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Characteristics of the psychopathological status of oral lichen planus: a systematic review and meta-analysis

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ABSTRACT

Oral lichen planus (OLP) is a chronic inflammatory disease of the oral mucosa having no clear aetiology or pathogenesis. The influence of psychological disturbances on OLP has been widely discussed but still bears the controversy. This study aimed at assessing scientific evidence between the OLP and psychological alterations of the patient. We searched seven important databases for studies on OLP and psychological factors (anxiety, depression, stress, sleep disorders, etc.) published between 1 January 2000, and 1 October 2020. Case-control and cross-sectional studies were incorporated into this study. The meta-analysis used a random-effects model assessed by using the I^2 statistic. Dichotomous variables used the odds ratio and 95% confidence interval (CI), and continuous variables used the mean difference with 95% CI. Finally, 26 studies were included in the review. A meta-analysis of 13 studies showed there was a significant association of OLP with anxiety, depression and stress compared with healthy controls. Certain personality characteristics and sleep disorders also influence the patient of OLP. Therefore, psychological and psychiatric examinations should be carried out routinely for patients with OLP and improve the prognosis of the disease. © 2022 Australian Dental Association

Keywords: Anxiety, depression, meta-analysis, oral lichen planus, psychological problems, stress.

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INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory disease of the oral mucosa mediated by cellular immunity, which is quite common in clinical practice, having a prevalence of 0.1%–4%.[1–3] The causes of OLP are not clear, but it is related to infection, systemic diseases, genetic and psychological factors.[3] OLP can be divided into a reticular type, plaque type, atrophy type, blister type and erosion type, which is clinically divided into erosion and non-erosion types.[2] The chief complaints of patients with OLP include a burning sensation of the rough mucous membranes and severe pain that can affect eating and speaking, and swallowing difficulties, which are present in two-thirds of patients with OLP.[4] Long-term erosion of the mucous membranes has a potential risk of malignant transformation, which the World Health Organization (WHO) classifies as an oral potentially malignant disorder (OPMD).[5] A 2019 study found a malignant conversion rate of 0.8%–1.5% for OLP.[6] The risk of developing cancer might result in poor mental health, leading to changes in mood and deterioration in the quality of life, which might eventually exacerbate the pain caused by OLP. It is also necessary to consider that pre-existing mood disorders might affect patients' perception of pain and their ability to cope with the disease and its symptoms and contribute to the development and worsening of the disease.

A 2016 case-control study by Pippi *et al.* found depression and poor self-control were significantly associated with OLP, especially reticulated OLP,[7] and a 2018 study by Radwan-Oczko *et al.*[8] found the perceived stress of OLP was significantly correlated with increased depression and decreased quality of life. In contrast, however, a 2015 study found the symptoms of anxiety, depression and stress in patients with OLP were not significantly higher than those of the control group.[9] Although there are several psychological studies of OLP patients, the causal relationship between OLP and mental health is inconclusive. Therefore, the overall psychopathological status of OLP patients needs to be analysed systemically.

The primary aim of this systematic review was to calculate the pooled estimates of the odds ratios (ORs) and the mean difference (MD) in the associations of psychological disorders with the presence (cases) vs. the absence (controls) of OLP. The analysis tried to identify the relationship between psychiatric conditions and OLP in order to target the problem and improve the psychological well-being of patients with OLP.

METHODS

Search methods

Literature retrieval was carried out based on the criteria of the Preferred Reporting Items for System Review and Meta-analyses (PRISMA).[10] Two authors independently searched English and Chinese articles in seven databases: PubMed, EMBASE, Web of Science, Science Direct, the Cochrane Database, the Wanfang Database and the China National Knowledge Infrastructure (CNKI). The electronic bibliographic search was carried out in December 2020. The following search terms were used: (Psychology OR Psychological OR "Psychological Side Effects" OR Psychologist OR Depression OR "Depressive Symptom" OR "Emotional Depression" OR "Psychological Stress" OR "Psychologic Stress" OR "Mental Suffering" OR Anxiety OR Hypervigilance OR Nervousness OR "Social Anxiety" OR Anger OR "Personality Trait") AND ("Oral lichen planus" OR "lichen planus").

