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#### **REVIEW ARTICLE**

# Association between Dietary Acid Load and Depression, Anxiety, and Stress: A Systematic Review

Mohammad Javad Zare, Samaneh Madani, Afsane Ahmadi\*

Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

ARTICLE INFO	ABSTRACT
Keywords: Dietary acid load Depression Anxiety Stress Mental health	<ul> <li>Background: Several studies have suggested a potential association between diet and mental disorders. This systematical review investigated the association between dietary acid load (DAL) and mental health outcomes such as depression, anxiety, and stress.</li> <li>Methods: Online databases including PubMed, Scopus, and Web of Science searched for published studies using relevant keywords until January 2024.</li> </ul>
*Corresponding author: Afsane Ahmadi, PhD;	<b>Results:</b> Seven studies were included in this systematic review, of which 6 were on adults. Five out of six studies on depression evaluated dietary acid load (DAL) with potential renal acid load (PRAL) method of which 3 of them reported a significant association. Three out of five studies that used net endogenous acid production (NEAP) method also presented a significant direct association. Furthermore, five studies examined the relationship between DAL and anxiety and all revealed a significant direct association. Moreover, a direct association between DAL and stress was noticed in two other studies. In terms of children and adolescents, a prospective study found no association between DAL and overall mental health among children and adolescents.
Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran. Tel: +98-71-37251001 Email: ahmadi.afsane@gmai.com Received: June 15, 2024 Revised: September 10, 2024 Accepted: September 16, 2024	<b>Conclusion:</b> Dietary acid load, especially PRAL, may be associated with psychological disorders like depression, anxiety, and stress among women. However, in the interpretation of these findings, it should be considered that the heterogeneity among studies is high as most of them conducted the study on women and participants had underlying diseases; so the conclusion cannot be extended to the overall population due to the limited number and design of current studies.

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#### Introduction

Mental health is one of the significant components of a healthy lifestyle (1). According to the World Health Organization (WHO) report, the worldwide prevalence rate of depression is estimated to be around 4.4%, and for anxiety disorder to be 3.6% (2). Mental disorders such as depression and anxiety are complex conditions that involve biological, social, and environmental factors (3) and can have a profound impact on society, leading to a decrease in quality of life and work performance, as well as an increase in healthcare costs and mortality rates. Therefore, investigations on related factors of mental health can lead to

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enhancement in the prevention and treatment of different mental problems (1, 4, 5). Several studies have suggested a potential association between diet and mental disorders (5, 6). For instance, a metaanalysis indicated a significant direct association between the inflammatory potential of diet with depression, anxiety, and distress (7). Also, diet may impact brain function through the impression of the gut-brain barrier axis and gut microbiotome (5, 8, 9). In addition, an inverse association between a high intake of base-inducing foods like vegetables and fruits and a positive association between acidinducing foods like red or processed meat and depression has been found in some studies (10-13).

Various methods have been developed to assess dietary acid load (DAL), including net endogenous acid production (NEAP) and potential renal acid load (PRAL). NEAP assesses protein to potassium ratio, while PRAL evaluates protein, phosphorus, potassium, magnesium, and calcium intake (14, 15). The relationship between DAL and different aspects of mental health has been investigated in several studies. Milajerdi et al. found a significant direct association between DAL and depression and anxiety in adults (16), which was also observed in another cross-sectional study focused on women (17). However, a study in children and adolescents did not find any significant association between DAL and depression or anxiety. Nevertheless, participants with higher DAL exhibited higher levels of emotional problems and hyperactivity (18). As these studies have been conducted on different populations and have used different methods for assessing DAL and mental outcomes; therefore, we conducted a systematic review to summarize all available studies and provide a comprehensive understanding of the association between DAL and depression, anxiety, and stress.

#### **Materials and Methods**

#### Search Strategy

This study was conducted based on the PRISMA guideline for reporting systematic reviews and meta-analyses (19). PubMed, Scopus, and Web of Science online databases were used to search for published studies until January 2024. Keywords used in the search strategy included mental health-related terms and dietary acid load terms. In addition, the reference list of relevant studies was searched for possible eligible studies for review. No restriction was considered for the time of publication or study design.

