Effect of Khat (Catha edulis Forsk) on Neurobehavioral Functions: Systematic review and Meta analysis

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Abstract

Background: Khat (Catha edulis forks, family: celastraceae) is a plant grown in East-Africa and the south west of the Arabian Peninsula. People uses for its pleasant stimulant effect of physical activity, consciousness, motor and mental functions as well as its anti-fatigue action. Although there is a rich body of research available regarding the effect of acute and chronic khat dosing in animal models, research on the behavioral and cognitive effects of khat in human subjects is not extensive and several of the available studies have been done only in the context of observational and single-case studies.

Objective: To determine the level of evidence of toxicity of Khat (Catha edulis Forsk) on Neurobehavioral Functions.

Methods: Key words representing major broad subject areas including: Khat, learning memory, working memory, cognitive flexibility, motor activities and other psychological disorders were used to search in the electronic databases. Randomized controlled trials (RCTs) and Cross sectional study investigating the effect of khat on neurobehavioral were included. Studies involving human participants reporting behavioral change and the experimental animal models were included in the present systemic review. Meta analysis was conducted to examine the effect of khat on neurobehavioral functions. Quality assessment was performed using the PEDro scale with subsequent data extraction.

Result: Out of the 260 studies, eight studies met inclusion criteria for this review. Of these, four studies were included in the meta-analysis. Meta-analysis results suggested that there were significant difference between khat exposed and control group for the neurobehavioral changes. The Pedro score was 6, meeting the cut off score for high quality.

Conclusion: Although a number of studies regarding the current topic is limited, there is the high quality of evidenced that khat (Catha edulis) induced neurobehavioral changes.

Key words: Khat, learning memory, working memory, cognitive flexibility, motor activities, psychological disorders

Introduction

Khat (Catha edulis, family: Celastraceae) is a plant grown in East-Africa (mainly in Somalia, Kenya, Djibuti, Yemen and Ethiopia) and the south west of the Arabian Peninsula. In these countries the chewing of khat is very common; it is consumed as qat and kat in Yemen; chat in Ethiopia; miraa, kijiti, gomba, mbachu or veve in Kenya; and as mairungi in Uganda [1]. Khat is chewed habitually by users for its euphoric effects and as a recreational drug [2, 4]. The psychostimulant component of the khat is cathinone, which is released within 15–45 minutes during chewing [3, 9]. Recent reports indicate that 80–90% of East African males and 10–60% of the East African females use khat on a daily basis [10, 11, 12, 13]. In Ethiopia, recent estimates of prevalence approach 50%, with 17% self-described as daily users, predominantly men [7]. Interestingly, there is evidence to suggest that the gender differences in the khat use disappear in Western countries. A recent survey conducted in London, UK, showed that 78% of men and 76% of women of Somali background had used khat, with 76% of participants reporting using more khat in London than they had in Somalia [13]. Users of khat report feeling as if they are able to think more clearly and more quickly while chewing khat. Other self-reported the acute effects of khat include increased levels of alertness, enhanced ability to concentrate, friendliness, contentment and flow of ideas. This is usually followed by excessive tension, anxiety, emotional instability, irritability, and restlessness within 2 hours, followed by feelings of low mood, numbness, lack of concentration, sluggishness,

and insomnia [5, 8]. Although there is no specific neuropsychological data on the effects of khat, Some limited studies and single case reports suggest long-term effects of khat on behavioral and cognitive functions range from insomnia, anxiety, irritability, agitation and aggression to major problems such as schizophrenic, psychotic disorder, paranoid delusions, mania, and depression, as well as an apparent increase in suicidal depression and an increased relative risk of hallucinations (11, 37, 38, 39). In addition to the studies reporting the effect of Khat (Catha edulis Forsk) on neurobehavioral functions, establishing the pooled effect is required to emphasize its potential effect. Therefore, the aim of this systematic review and meta-analysis was to determine the level of evidence for the effect of Khat (Catha edulis Forsk) on Neurobehavioral Functions.

Methods

Protocol and registration

The present systematic review was conducted according to the Cochrane guidelines [15] and has been presented based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [16].

Eligibility criteria

Types of studies

Randomized controlled trials (RCTs) and Cross sectional study were included in this study. These included parallel and crossover designs. Only Articles published in English language were included. Brief trial reports, abstracts and proceedings from the conference were excluded.

