

Therapeutic Success of the Ketogenic Diet as a Treatment Option for Epilepsy: a Meta-analysis

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Abstract

Objective: To systematically evaluate therapeutic success of the ketogenic diet (KD) as a treatment option for epilepsy.

Methods: Using MEDLINE and Google Scholar search, we searched for studies investigating the therapeutic success of ketogenic diet for epilepsy. We estimated therapeutic success rate for ketogenic diet as a treatment option for epilepsy and its 95% CIs using generic inverse variance method.

Findings: A total of 38 studies met the inclusion criteria. In retrospective studies, the weighted success rate of the patients who take the KD as a treatment option for epilepsy was 58.4% (95% confidence interval (95%CI)=48.7% - 69.9%) at 3 months (n=336); 42.8% (95%CI =36.3% - 50.3%) at 6 months (n=492), and 30.1% (95%CI =24.3% - 37.2%) at 12 months (n=387); in prospective studies, weighted success rate was 53.9% (95%CI 45.5% - 63.8%) at 3 months (n=474); 53.2% (95%CI =44.0% - 64.2%) at 6 months (n=321), and 55.0% (95%CI =45.9% - 65.9%) at 12 months (n=347).

Conclusion: This meta-analysis provides formal statistical support for the efficacy of the ketogenic diet in the treatment of epileptic patients.

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Key Words: Ketogenic Diet; Epilepsy; Meta-Analysis; Children

Introduction

Epilepsy is the most common serious neurological condition in the world, with an estimated prevalence of 1% of the population^[1]. Traditional epilepsy management includes pharmacological treatment, epilepsy surgery, and vagal nerve stimulation. Despite these therapies, 25% of children continue to have uncontrolled seizures. The ketogenic diet (KD), which has been in use since 1921, is a treatment option for many of these epilepsy patients. Ketogenic diet is high in fat, moderate in protein and low in carbohydrates.

This combination of energy results in a sustained ketosis that somehow serves to abate seizures through an unknown mechanism. In the following years, with the use of anti-epileptic drugs such as phenytoinum natricum, ketogenic diet is not widely used in epilepsy treatment. While in the recent years, with the increase of drug resistance and adverse effect of anti-epileptic drugs, ketogenic diet was newly considered and promoted in epilepsy treatment. Recently, A review suggests that in children, the ketogenic diet results in short to medium term benefits in seizure control, the effects of which are comparable to

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modern antiepileptic drugs^[2].

In this article, existing studies (retrospective studies and prospective studies) were collected and used to systematically evaluate therapeutic success of ketogenic diet at different duration. Individual studies were summarized using meta-analysis of generic inverse variance method.

Subjects and Methods

Search Strategy and Selection Criteria

As the basis for our analysis, we performed a MEDLINE search of the literature from 2000 to December 2011. The search themes were combined as "(ketogenic diet or ketosis or ketone) and (epilepsy seizures or focal seizures or seizures or epilepsy or refractory seizures or generalized seizures)". In addition, we performed a Google Scholar search.

Two investigators independently reviewed titles and abstracts, and selected articles addressing ketogenic diet and epilepsy. Disagreements were resolved by discussion and consensus. On a second sift, we selected original studies on ketogenic diet and epilepsy with the following inclusion criteria:

1. Addressing ketogenic diet and epilepsy.
2. The study should provide sample size.
3. The study should provide the percentage of seizure reduction with the corresponding ketogenic diet duration.
4. KD type including Johns Hopkins protocol, modified Atkins diet, classical ketogenic diet.

Definitions

For the purpose of meta-analysis, therapeutic success was defined as $\geq 50\%$ seizure reduction at follow-up.

Data Extraction and Analysis

For each study included, the full text was retrieved and the following data were extracted: authors, year of publication, size, gender and mean (or range) of age of the sample, and ketogenic diet duration. For each included study, we extracted the percentage of seizure reduction with the corresponding ketogenic diet duration.

Two investigators performed the extraction of the data in duplicate to avoid errors. The percentage of seizure free, $>90\%$ decrease, $>50\%$ decrease were always selected when available; otherwise the number of seizure free, $>90\%$ decrease, $>50\%$ decrease were recorded. We pooled studies that present percentages or the subjects that could be defined as therapeutic success.