### Inclusion and Exclusion Criteria

Studies with the following criteria were included: (i) Observational studies with prospective, casecontrol, or cross-sectional designs; (ii) Measurement of the dietary acid load of the diet; and (iii) Assessment of the mental disorders as outcome in all age groups. If a finding from one data set was published in more than one article, a paper with more complete findings was included. Letters, comments, short communications, reviews, meta-analyses, and ecological studies were excluded.

# Data Extraction

In this study, two authors separately collected the information in the articles, including the first author's name, date of publication, the characteristics of the participants, age, gender, country, sample size, method of exposure and outcome assessment, length of the follow-up period and the results.

### Quality Assessment

The quality of the studies was evaluated by the Newcastle-Ottawa Scale (NOS) indecently by two authors. This checklist consisted of three parts (selection, comparability, exposure/outcome). Finally, based on the scores obtained, the studies were divided into three groups of good, fair, and poor quality. Studies with seven or more points were considered as good; while five to seven were regarded fair and less than five was defined as poor quality (20).

#### Results

Six-hundred and nine studies were identified in the initial search; while 232 studies were excluded due to duplication. Moreover, after screening by title and abstract, 363 studies were excluded for being unrelated. Fourteen full-text articles of potentially relevant studies remained for full-text review. Of these, 7 studies were excluded because of being irrelevant (n=6) and being review article (n=1) and overall, 7 studies were included. The flow diagram of study selection is displayed in Figure 1.

#### Characteristics of Studies

Table 1 provides a summary of the characteristics of the studies included in this systematic review. A total of 7 studies were reviewed, consisting of 3 observational cohort studies (18, 21, 22), and 4 crosssectional studies (16, 17, 23, 24). Of the 6 studies on adults, 4 were conducted on women (17, 21, 23, 25). The studies were conducted in various countries, including Iran (16, 17, 23, 24), USA (21), Germany (18), and Australia (22). Four studies reported data for DAL using both PRAL and NEAP methods (17, 21, 23), while 3 studies reported only PRAL (18, 25), and one presented only NEAP (16). Two studies also demonstrated DAL by following the equation DAL (mEq/day)=[PRAL+(body surface area [m2]×41 [mEq/day])/1.73 m2] (17, 24).