Diagnostic criteria

The patients with OLP were enrolled in the studies based on their clinical and histopathological diagnosis.[11]

Inclusion criteria

The inclusion criteria were: studies written in English or Chinese; the words 'OLP' and 'psychological factors' were found in the title, abstract or keywords; an observational study with a comparison or control group; and use of standardized and validated instruments that assessed psychological factors;

Exclusion criteria

The exclusion criteria were: articles that mentioned OLP, but did not study its relationship with psychiatric measures; the article was not a case-control study, such as summary articles, letters to editors, meeting abstracts, patent inventions, unpublished papers or papers whose full-text could not be obtained.

Data extraction

Two reviewers (LKY and HWX) selected the relevant papers independently based on their titles and abstracts and assessed the studies' questions and objectives in the first round. The second round was mainly based on inclusion and exclusion criteria to screen the full text. Articles in the reference list of included studies were also included in the meta-analysis if they met the inclusion and exclusion criteria. If there were differences of opinion between the two reviewers about what studies should be included, the third author (HH) decided. A standard data extraction Excel form is compiled, which includes title, publication year, author, type of design, OLP diagnostic criteria, number of cases in OLP and control group, sex, age, psychometric scale, results, etc. The data were entered into Excel form independently by two reviewers and cross-checked.

Evaluation of quality

Two authors evaluated the quality and risk of bias of the individual studies listed in Table 2 using the Newcastle-Ottawa Scale (NOS).[12] The three evaluation criteria mainly involved subject selection, comparability and exposure (case–control). Research quality was divided into high quality = 7–9 points, medium quality = 4–6 points and low quality = 0–3 points.

Statistical analysis

The I^2 index was used to assess the statistical heterogeneity of the studies. When $P > 0.1$ and $I^2 < 50\%$, the studies were considered to be sufficiently homogeneous, and a fixed-effects model was used. When $P < 0.1$ and $I^2 \geq 50\%$, the studies were considered heterogeneous, and a random-effects model was used. Dichotomous variables (such as whether there was anxiety or depression) are expressed as an association estimate; we used the OR and 95% confidence interval (CI). Continuous variables that are measured on the same scale (e.g. the scores on a quantitative scale) are expressed as the mean and standard deviation (SD) reported in the study, resulting in an estimate of the MD with 95% CI.[13,14] Stata version 15.0 was used for all the tests.

RESULTS

Literature search

The flow chart (Fig. 1) shows the process of literature retrieval and screening for exclusion. We retrieved a total of 2554 records of published articles: 303 from PubMed, 788 from Embase, 734 from Web of