Participants

Studies involving human participants reporting behavioral change and the experimental animal models were included. For the purpose of the present review, the focus is being about the change in cognitive flexibility, learning, and memory, working memory, motor activities and other psychological disorders. Those studies that report with human participant using other drugs in addition to khat were not included. Studies that have included participants with systemic illness, central nervous system disorders were also excluded.

Intervention

The intervention of interest was the khat effect on the neurobehavioral functions such as cognitive flexibility, learning, memory, working memory and motor activities. Studies with khat administration performed as the only intervention or with other interventions were included if the same other interventions were applied in the control group. If the exclusive effect of khat administration could not be defined in studies involving multiple interventions, those were excluded.

Comparison

Control groups included no treatment or any form of intervention.

Outcome measures

The primary outcome measures were that assessing neurobehavioral change, such as cognitive flexibility, learning, memory, working memory, motor activities and other psychological disorders. Studies evaluating toxicity, as at least one of outcome measures were included.

Data sources and search strategy

An electronic literature search from the database inception was performed since December 2014 in the following databases: MEDLINE, Cochrane Library, Pubmed, Academic Search Complete, SPORTDiscus, ScienceDirect, Scopus, Web of Science, PEDro and Google Scholar. The search strategy was modified using Boolean logic. Search strategies were established in consultation with a university librarian. Two reviewers (Birhane Alem Berihu and Gebrekidan Gebregzabher Asfeha) independently conducted the database searches. In addition, eight relevant journals (figure 1) and reference lists of included studies and previous systematic reviews were manually searched.

Study selection

Two reviewers (Birhane Alem Berihu and Gebrekidan Gebregzabher Asfeha) independently reviewed all articles for eligibility (figure 1). Any disagreements regarding study inclusion between two reviewers were resolved through discussion.