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<ul> <li>/</li> <li>DAL was not assert the total population is the total population is sion (OR: 1.2; 1.0 respectively; no sobserved in men. Higher PRAL was higher odds of an DAL<sup>+</sup> was not signal</li> </ul>	DAL was not ass the total populati the total populati i) DAL or PRAL his sion (OR: 1.2; 1.0 respectively; no s observed in men. Higher PRAL wa higher odds of an DAL† was not sig	<ul> <li>DAL or PRAL his sion (OR: 1.2; 1.0 respectively; no s observed in men. Higher PRAL wa higher odds of an DAL<sup>†</sup> was not sig</li> </ul>	sion (UK: 12; 1.0 respectively; no s observed in men. Higher PRAL wa higher odds of an DAL† was not sig	observed in men. Higher PRAL wa higher odds of an DAL† was not sig	DAL† was not sig	anxiety.	Higher DAL may in depression sco	oonooining accord	tients with multip	tients with multif	concerning association title the second seco	Higher DAL indident	Higher DAL indi depression and 97	Higher DAL indi depression and 9 <sup>th</sup> to participants in Although both Pl show a significan	Higher DAL indi depression and 97 to participants in Although both PI show a significan sion, it seems tha	Higher DAL indi depression and 9, to participants in Although both PI show a significan sion, it seems tha DAL were morel anxiety, stress, at	Higher DAL indi depression and 97 to participants in Although both PF show a significan sion, it seems tha DAL were morel anxiety, stress, at	Higher DAL indi depression and 9 to participants in Although both PI show a significan sion, it seems tha DAL were morel anxiety, stress, at	Higher DAL indi depression and 97 to participants in Although both PI show a significan sion, it seems tha DAL were morel anxiety, stress, at	Higher DAL indi depression and 97 to participants in Although both Pl show a significan sion, it seems tha DAL were more l anxiety, stress, at	Higher DAL indi depression and 9 to participants in Although both PI show a significan sion, it seems tha DAL were morel anxiety, stress, at	Higher DAL indi depression and 97 to participants in Although both PI show a significan sion, it seems tha DAL were morel anxiety, stress, at
<b>association</b> <b>association</b> <b>association</b> <b>association</b> <b>association</b> <b>association</b> <b>association</b> <b>b</b> (95%CI) <b>b</b> (1.07 (0.95- D/ 1.13 (1.01-1.13) D/ 1.13 (1.01-1.13) D/ 1.13 (0.86- do 0.97 (0.86- Hi 1.09) high <b>b</b> (1.09) high	1.07 (0.95- D/ 1.20) the 1.13 (1.01-1.13) D/ 1.00 (0.89- sio 1.13) res 1.13) ob 1.13) ob 1.13) hig 1.09) hig 1.09) an		1.00 (0.89- <sup>510</sup> 1.13) res 0.97 (0.86- <sup>0b</sup> 1.09) hij DA DA	0.97 (0.86- ob 1.09) (0.86- ob 1.09) DA	D/ an		β=0.09 (0.03- Hi 0.15) in	$\beta = 0.11 (0.05 - color)$		β=0.07 (0.01- 0.14)	β=0.07 (0.01- 0.14) β= 0.10 (0.04- 0.16)	$\begin{array}{c} \beta = 0.07 \ (0.01 - 0.14) \\ \beta = 0.10 \ (0.04 - 0.16) \\ 0.16) \\ 0.16) \\ 1.92 \ (1.52 - 2.64) \\ 1.92 \ (1.35 - 0.16) \\ \end{array}$	$\begin{array}{c} \begin{array}{c} \mu = 0.07 \ (0.01 - 0.14) \\ \mu = 0.10 \ (0.04 - 0.16) \\ 0.16) \\ 0.16) \\ 2 \ (1.52 - 2.64) \\ 1.92 \ (1.35 - 0.12) \\ 2.74) \\ \end{array}$	$\begin{array}{c} \beta = 0.07 \ (0.01 - 0.14) \\ \beta = 0.10 \ (0.04 - 0.16) \\ \beta = 0.10 \ (0.04 - 0.16) \\ 0.16) \\ 1.92 \ (1.52 - 2.64) \\ 1.92 \ (1.35 - 0.6) \\ 2.74) \\ 1.15 \ (0.60 - Al \ blue \ b$	$\begin{array}{c} \beta = 0.07 \ (0.01 - 0.14) \\ \beta = 0.10 \ (0.04 - 0.16) \\ \beta = 0.10 \ (0.04 - 0.16) \\ 0.16) \\ 2 \ (1.52 - 2.64) \\ 1.92 \ (1.52 - 2.64) \\ 1.92 \ (1.35 - 0.0) \\ 2.74) \\ 1.15 \ (0.60 - AI) \\ 1.17 \ (0.67 - 0.0) \\ 1.27 \ (0.67 - 0.0) \\ 0.0 \\ $	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} $	$\begin{array}{c} \begin{array}{c} \mu = 0.07 \ (0.01-0.014) \\ 0.14) \\ \mu = 0.10 \ (0.04-0.16) \\ 0.16) \\ 1.92 \ (1.52-2.64) \\ 1.92 \ (1.52-2.64) \\ 1.92 \ (1.35-0.016) \\ 1.92 \ (1.35-0.016) \\ 1.15 \ (0.60-0.016) \\ 1.15 \ (0.67-0.016) \\ 1.127 \ (0.67-0.016) \\ 1.13-0.016 \\ 1.13-0.006 \\ 1.13-0.$	$\begin{array}{c} \beta = 0.07 \ (0.01-\\ 0.14) \\ \beta = 0.10 \ (0.04-\\ 0.16) \\ 0.16) \\ 1.92 \ (1.52-2.64) \\ 1.192 \ (1.35-\\ 0.135-\\ 1.274) \\ 2.74) \\ 1.15 \ (0.60-\\ Al \\ 1.15 \ (0.60-\\ Al \\ 1.15 \ (0.67-\\ 0.13-$	$\begin{array}{c} \beta = 0.07 \ (0.01-0.14) \\ 0.14) \\ \beta = 0.10 \ (0.04-0.16) \\ 0.16) \\ 1.92 \ (1.52-2.64) \\ 1.192 \ (1.35-0.64) \\ 1.192 \ (1.35-0.64) \\ 1.15 \ (0.60-0.67) \\ 1.15 \ (0.67-0.67) \\ 1.127 \ (0.67-0.67) \\ 1.13-0.00 \\ 1.13-0.0$	$\begin{array}{c} \begin{array}{c} \mu = 0.07 \ (0.01-0.14) \\ \mu = 0.10 \ (0.04-0.16) \\ \mu = 0.10 \ (0.04-0.16) \\ \mu = 0.10 \ (0.04-0.15) \\ \mu = 0.10 \ (0.04-0.15) \\ \mu = 0.127 \ (0.50-0.15) \\ \mu = 0.115 \ (0.67-0.15) \\ \mu = 0.127 \ (0.13-0.15) \\ \mu = 0.127 \$	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} $	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} $
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NTHOV/YEAR		Adults Bahari					Saul <i>et al.</i>	(77)	(77)	(77)	(77)	Milajerdi <i>et</i> al. (16)	Milajerdi <i>et</i> al. (16)	Milajerdi <i>et al.</i> (16) Daneshzad <i>et al.</i> (23)	Milajerdi <i>et</i> al. (16) Daneshzad <i>et al.</i> (23)	Milajerdi <i>et</i> al. (16) Daneshzad <i>et al.</i> (23)	Milajerdi <i>et</i> al. (16) Daneshzad <i>et al.</i> (23)	Milajerdi <i>et</i> al. (16) Daneshzad <i>et al.</i> (23)	Milajerdi <i>et</i> al. (16) Daneshzad <i>et al.</i> (23)	Milajerdi <i>et</i> al. (16) Daneshzad <i>et al.</i> (23)	Milajerdi <i>et</i> al. (16) Daneshzad <i>et al.</i> (23)	Milajerdi <i>et</i> al. (16) Daneshzad <i>et al.</i> (23)