Given the high number of potential ketogenic diet duration, we restricted our analysis to those for which the therapeutic success was assessed by at least 3 studies. Therapeutic success was analyzed separately according to the duration of ketogenic diet.

We used SAS (r) Software 9.2 to analyze data. The statistical heterogeneity of the included studies was assessed by using the χ^2 test and the I^2 index. The latter examines the percentage of total variation across studies that are due to heterogeneity between studies rather than by randomness. A value of I^2 greater than about 70% indicates a high level of heterogeneity. Since the results showed no statistical heterogeneity, we estimated therapeutic success rate for ketogenic diet as a treatment option for epilepsy and its 95% confidence interval (95%) CIs using generic inverse variance method^[3]. Using generic inverse variance method, each study estimate of the success rate is given a weight that is equal to the inverse of the variance of the effect estimate.

Findings

The MEDLINE search produced 933 citations. Records after duplicates removed resulted in 933 citations. Review of titles and abstracts resulted in the selection of 55 articles, among which 38 articles met the inclusion criteria. Selected characteristics of the 38 included articles are reported individually in Table 1^[4-41].

Table 2 provides the mean and range of success, and weighted success rate and 95% CI of ketogenic diet. In retrospective studies, the weighted success rate of the patients who take the KD as a treatment option for epilepsy was 58.4% (95% confidence interval (95%CI)=48.7% - 69.9%) at 3 months (n=336); 42.8% (95%CI

Table 1: Summary of 38 studies investigating ketogenic diet and epilepsy

Study	Author, Reference	Prospective/ Retrospective	Year	Sample Size Number	Male	Median /Mean/Range Age of Study Population (years)
1	Roberto, et al	Prospective	2011	24	16	6 [mean]
2	Mara, et al	Prospective	2011	18	9	29 [median]
3	Maria, et al	Prospective	2010	50	23	4.6 [mean]
3	Maria, et al	Prospective	2010	33	15	8.25 [mean]
4	Yoon, et al	Retrospectively	2011	20	12	6.9 [mean]
5	Rima, et al	Prospective	2011	15	NR	5 [mean]
6	Amnon, et al	Prospective	2009	9	2	28 [mean]
7	Pavel, et al	Prospective	2010	12	4	24-65 [range]
8	Eric, et al	Prospective	2010	5	3	4-18 [range]
9	Eric	Prospective	2011	30	11	7 [mean]
10	Dekker	Retrospective	2010	43	NR	2-19 [range]
11	Amanda	Prospective	2010	104	59	1.2 [mean]
12	Beniczky	Retrospective	2010	50	27	1-14.5 [range]
13	Anastasia, et al	Retrospective	2010	50	22	4.5 [mean]
14	Giangenaro, et al	Prospective	2009	38	22	3.1 [mean]
15	Suvasini, et al	Prospective	2009	27	NR	2.5 [mean]
16	Natacha, et al	Retrospective	2009	17	NR	2.7 [mean]
16	Natacha, et al	Retrospective	2009	10	NR	6.4 [mean]
17	John, et al	Prospective	2009	20	NR	1-10 [range]
18	Elizabeth, et al	Prospective	2008	73	40	2-16 [range]
19	Eric	Retrospective	2008	13	6	NR
19	Eric, et al	Retrospective	2008	20	13	NR
20	Eric, et al	Prospective	2007	30	11	31 [mean]
21	Eric, et al	Prospective	2007	10	6	4-25 [range]
21	Eric, et al	Prospective	2007	10	4	3-16 [range]
22	Joo, et al	Prospective	2007	40	24	4.3 [mean]
22	Joo, et al	Prospective	2007	36	19	3.7 [mean]
23	Hoon-Chul, et al	Prospective	2007	14	NR	7.4 [mean]
24	So-Hee, et al	Retrospective	2006	43	24	1.6 [mean]
25	Eric, et al	Prospective	2006	20	9	8.1 [mean]
26	Elisabeth, et al	Prospective	2006	150	85	5.3 [mean]
27	Christina, et al	Prospective	2005	24	17	5.8 [mean]
27	Christina, et al	Prospective	2006	24	17	4.8 [mean]
28	Mark, et al	Retrospective	2005	26	6	6.1 [mean]
29	Hoon-Chul, et al	Retrospective	2005	199	110	4.8 [mean]
30	Seyed, et al	Prospective	2010	24	NR	1-16 [range]
31	Giangenaro, et al	Prospective	2002	56	36	10.4 [mean]
32	Bernhard, et al	Retrospective	2001	134	NR	7.5 [mean]
33	Cheryl, et al	Prospective	2001	150	NR	NR
34	Mackenzie, et al	Retrospective	2003	45	25	14.4 [mean]
35	James, et al	Retrospective	2005	10	10	0.5 [mean]
36	Vykunta, et al	Prospective	2011	19	15	2.5 [median]
36	Vykunta, et al	Prospective	2011	19	16	3 [median]
37	Giangenaro, et al	Retrospective	2011	15	13	12.4 [mean]
38	Roberto, et al	Prospective	2006	11	7	5 [mean]