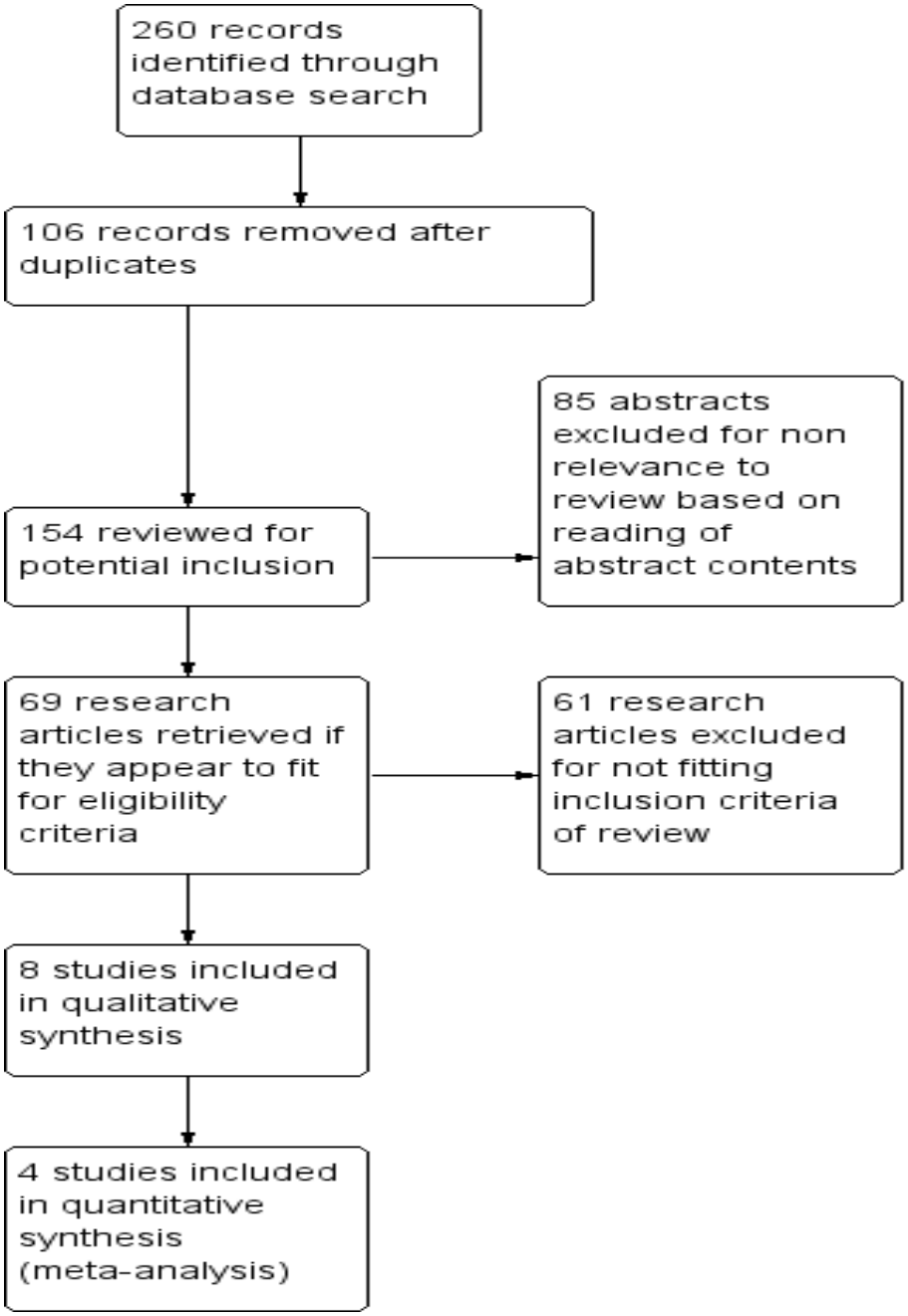

Figure 1: The process of study selection according to the PRISMA flow diagram.

Data extraction

One reviewer (Birhane Alem Berihu) extracted data from the included studies (table 1) with the standardized form and another reviewer (Gebrekidan Gebregzabher Asfeha) checked the data to ensure accuracy. Any disagreements were resolved by consensus. For conducting meta-analysis, outcome data were assessed for eligibility and scores were extracted from relevant included studies. Missing data were not sought by contacting the authors.

Table 1: Characteristics of the included studies.

Study	Study design	Intervention	Outcome measure	Reported results
Saeed obeid et al., 2014	Randomizing control trial	Khat (Catha Edulis) and Spatial Memory	Khat (Catha edulis) exposed rats induce impaired learning and memory,	A Significant difference was found between the groups
Nikajima et al., 2014	Cross - sectional study	Khat (Catha Edulis) and sleep quality	Khat chewer showed greater sleep disturbance as compared to non users	A significant difference was found between the groups
Colzato et al, 2012	Cross - sectional study	Khat (Catha Edulis) and response conflict	Khat use is associated with specific impairments in behavioral control:	Khat users significantly affected by stimulus-induced response conflict.
Colzato et al., 2011	Cross - sectional	Khat (Catha Edulis) and inhibitory control	khat use impairs both cognitive flexibility	Khat users significantly worse than controls on tasks tapping into cognitive flexibility
Kimani et al., 2008	Randomized control trial	Khat (Catha edulis) and locomotor behavior	Showed that repeated single daily khat causes behavioral sensitization, affecting both locomotor and anxiety behaviors.	A Significant difference was found between the groups
Kimani et al., 2008	Randomized control trial	Khat (Catha edulis) and spatial learning and memory	khat extract has a selective effect on spatial learning and memory	A significant difference was found between the groups
Laminal et al., 2009	A cross-sectional Study	Khat (Catha edulis) and academic, health and psychosocial, Effects on "mature" students	Insomnia was the major health problem indicated by 50% of the students	A Significant difference was found between the participants
Bongard et al., 2011	A cross-sectional Study	Khat (Catha Edulis) Use and Anger	Regular khat chewing is associated with disturbances in emotion regulation processes.	A Significant difference was found between the participants

Assessment of methodological quality and risk of bias

The methodological quality of the included studies was assessed using the PEDro scale (Table 2). A study with the score of 6 or above was considered of high quality [17], whereas that with the score of 5 or below was noted as low quality. The risk of bias in the included studies was assessed using 7 criteria recommended by the Cochrane Collaboration [15]. The results of assessing risk of bias were planned a priori to be used in evaluating the quality of evidence and in sensitivity analysis where appropriate. Two reviewers independently assessed both the methodological quality and risk of bias of the included studies. Any disagreements were resolved by consensus.