1, 3, 4, 5, 6, 7, 8, 10, 15, 19, 27, 29, 34	1, 3, 5, 8, 20, 21, 22, 23, 24	2, 3, 5, 8, 28, 30, 31, 32, 33	of Mental Disor- re; FSS: Fatigue 2: Strengths and 7 mass index (3), duration at night enopausal status (5), estrogen and or (30), pubertal
Good	Good	Good	I Manual uestionnai luestionnai check; SD check; SD, bod; c2), bod; 12), sleep (19), m check ((19), m check ((19), m check (19),
A significant direct association was found between DAL (PRAL, NEAP, DAL†) and depression, anxiety, and stress	PRAL indicates a significant direct associa- tion with depression in breast cancer survi- vors, especially among younger adults<55 and patients with a sedentary lifestyle	No significant prospective association was observed between PRAL and mental health. Association between PRAL and mental health was just significant among 10-year- old cross-sectional analysis	ical Studies; DSM-5: Diagnostic and Statistica iety and Stress Scale; FFQ: food frequently q nal acid load; PSQI: Pittsburgh Sleep Quality) nEq/ day]/1.73 m2] ‡Adjustment: age (1), gend ications (10), lipid profile (11), blood pressure ( its use (18), dietary intake of omega-3 fatty aci the use (24) metabolic equivalents in minutes p sorders and chronic diseases (29), (30), sedenti er (37), MUFA (38).
3.42 (1.87- 6.23) 3.47 (1.90- 6.33) 3.67 (2.04- 6.58) 3.63(1.97-6.71) 3.31 (1.81- 6.06) 3.37 (2.09- 6.06) 3.79 (2.09- 6.06) 3.72 (1.64- 5.58) 3.02 (1.64- 5.58) 3.02 (1.64- 5.58) 3.03 (1.66-5.43)	1.17 (0.98-1.41) 1.34 (1.11-1.62)	1.04 (0.5-2.15) 1.25 (1.02- 1.53) 1.12 (0.67- 1.88)	for Epidemiologi Depression, Anx AL: Potential ren $area [m2] \times 41$ [m tamin D (9), medi and antidepressar and antidepressar 3), intakes of veg $\hat{r}$ psychological dii tion level (36), fib
Depression Anxiety Stress Depression Anxiety Stress Depression Anxiety Stress	Depression Depression	Mental health	Y Questionnaire twenty-one-item id production; PF L + (body surface tray intake (8), vi supplement use . of vitamin B12 (2) family history of family (35), educat
NEAP PRAL DAL†	NEAP PRAL	PRAL	QES: Dietaa b) DASS-21: •; DASS-21: • DAL: [PRA] DAL: [PRA] take (7), ene ditions (17), 22), intakes ( 22), intakes ( study (28), dietary repo
	7.3	15	tory-II; D ion Scale AP: net en Survey. † 5), fiber in 5), fiber in 5), fiber in 10 fiber in 20 fiber
DASS-21	CES-D	SDQ	ession Inven dies Depress n Scale; NEA orm Health nent intake (( resence of cl orbidities at l and outside h ad viri
I68-item FFQ	24-h re- calls, 4 times	80-item FFQ	: Beck Depr niologic Stua d Depression I tem Short F (5), supplerr oking (16) p nber of coma ant sleeping a
447 healthy wom- en/31.68±7.64	2975 breast cancer survivors (100% wom- en)/50	1685 children and adolescents 2350 children 2061 adolescents	ntory; BDI- II: The Center for Epidern ospital Anxiety and c; SF-36: Rand 36- ), physical activity iage status (15), sm one status (21), nun atus (26), hours spe ation (32), recruitm
Cross- sectional/ Iran	Cohort/ USA	Cohort Cross- sectional 10-years- old Cross- sectional 15-years- old	mxiety Inve on: CES-D: ; HADS: H uestionnaii uestionnaii iic status (4 0), living al receptor sta receptor sta
Mozaffari <i>et</i> al. (17)	Wu <i>et al.</i> (21) Children	Bühlmeier et al. (18)	BAI: Beck A ders-5 <sup>th</sup> Editi, severity scale Difficulties Q socio-econon (13), nap time at baseline (2 <sup>1</sup> progesterone status (31), pa