*NR indicates not reported

=36.3% - 50.3%) at 6 months (n=492), and 30.1% (95%CI= 24.3%- 37.2%) at 12 months (n=387); in prospective studies, weighted success rate was 53.9% (95%CI 45.5% - 63.8%) at 3 months (n=474); 53.2% (95%CI =44.0% - 64.2%) at 6 months (n=321), and 55.0% (95%CI =45.9% - 65.9%) at 12 months (n=347). In addition, weighted success rate for 1 month and 12 months in prospective study was 51.6% (95% CI=41.0% -

65.1%) at 1 month (n=212), 58.5% (95% CI=48.1% - 71.2%) at 12 months (n=278).

Fig. 1 and 2 show the mean weighted therapeutic success rate of ketogenic diet in included retrospective and prospective study respectively.

The Pearson's correlation coefficient (rho) of therapeutic success rate and age in ketogenic diet treatment is shown in Fig. 3 and 4. There was a

Table 2. The therapeutic success of ketogenic diet with the corresponding ketogenic diet duration

Summary of Therapeutic Success of Ketogenic Diet	3M				6M				12M				
	Meta-analysis Studies Included	Total Number of Cases	Mean and Range of Success Rates (%)	Weighted Success Rates and 95%CI (%)	Meta-analysis Studies Included	Total Number of Cases	Mean and Range of Success Rates (%)	Weighted Success Rates and 95%CI (%)	Meta-analysis Studies Included	Total Number of Cases	Mean and Range of Success Rates (%)	Weighted Success Rates and 95%CI (%)	
Retrospective study	Remain diet	24, 34, 35	101	86.1 (81.4-100.0)	86.1 (64.7-100.0) (Q=0.0001, P=0.9990)	13, 24, 29, 34, 35	350	65.1 (58.1-76.9)	65.1 (55.2-77.0) (Q=0.0004, P=1.0000)	28, 29, 34, 35	283	45.9 (44.4-46.2)	45.9 (37.3-56.5) (Q=0.0000, P=1.0000)
	Seizure free	10, 12, 24, 32	370	18.6 (15.7-34.9)	19.1 (14.8-24.8) (Q=0.0003, P=1.000)	13, 24, 29, 32	426	16.2 (8.0-39.5)	18.1 (14.0-23.5) (Q=0.0171, P=0.9998)	28, 29, 32	359	11.1 (6.5-17.1)	12.1 (8.7-16.9) (Q=0.0046, P=0.9977)
	>90% Decrease	10, 12, 32, 35	240	26.3 (16.4-53.8)	20.1 (15.2-26.7) (Q=0.0048, P=0.9999)	32, 34, 35	192	16.1 (12.7-46.2)	17.0 (11.6-25.0) (Q=0.0189, P=0.9905)	32, 34, 35	192	12.3 (11.2-46.2)	15.0 (10.0-22.6) (Q=0.0390, P=0.9807)
	>50% Decrease	10, 12, 16, 24, 28, 32, 35	336	57.1 (20.0-100.0)	58.4 (48.7-69.9) (Q=0.0089, P=1.0000)	13, 16, 24, 28, 29, 32, 35	492	42.3 (19.2-61.5)	42.8 (36.3-50.3) (Q=0.0676, P=1.0000)	28, 29, 32, 35, 37	387	28.9 (19.1-53.3)	30.1 (24.3-37.2) (Q=0.0056, P=1.0000)
Prospective study	Remain diet	14, 15, 23, 25, 31	155	82.6 (64.3-92.1)	82.6 (65.4-100.0) (Q=0.0014, P=1.0000)	14, 15, 17, 21, 23, 25, 31	195	59.5 (37.5-85.0)	55.8 (46.8-66.5) (Q=0.0092, P=1.0000)	2, 3, 5, 14, 15, 17, 31, 33	357	47.3 (8.9-77.8)	50.8 (42.1-61.3) (Q=0.1011, P=1.0000)
	Seizure free	3, 11, 20, 23, 25, 27, 30, 31, 36	343	16.6 (3.3-28.6)	17.7 (13.4-23.5) (Q=0.0089, P=1.0000)	11, 15, 17, 20, 22, 23, 25, 31	347	23.3 (3.3-30.6)	26.9 (20.9-34.5) (Q=1.0223, P=0.9981)	5, 11, 15, 17, 26, 33	466	15.9 (6.6-29.8)	17.7 (13.8-22.8) (Q=0.1562, P=0.9995)
	>90% Decrease	3, 11, 15, 18, 21, 25, 27, 30	339	16.5 (4.1-45.8)	19.0 (14.2-25.4) (Q=0.9457, P=0.9986)	3, 8, 11, 15, 17, 21, 22, 25	355	16.3 (5.0-34.0)	19.0 (14.3-25.2) (Q=1.4530, P=0.9991)	3, 11, 15, 17, 26, 33	484	16.1 (7.4-35.0)	16.6 (13.1-21.2) (Q=0.0879, P=0.9999)
	>50% Decrease	2, 3, 11, 18, 20, 21, 23, 27, 30, 36	474	52.2 (10.0-66.7)	53.9 (45.5-63.8) (Q=0.5554, P=1.0000)	2, 3, 8, 11, 15, 20, 21, 23, 25	321	52.3 (22.2-65.0)	53.2 (44.0-64.2) (Q=0.0798, P=1.000)	2, 3, 5, 11, 15, 33	347	53.6 (16.7-76.9)	55.0 (45.9-65.9) (Q=0.0528, P=0.9999)