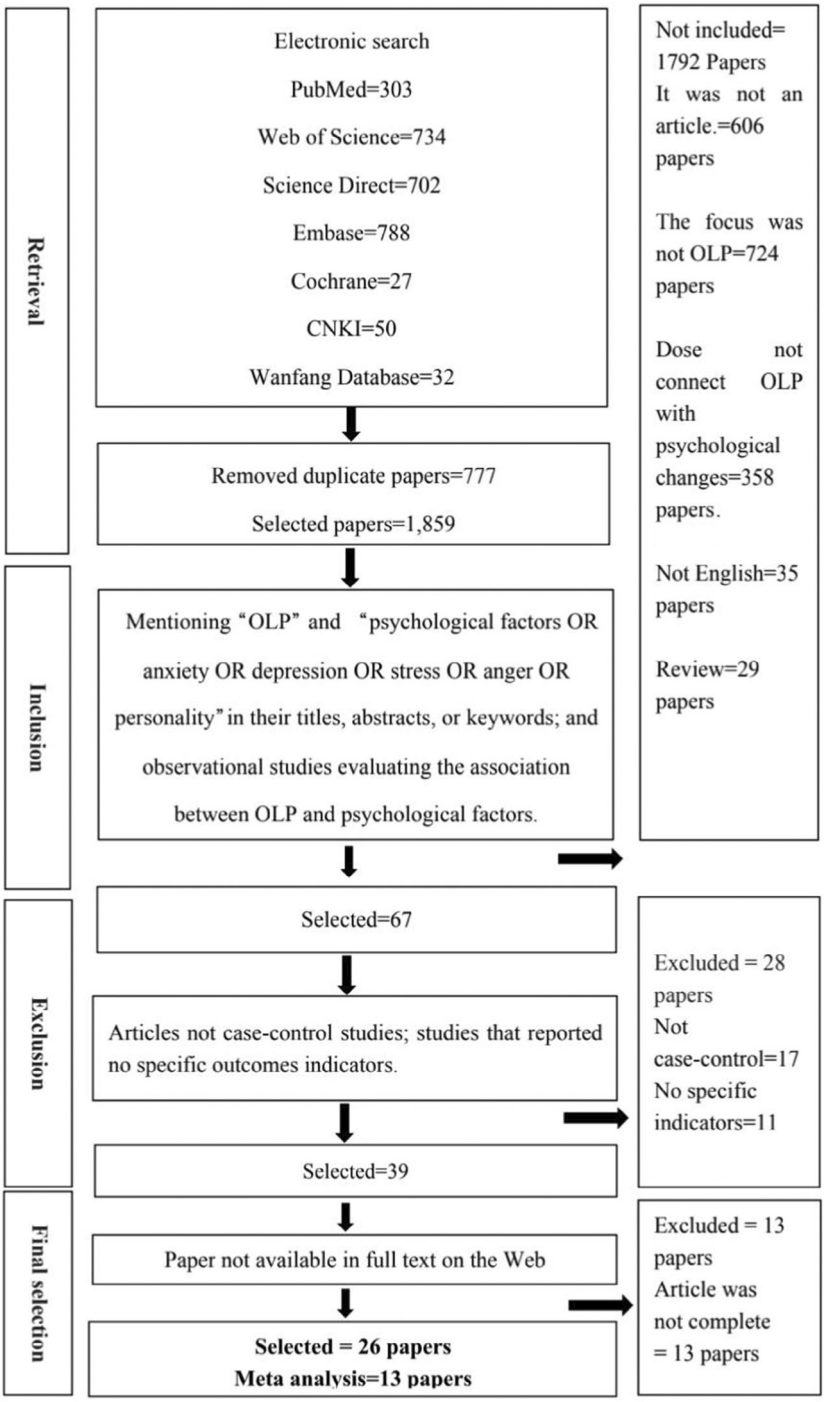

Fig. 1 Flowchart of study selection.

Science, 702 from Science Direct, 27 from the Cochrane Database, 50 from the CNKI and 32 from the Wanfang Database. After removing duplicates, 1859 articles remained. After screening the titles and abstracts, the remaining 67 articles were evaluated by reading their full text. Of these, 28 articles did not meet the inclusion criteria and the full text of 26 articles could not be obtained; thus, 13 studies were included in the meta-analysis.

Study characteristics

Our analysis included 26 studies, which are shown in Table 1. Anxiety, depression, stress, anger and personality traits were the outcome indicators. There were 2548 participants, ranging in age from 18 to 70 years. The sample was predominantly women, with a gender ratio of 2.3:1, which is consistent with the gender difference in OLP. All the studies used a