Data analysis

Values at the end of the intervention from each relevant included study were pooled for meta-analysis. Because different result scales were used across studies, a standardized mean difference (SMD) was calculated with 95% confidence intervals (CI) (figure 2). Heterogeneity was assessed using I^2 statistic to decide which random effect model or fixed effect model would be used. I^2 value <40% was a consideration of homogeneity [18]. Meta-

analyses were conducted to examine the effects of khat on neurobehavioral function in comparison with Control groups included no treatment or any form of intervention. Publication bias was assessed by graphically examining the symmetry of a funnel plot. Review Manager 5.3 was used for all analyses and generating the funnel plot (Figure 3).

Result

Study selection

The process of the selecting studies to be included in this review is illustrated in Figure 1. Eight articles from a total of the 260 records were included in this systematic review.

Characteristics of studies

The characteristics of the included studies are presented in Table 1. Three studies were RCTs and the five studies were cross sectional studies published in English.

Study population

In the present Meta analysis a total of 139 participants were involved. The clinical symptoms were Anger, spatial learning and memory and locomotor behavior [21, 22, 26, 35].

Interventions

There were variations in khat intervention between the studies. Six studies used khat as the only intervention [19, 20, 21, 22, 23, 26]. In the two studies involving the multiple comparisons, one group received only khat and another group received khat and tobaco [24] or khat and methylphenidate [35]. The route of administration in which khat applied were through intraperitoneal injection using experimental animal studies in three studies [21, 22, 35]. Khat user human participant in five studies [19, 20, 23, 24, 26]. There were also diversities in comparison interventions. These included Khat (Catha edulis) and spatial working memory [20, 21, 22, 35], Khat (Catha edulis) and academic, health and psychosocial effects [23], Khat use and risk of conflict in humans [19]; khat (Catha edulis) extract on locomotor behavior [21]; Khat Use and Trait Anger [26] and Khat and sleep quality [24].

Primary outcomes

Studies analysed in this review revealed that khat (catha edulis) shows significant effect on neurobehavioral change, such as cognitive flexibility, learning and memory, working memory, motor activities and other psychological disorders.

Methodological quality and risk of bias

The results for PEDro score of each study are presented in Table 2. The scores ranged from 5 to 6. Three studies were considered of the lower quality (19, 20, 23) and five studies of higher quality [21, 22, 24, 26, 35]. Three criteria which were blinding of subjects, interventions and assessors were unsatisfied in three studies. Figure 2, shows the summary of assessing risk of bias. As no studies successfully blinded participants, and assessors, there were high risk of performance bias and detection bias across studies.

Table 2: PEDro scale

Authors of study	PEDro scale criteria											
	1[a]	2	3	4	5	6	7	8	9	10	11	Total Score
Saeed obeid et al., 2014	y	y	y	y	n	n	n	y	y	y	y	7
Nikajima et al., 2014	y	n	n	y	n	n	y	y	y	y	y	6
Colzato et al, 2012	y	n	n	y	n	n	n	y	y	y	y	5
Colzato et al, 2011	y	n	n	y	n	n	n	y	y	y	y	5
Kimani et al., 2008a	y	y	y	y	n	n	n	y	y	y	y	7
Kimani et al., 2008b	y	y	y	y	n	n	n	y	y	y	y	7
Lamina et al., 2009	y	n	n	y	n	n	n	y	y	y	y	5
Bongared et al., 2011	y	n	y	y	n	n	n	y	y	y	y	6

PEDro Criteria

Item 1: (Not scored) eligibility criteria specified.
Item 2: Subjects were randomly allocated.
Item 3: Allocation was concealed.
Item 4: Groups were similar at baseline for most important prognostic indicators.
Item 5: There was blinding of all subjects.
Item 6: There was blinding of all therapists.
Item 7: There was blinding of assessors of outcomes.
Item 8: Measures of at least one key outcome were collected from 85% of subjects initially allocated.
Item 9: Intention-to-treat analysis was performed.
Item 10: Between-group comparisons reported for at least one key outcome.
Item 11: Study provided point measures and measures of variability for at least one key outcome.
Criteria 1[a] was not counted for PEDro scale