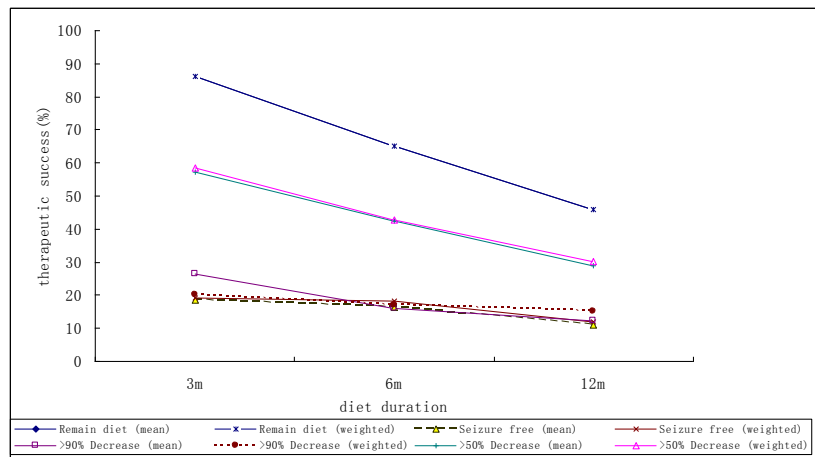


Fig 1: The mean weighted therapeutic success rate according to the duration of ketogenic diet in included retrospective study

negative correlation between therapeutic success rate and age at 3 months in retrospective study.

Discussion

Over the past 90 years since its introduction, the ketogenic diet has been shown to be extremely successful in existing studies. Although many studies have investigated the therapeutic success of ketogenic diet, a comprehensive and quantitative summary at different diet duration

has been lacking. In most instances, however, results were fairly consistent in the direction of therapeutic success of ketogenic diet, even though studies differed in the estimation of effect extent. In this meta-analysis, compliance of patients was found to be decreased with the prolonged ketogenic diet duration. It is reported that the initial 3 months on the diet are typically considered a trial period. So the surveillance for the compliance should be carried out especially in the initial 3 months. Vining et al reported that 71% of patients with 50% seizure at 3 months could stay on the diet until the KD duration reached one year^[42].