Table 1. Overview of the included studies

	Author(s), year[ref]	N (women:men)	N (women:men) controls	Questionnaires	Significant findings compared to control(s) (*P*)	Notes
1	Chaitanya *et al.* 2020[2]	30 (22:8)	30 (22:8)	HADS	Higher level of anxiety ($P < 0.0002$) and depression ($P < 0.0001$)	Significant difference between two groups on serum cortisol levels ($P < 0.0001$)
2	Hena Shaw *et al.* 2020[22]	43 (29:14)	42 (27:15)	DASS-42	OLP group had significantly higher depression ($P < 0.0001$), anxiety ($P < 0.0001$) and stress ($P < 0.0001$)	Mean serum and salivary uric acid levels were significantly lower in OLP subjects compared with the controls
3	Alessandra *et al.* 2020[24]	21 (15:6)	21 (15:6)	BAI, BDI, PSS-14	Significant differences in anxiety, depression and perceived stress scores ($P = 0.001$, $P = 0.005$, $P = 0.026$, respectively)	No association between the disease and salivary flow rate ($P = 0.29$) or the pattern of salivary cortisol secretion
4	Barbara Manczyk *et al.* 2019[4]	26 (18:8)	26 (14:12)	DASS-21	Higher level of anxiety ($P = 0.018$), depression ($P = 0.006$) and stress ($P = 0.003$)	
5	Marta Vilar-Villanueva *et al.* 2019[6]	48 (41:7)	40 (25:15)	HADS OHIP-14	Higher level of anxiety ($P < 0.01$) and depression ($P < 0.05$)	43.5% of patients with reticular OLP exhibited signs of anxiety, compared to 28% of patients with atrophic/ulcerative OLP
6	Zucoloto *et al.* 2019[3]	45 (35:10)	87 (67:20)	HAM-A, OHIP-14	No differences were found in the scores for the HAM-A dimensions of psychic anxiety and somatic anxiety	
7	Meihua Zhang *et al.* 2019[11]	100 (42:58)	100 (51:59)	SAS, SDS,	Significant differences were found for the SAS score and SDS score ($P < 0.05$)	Higher scores on the OHIP-14 dimensions of physiological discomfort and social limitation
8	Chao Yang *et al.* 2018[12]	45 (28:17)	45 (31:14)	HADS, OHIP-14	Higher levels of anxiety ($P < 0.001$) and depression ($P < 0.001$).	Levels of 5-HT and NE were lower; CTH and CORT levels were higher ($P < 0.05$).
9	Juan Li *et al.* 2018[9]	139 (94:45)	115 (79:36)	BAI, BDI	Higher levels of anxiety ($P < 0.05$) and depression ($P < 0.05$)	In the OLP group, life quality was positively associated with oral health, which was positively correlated with anxiety ($P < 0.001$) and depression ($P < 0.001$)
10	Yixin Zhou *et al.* 2018[8]	80 (53:27)	49 (28:21)	SAS, SDS, EPQ	Higher level of subjective depression in OLP with the course of disease ($P = 0.005$)	The rates of anxiety (39%) and depression (50%) were higher than the rates in the healthy control group (20%)
11	Akanksha Gupta *et al.* 2017[21]	39 (25:14)	39 (25:14)	DASS-21	Significant differences in depression scores ($P = 0.01$) and stress scores ($P = 0.009$)	No differences were found in anxiety scores ($P = 0.693$)
12	Masoumeh Mehdipour *et al.* 2016[27]	32 (19:13)	31 (13:18)	STAXI-2	Significant differences on the SAngP, TAngT and AXI ($P < 0.05$)	A significant relationship was found between pain intensity and reactional anger traits (TAngR)
13	Pia Lopez-Jornet *et al.* 2016[28]	33 (26:7)	32 (24:8)	HADS, PSQI, ESS	OLP patients had significantly higher	Poor sleep quality (PSQI) was reported by 54.4% of OLP patients, but only 31% of the control subjects
14	Alves *et al.* 2015[25]	48 (42:6)	48 (42:6)	STAI, SRQ-20, SF-36	A significant difference ($P = 0.033$) was found in state anxiety and the prevalence of depressive symptoms	No significant difference ($P = 0.087$) in trait anxiety was found
15	Chaithra Kalkur *et al.* 2015[20]	25	25	DASS-42	No differences were found in the scores for anxiety, depression or stress on the DASS-42	
16	Adamo *et al.* 2014[1]	50 (24:26)	50 (24:26)	PSQI, ESS, HAM-A, HAM-D	Depression ($P < 0.001$), anxiety ($P < 0.001$) and daytime sleepiness ($P < 0.001$) were found to be significantly different	Depression, anxiety and daytime sleepiness were positively correlated with sleep disturbances ($P < 0.001$)

(continued)

Table 1 (continued)