Int J Nutr Sci March 2025;10(1)



Figure 1: Flowchart of study screening and selection process.

#### Dietary Acid Load and Depression

Six studies evaluated the association between DAL and depression; while four reporting a significant association. Table 1 summarizes the key results of the included studies. Bahari et al. found no significant association between DAL and depression among participants. Meanwhile, in a sex-stratified analysis, the study revealed 20% higher odds for depression in women, while this association was not significant among men (24). A prospective study on patients with multiple sclerosis observed a direct significant association between DAL and depression (22). Milajerdi et al. in a cross-sectional study observed a significant direct association between NEAP and depression among healthy adults (16). In another cross-sectional study on healthy women using PRAL, NEAP, and DAL (calculated by PRAL with considering body surface area) method, a significant direct association was visible between DAL and depression (17). Meanwhile, in another cross-sectional study on diabetic women, no significant association was seen between DAL and depression (23). A Longitudinal study by Wu et al. (21) on breast cancer survivors noted a significant direct association between PRAL and depression, especially among younger adults (age<55 years) and participants with a sedentary lifestyle had no association by NEAP method.

#### Dietary Acid Load and Anxiety and Stress

A significant direct association was observed between DAL and anxiety in all five studies that evaluated this association. Four studies illustrated a significant direct association between PRAL and anxiety and two between NEAP and anxiety. Two studies assessed the association between DAL and stress and both of them showed a significant direct association. Moreover, one study observed a significant direct association between DAL and sleep among diabetic women.