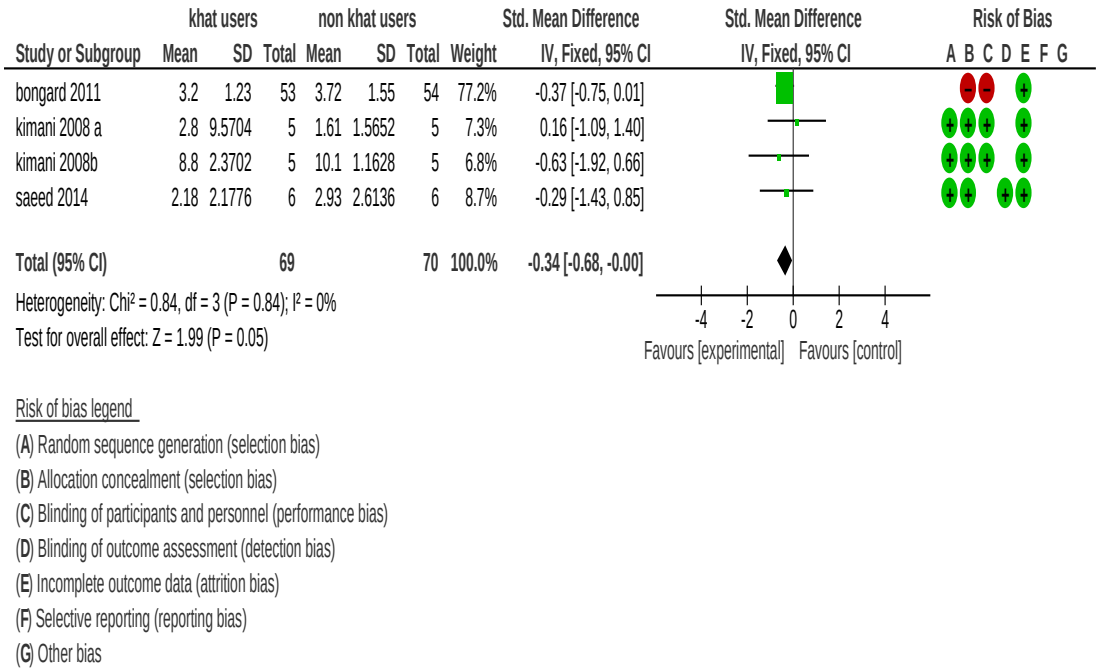

Figure 2: Forest plot of comparison: 1 khat users versus non khat users, outcome: neurobehavioral changes.

Publication bias

It was difficult to determine if there was publication bias from the funnel plot because of the small numbers of studies (figure 3).

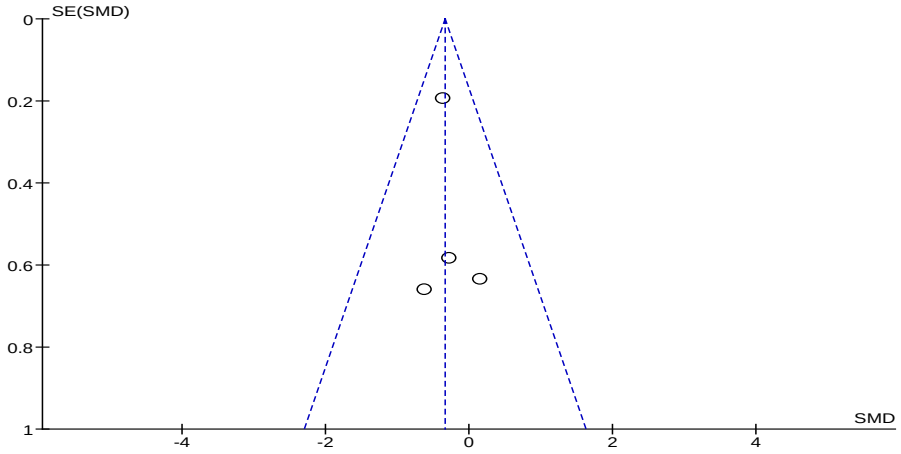

Figure 3: Funnel plot of comparison: 1 khat users versus non khat users, outcome: neurobehavioral changes.

Effects of khat

In total, four studies out of eight included studies were eligible for meta-analysis. As homogenicity was evidenced in all meta-analyses ($Chi^2 = 0.84$, df = 3 (P = 0.84); $I^2 = 0\%$), the fixed effect model was used and it generated the weights from inverse variance weighting. In terms of the effects of khat (Catha edulis) in comparison with the control group, four studies were identified [21, 22, 24, 35]. The overall estimate of the effect suggested that there were significant difference between khat exposed and control group for the induction of neurobehavioral changes (SMD -0.34, 95% CI -0.68 to -0.00, P = 0.05) (Figure 2).