	Author(s), year[ref]	N (women:men)	N (women:men) controls	Questionnaires	Significant findings compared to control(s) (*P*)	Notes
17	Nadendla *et al.* 2014[26]	20	20	HAM-A	The mean anxiety scores of the OLP group were highly significantly different ($P < 0.001$)	The mean salivary cortisol level of the OLP group was significantly higher than the control group ($P < 0.001$)
18	Sandhu *et al.* 2014[29]	49 (26:23)	49 (26:23)	HADS	The mean HAD anxiety score was 8.0 (SD = 4.14) and the mean HAD depression score was 3.5 (SD = 3.27)	63% of the patients perceived stress with the onset and waxing/waning of OLP lesions
19	Chunhui Li *et al.* 2014[10]	120 (72:48)	80 (54:26)	HADS	Higher levels of anxiety ($P < 0.05$) and depression ($P < 0.05$)	
20	Kruna Valter *et al.* 2013[13]	50 (38:12)	50 (35:15)	STAI, BDI	Patients with OLP were significantly more anxious, depressed and stressed in both OLP stages	No differences in the levels of anxiety, depression or stress were found between the two stages of OLP disease (acute vs. remission period)
21	Charu Kapoor *et al.* 2013[14]	25	25	DASS-42	Higher level of depression ($P < 0.05$). Anxiety and stress were not significantly different ($P > 0.05$)	The difference in MC counts was highly significant ($P < 0.05$)
22	Carla Girardi *et al.* 2011[5]	31 (27:4)	31 (27:4)	BDI, BAI, LISS	No statistically significant differences in anxiety ($P = 0.061$) or depression ($P = 0.832$) scores	No significant correlations were found between DHEA and cortisol levels and the depression and anxiety scores
23	Ivanovski *et al.* 2005[7]	40 (40:0)	20 (20:0)	MMPI-202	Mean values for hypochondriasis, depression and hysteria were all significantly different in the reticular and erosive OLP groups	Significant moderate positive correlations were observed between the clinical scale for hysteria and cortisol, CD3, CD4 and CD8 markers
24	Chaudhary *et al.* 2004[19]	41	73	GHQ-28, HADSs	Significantly higher stress ($Z = 4.331$; $P < 0.05$), anxiety ($Z = 4.260$; $P < 0.05$) and depression levels ($Z = 4.942$; $P < 0.05$)	There were no significant differences in anxiety, depression or stress between OLP patients and positive controls
25	Koray *et al.* 2003[23]	40 (24:16)	40 (22:18)	STAI	Higher levels of state anxiety ($P < 0.001$) and trait anxiety ($P < 0.001$)	The difference in cortisol was highly significant ($P < 0.001$)
26	Vallejo *et al.* 2001[18]	80 (52:28)	80 (52:28)	HAM-A, MADRS	Higher levels of depression ($P < 0.001$) and anxiety were significant ($P < 0.001$)	Erosive OLP patients scored higher ($P < 0.05$) on the MADRS scale than non-erosive patients did

HADS = Hospital Anxiety and Depression Scale; DASS = Depression Anxiety Stress Scale 21; BDI = Beck Depression Inventory = BAI = Beck Anxiety Inventory; PSS-14 = Perceived Stress Scale; OHIP-14 = Oral Health Impact Profile[14]; HAM-A = Hamilton Anxiety Scale; SAS = Self-rating Anxiety Scale; SDS = Self-rating Depression Scale; EPQ = Eysenck Personality Questionnaire; E-OLP = Erosive oral lichen planus; STAXI-2 = State-Trait Anger Expression Inventory-2; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; STAI = State-Trait Anxiety Inventory; SRQ-20 = Self Reporting Questionnaire-20; SF-36 = Generic quality of life; SAngP = Physical Anger Statement; TAngT = Anger trait as outburst; AXI = Anger expression-in; TAngR = Reactional anger trait questionnaire; HAM-D = Hamilton rating scale for Depression; LISS = Lipp's Inventory of Stress Symptoms for Adults; MMPI-202 = Minnesota Multiphasic Personality; GHQ-28 = General Health Questionnaire-version 28; DHEA = dehydroepiandrosterone; MADRS = Montgomery-Asberg Depression Rating Scale.

case-control design (individuals with OLP vs. healthy controls). Most of the studies (Table 1) used professional psychometric scales, mainly focusing on anxiety and depression. The following instruments were used: seven studies used the Hospital Anxiety and Depression Scales (HADS),[15–21]; five studies used the Depression Anxiety Stress Scale (DASS)[9,22–25]; four studies used the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI)[26–29]; three studies used the State-Trait Anxiety Inventory (STAI),[28,30,31]; four used the Hamilton Anxiety Rating Test (HAM-A)[32–35]; one study used the Hamilton rating scale for Depression (HAM-D)[34]; two studies used the Self-rating Anxiety Scale (SAS) and the Self-rating Depression Scale (SDS)[36,37]; one study used the State-Trait Anger Expression Inventory-2 (STAXI-2)[38]; and one study used the Montgomery-Asberg Depression Rating Scale (MADRS).[32] Two studies on personality characteristics used the following scales: one study used the Eysenck Personality Questionnaire (EPQ)[36] and the other used the Minnesota Multiphasic Personality Inventory (MMPI-2).[39] The measures of OLP and stress also varied with two different scales: one used the Perceived Stress Scale (PSS-14)[26] and the other

used the Lipp Inventory of Stress Symptoms for Adults (LISS).[29] In addition, two studies used the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) to investigate the sleep quality of OLP patients.[18,34]

Quality evaluation

The quality scores of the studies are shown in Table 2. The average quality score of the 26 studies was 6.73 (medium quality). Compared with comparability, they scored higher for both selection and exposure.