# Dietary Acid Load and Mental Health Among Children and Adolescents

A study conducted by Bühlmeier *et al.* aimed to assess the mental health of children and adolescents using SDQ subscales at the ages of 10 and 15 years, through cross-sectional and prospective associations. The study revealed a significant direct association between PRAL and emotional problems (Odds Ratio: OR=1.33; 95%Confidence interval: 95%CI=1.15; 1.54) as well as hyperactivity (OR=1.22; 95%CI=1.04; 1.43) in the 10-year-old cross-sectional analysis. However, no significant association was observed in the 15-year-old cross-sectional and prospective analyses (18).

# Quality of Studies

Findings on quality assessment of the seven included articles showed the good quality. The results of the quality assessment are available in Appendix 2.

# Discussion

This study presents a systematic review of the literature to investigate the association between DAL and mental health outcomes. The review included seven studies, with six conducted on adults. Five out of six studies on depression evaluated DAL with PRAL method of which 3 of them reported a significant association. Three out of five studies that used NEAP method also reported a significant association. Furthermore, five studies examined the relationship between DAL and anxiety, while all showed a significant association. Also, an association between DAL and stress was exhibited in two other studies. In terms of children and adolescents, one study displayed a significant association between PRAL and emotional problems and hyperactivity in a 10-year-old cross-sectional analysis, but no association was indicated in the 15year cross-sectional and prospective analysis.

Previous researches demonstrated the association between the intake of alkaline food items such as vegetables and a high intake of acidic food items like meat with depression and anxiety (26-29). The overall dietary intake patterns, such as having a Western dietary pattern (mainly acidic), were shown to be associated with the severity of depression (30, 31). In contrast, adherence to a Mediterranean diet (mainly alkaline) revealed an inverse association with psychological disorders (32). There are several hypotheses about the mechanisms by which DAL may affect mental health. One hypothesis is that an acidic diet can induce low-grade metabolic acidosis that can contribute to an elevated glucocorticoid level such as cortisol; and there are increasing evidences for a relationship between high cortisol level and psychological disorders (33-38).

The other possible underlying mechanism is the role of neuroinflammation in mental disorders. It has been shown that inflammation and inflammatory potential of diets can be related to mental disorders (7, 39). A hypothesis suggests a possible relationship

between a higher DAL and inflammatory markers such as C-reactive protein (CRP) and the inflammation that leads to mental disorders (17, 40-42). The other is the overstimulation of acid-sensing ion channel 1a (ASIC1a) as a part of degenerin/epithelial Na channels due to a decrease in PH after consuming a diet with higher scores for DAL. ASIC1a, when expressed in the nervous system, especially the amygdala, may be associated with psychological disorders (43-45).

Among the strengths of the current systematic review, the novelty of this issue and the gathering of all available evidences on the association between dietary acid load and mental health outcomes can be described. However, some limitations should be addressed in interpreting the findings as the included studies were only seven studies and three of them have been conducted in Iran. Also, four of the studies conducted on adults were only on women. The high differences between exposure and outcome measurements and the difference between participants' health status resulted in an increase in the rate of heterogeneity in this field. Therefore, the major limitations are the age groups, health status, and gender differences in the study populations. The association between DAL and mental outcomes may be caused by overlaps between vegetable and fruit intake as alkaline and anti-inflammatory food items; on the other hand, protein and especially meat intake is both acidic and pro-inflammatory. It's recommended for future studies to investigate the association between DAL and different aspects of mental health especially in healthy populations of both genders. Moreover, assessing this relationship in patients with chronic kidney diseases (CKD) seems advantageous considering the electrolytes and dietary changes in this condition.

#### Conclusion

It seems that dietary acid load, especially PRAL, could be associated with anxiety and depression, especially in women. However, these conclusions are not robust due to the limited number and design of current studies. Future prospective studies in both gender and different age groups should be conducted to conclude the association between dietary acid-base intake and mental health.

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# **Authors' Contribution**

A.A determined the subject of systematic review, MJ.Z and S.M did the initial screening, data extraction, quality assessment and wrote the main text of the manuscript, A.A rechecked the data extraction, quality assessment and written text.

# **Conflict of Interest**

All of authors declare not to have any of conflict of interest.

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