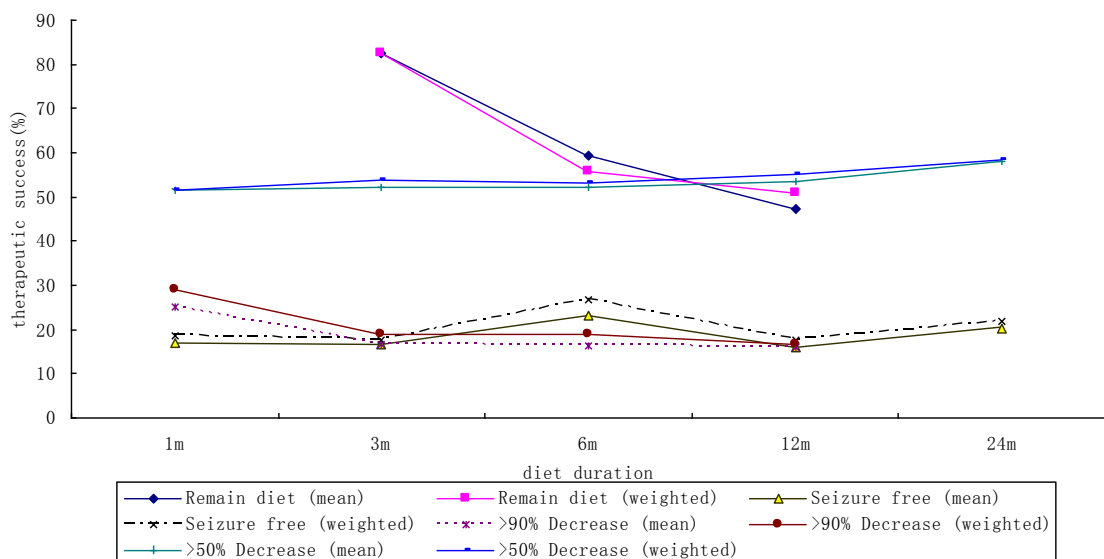


Fig. 2: The mean weighted therapeutic success rate according to the duration of ketogenic diet in included prospective study

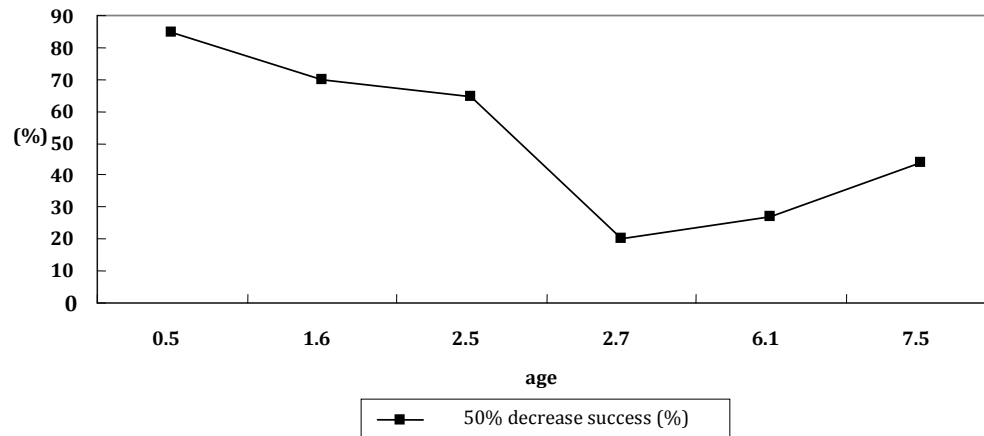


Fig. 3: The relationship of success rate of ketogenic diet and age at 3 month in included retrospective study