Discussion

Many authors have argued about the causal role of khat in exacerbating psychotic reactions. The intent of this systematic review and Meta analysis was to determine the level of evidence of effect of Khat (Catha edulis Forsk) on Neurobehavioral Functions. Finding of the present systematic review and Meta analysis suggests that there is high quality evidence of toxicity of Khat (Catha edulis Forsk) on Neurobehavioral Functions. Studies analysed in the present systemic review showed that the rodent and human research implicates a significant association between daily khat use and cognitive flexibility, working memory, learning memory, motor activities and other psychological disorders [19, 20, 21, 22, 23, 24, 26, 35] with repeated dosing. There are some issues to be considered in our meta-analyses. The research design varies between studies. Six studies used khat users and non users as the intervention [19, 20, 21, 22, 23, 26]. In two studies involving multiple comparisons, one group received only khat and another group received khat and tobacco and non users [24] or khat and methylphenidate and normal saline water [35]. Moreover, there were also diversities in comparison of the interventions. These included Khat (Catha edulis) and spatial working memory [20, 22, 35]; Khat (Catha edulis) and academic health and psychosocial effects [23] and Khat use and risk of conflict in humans [19]; khat (Catha edulis) extract on locomotor behavior [21]; Khat Use and trait Anger [26] and Khat and sleep quality [26]. Although, there were neurobehavioral changes following khat use in those khat exposed participants, the duration of the patient's symptoms was unclear in all eight studies [19, 20, 21, 22, 23, 24, 26, 35].

Bearing in mind the similarity in pharmacological components of khat (cathinone and cathine) and amphetamines, the findings analysed in our review are consistent with previous studies in humans showing impairments in working memory [28, 34, 36] and cognitive flexibility [40] as consequences of long-term amphetamine and methamphetamine use. A recent systematic review and meta-analysis of the neurocognitive deficits associated with users of methamphetamines indicates that the largest (medium to large) effect sizes are seen in the domains of executive functions, learning, and memory [27]. High effect sizes were seen in our meta-analysis in the domains of khat (Catha edulis) on neurobehavioral changes such as cognitive flexibility, learning memory, working memory, motor activities and other psychological disorders. Studies analysed in the present systemic review are also consistent with other contemporary reviews of the neuropsychological effects of amphetamines and methamphetamines in humans [28]. In psychotic patients, khat may aggravate thought disturbances (hallucinations and delusions), induce aggressive behavior, and create difficulties in treating these patients [29]. Regular users with a predisposition to psychotic symptoms, including schizotypal or schizoid traits and family disorders, also have an increased risk of khat-induced psychosis. The psychotic symptoms are abated rapidly when khat is withdrawn [30]. However, recently, Odenwald [31 challenged this assumption concluding that the causal relationship between general psychopathology and khat use remains unclear and that people with preexisting vulnerability should avoid using khat. Colzato et al. [32] study systematically looked into cognitive impairments in khat users so far reported that khat users exhibit impairments in the inhibition of overt manual responses, assumed to rely on proper dopaminergic functioning [33]. The ability to inhibit unwanted thoughts and actions is commonly considered an important part of executive control, but it represents just one of a larger set of cognitive control functions. To wind up, studies analysed in the present systematic review showed that Khat (Catha edulis Forsk) has a potential to be toxic for neurobehavioral functions. Therefore, future laboratory studies should focus on histopathological effect on the domains of the brain involved in implementation of neurobehavioral functions.

Conclusion

Although, the number of studies regarding the current topic is limited, there is the high quality of evidenced that khat (Catha edulis) induced neurobehavioral changes. Meta-analysis results suggested that there were significant difference between khat exposed and control group for the neurobehavioral changes. The PEDro score was 6, meeting the cut off score for high quality.

Abbreviations

SMD: standard mean difference; CI: confidence interval; I2: hetrogenicity.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Birhane Alem Berihu has put a substantial contribution to carry out the collection of data. Gebrekidan Gebregzabher Asfeha) independently reviewed all articles for eligibility. All authors read and approved the final manuscript.

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