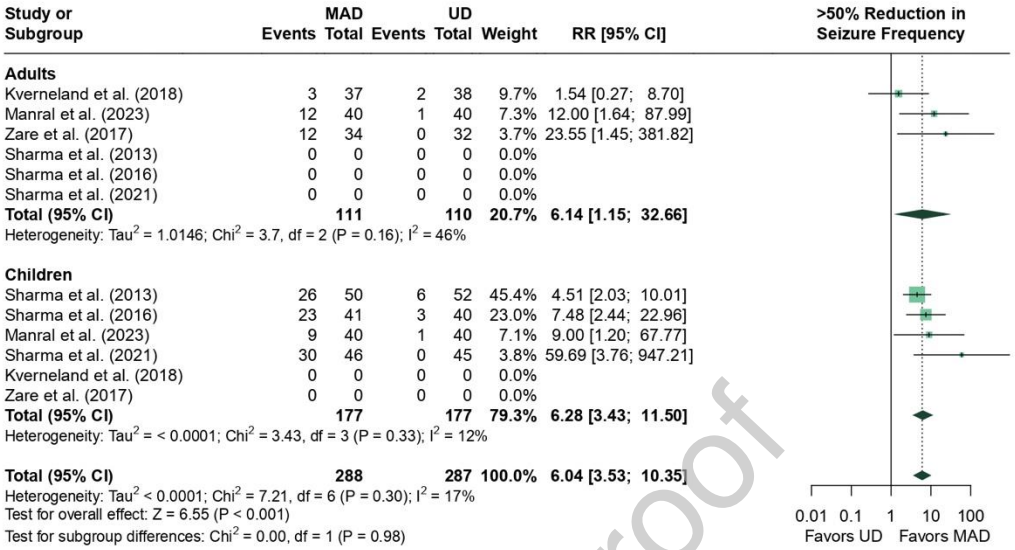

Figure 5. Single-arm meta-analyses of tolerability endpoints in patients with drug-resistant epilepsy treated with the Modified Atkins Diet (MAD): (A) constipation; (B) lethargy; and (C) anorexia.