In this study, the therapeutic success of ketogenic diet was underscored using generic inverse variance method. This method is applied in meta-analysis when the results show no statistical heterogeneity. Each study estimate of the success rate is given a weight that is equal to the inverse of the variance of the effect estimate. Using this method, we found that in retrospective study, the success rate for patients who achieved therapeutic success (>50% reduction in seizure frequency) were 58.4% at 3 month, 42.8% at 6 month, and 30.1% at 12 month respectively; and in prospective study, the success rates were 53.9% at 3 month, 53.2% at 6 month, and 55.0% at 12 month respectively. It is consistent with reported efficacy of ketogenic diet in controlling seizures that 56% had a >50% reduction^[43]. When the ketogenic diet duration prolonged, the efficacy was found decreased. The decreased success rates

may be related to the decrease of compliance. In addition, the influence of lost to follow up may be considered when in the designing period, especially for long observation period, and measures to control the loss of follow up may be carried out in retrospective studies. Therefore, the reported rates were lower in retrospective studies than in prospective studies at 12 months. Furthermore, we cannot calculate the efficacy for ketogenic diet considering the anti-epilepsy drugs treatment when taking the ketogenic diet, so there is a need for further studies to explore the interaction effect.

Guidance on the duration of dietary treatment is limited, and one study looked into the effect of the KD after its discontinuation, observing reduced benefit following cessation of treatment^[10]. Levy RG et al also point out the problem of poor persistence^[1]. The education level

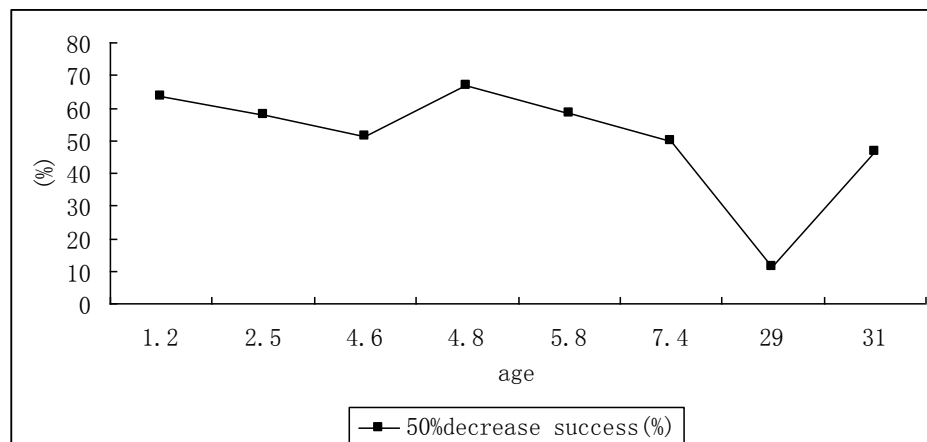


Fig. 4: The relationship of success rate of ketogenic diet and age at 3 month in included prospective study

and care of the patient's family, the knowledge of epilepsy treatment, and the complicated recipe for daily diet treatment as well as the side effect of ketogenic diet result in poor compliance. Common side effects of the ketogenic diet are gastrointestinal complaints and unfavorable lipid profiles. But Kessler et al reported that side effects are usually transient and the most common reason for discontinuation of treatment is lack of effectiveness^[44]. Anyway, for the ketogenic diet to be clinically meaningful, persistence or compliance would be quite important. And to improve therapeutic success of the ketogenic diet, some measures such as effectiveness evaluation, health education, supervision of compliance, awareness of epilepsy treatment, side effect minimizing, user-friendly recipe developing should be taken into consideration.

The ketogenic diet has been used with infants as young as 3 months and adults as old as 58 years. Although our analysis indicates the negative correlation between therapeutic success rate and age, this relationship was only found statistically significant at 3 month in retrospective study. There is a tendency for younger children to have higher success rate although this trend was not statistically significant. Ketogenic diet is currently used mainly for children who continue to have seizures despite treatment with antiepileptic drugs. Children's stomach capacity is small and the liver glycogen storage quantity is limited, so the energy storage level of children is lower than that of adults. Due to the higher energy storage level of adults and comparable stable blood glucose levels, the adult ketogenic diet practice is not as successful as in children. The results on less than 20% seizure free after treating with ketogenic diet for epileptic patients may be related to the age factor.

Conclusion

This meta-analysis provides formal statistical support for the efficacy of the ketogenic diet in the treatment of epileptic patients. There is a tendency for younger age patients to have higher success rate although this trend was not statistically significant. It shows the need for

further research on interaction effect considering both ketogenic diet and anti-epilepsy drugs.

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None of the authors of the present paper have information to declare regarding conflicts of interest

Conflict of Interest: None

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