Anxiety, Depression and Stress

Most studies have confirmed the correlation of OLP with anxiety, depression stress. However, there are three studies that contradict this finding.[9,29,35] The most commonly used scales were the HADS (seven studies) and the DASS (five studies).

Table 2. Quality ratings of the included studies based on the Newcastle–Ottawa quality assessment scale (N = 26)

First author of study, year	Selection	Comparability	Exposure/ outcome	Total
Chaitanya, 2020	3	1	3	7
Hena Shaw, 2020	4	2	2	8
Alessandra, 2020	4	1	2	7
Vilar-Villanueva, 2019	3	2	3	8
Manczyk, 2019	2	1	3	6
Zucoloto, 2019	4	1	3	8
Meihua Zhang, 2019	3	1	2	6
Chao Yang, 2018	2	1	3	6
Juan Li, 2018	3	1	3	7
Yixin Zhou, 2018	3	1	2	6
Gupta, 2017	2	1	2	5
Masoumeh Mehdipour, 2016	3	1	3	7
Lopez-Jornet, 2016	4	1	3	8
Alves, 2015	3	1	2	6
Chaithra Kalkur, 2015	3	1	3	7
Sandhu, 2014	3	1	2	6
Adamo, 2014	3	1	3	7
Nadendla, 2014	3	1	2	6
Chunhui Li, 2014	3	1	3	7
Kruna Valter, 2013	3	1	2	6
Charu Kapoor, 2013	3	1	3	7
Carla Girardi, 2011	3	1	3	7
Ivanovski K, 2005	4	1	2	7
Chaudhary,2004	3	1	3	7
Koray, 2003	3	1	2	6
Vallejo, 2001	3	1	3	7
Mean scores	3.11	1.07	2.58	6.73

Anxiety

According to six studies using the HADS[15,19–21] and the DASS,[23,24] anxiety symptoms were more common in patients with OLP than in healthy controls. The pooled OR of the six studies was 3.18 (95% CI: 1.55–6.51), which showed that, compared with the control group, the risk of anxiety was significantly higher in OLP patients (Fig. 2a). Moderate heterogeneity was observed among these studies (I^2 = 62.9). Seven studies used different diagnostic tools to measure anxiety, including the HADS,[17,18] DASS[9,22,25] and HAM-A.[32,33] Six studies found that anxiety was significantly higher in patients with OLP than controls. Only one found no difference in anxiety scores between OLP patients and controls.[9] The pooled MD for the studies that used the HADS was statistically significant, 1.51 (95% CI: 0.26–2.76). However, the MD was not significant for the DASS, 1.01 (95% CI: −0.03 to 2.04) or the HAM-A, 2.0 (95% CI: −0.71 to 4.71) (Fig. 3). The heterogeneity of these studies was greater than 90%.

Depression

Six studies used the HADS (four studies)[15,19–21] and the DASS (two studies)[23,24] to evaluate the depressive symptoms of OLP patients. The pooled OR was 4.17 (95% CI: 1.92-11.53), indicating that, compared with the controls, the risk of depression in OLP patients was significantly greater. There was a certain degree of heterogeneity among these studies (I^2 = 69.4%) (Fig. 2b). Five studies used different diagnostic tools to measure depression and OLP, including the HADS (two studies)[17,18] and the DASS (three studies).[9,22,25] The pooled MD of the DASS in these studies was statistically significant, 1.38 (95% CI: 0.68-2.08), but the MD of the HADS was not, 1.65 (95% CI: −0.12 to 3.41); the studies were highly heterogeneous (I^2 = 96.8%) (Fig. 4). However, all the research results showed that depression had a higher prevalence in OLP patients, compared with controls.

Stress

Three studies compared the stress symptoms between OLP patients and controls using the DASS-21 (two studies)[23,24] and the PSS-14 (one study).[26] The pooled OR was 4.14 (95% CI: 1.92–11.53), and there is no heterogeneity between the studies (I^2 = 0), indicating that stress symptoms might be one of the risk factors for OLP. However, three more studies measured the stress scores of OLP patients with the DASS-42,[9,22,25] and the pooled MD of these studies was not statistically significant, 0.93 (95% CI: −0.12 to 1.98), because of the high heterogeneity among the studies (I^2 = 91.0%).

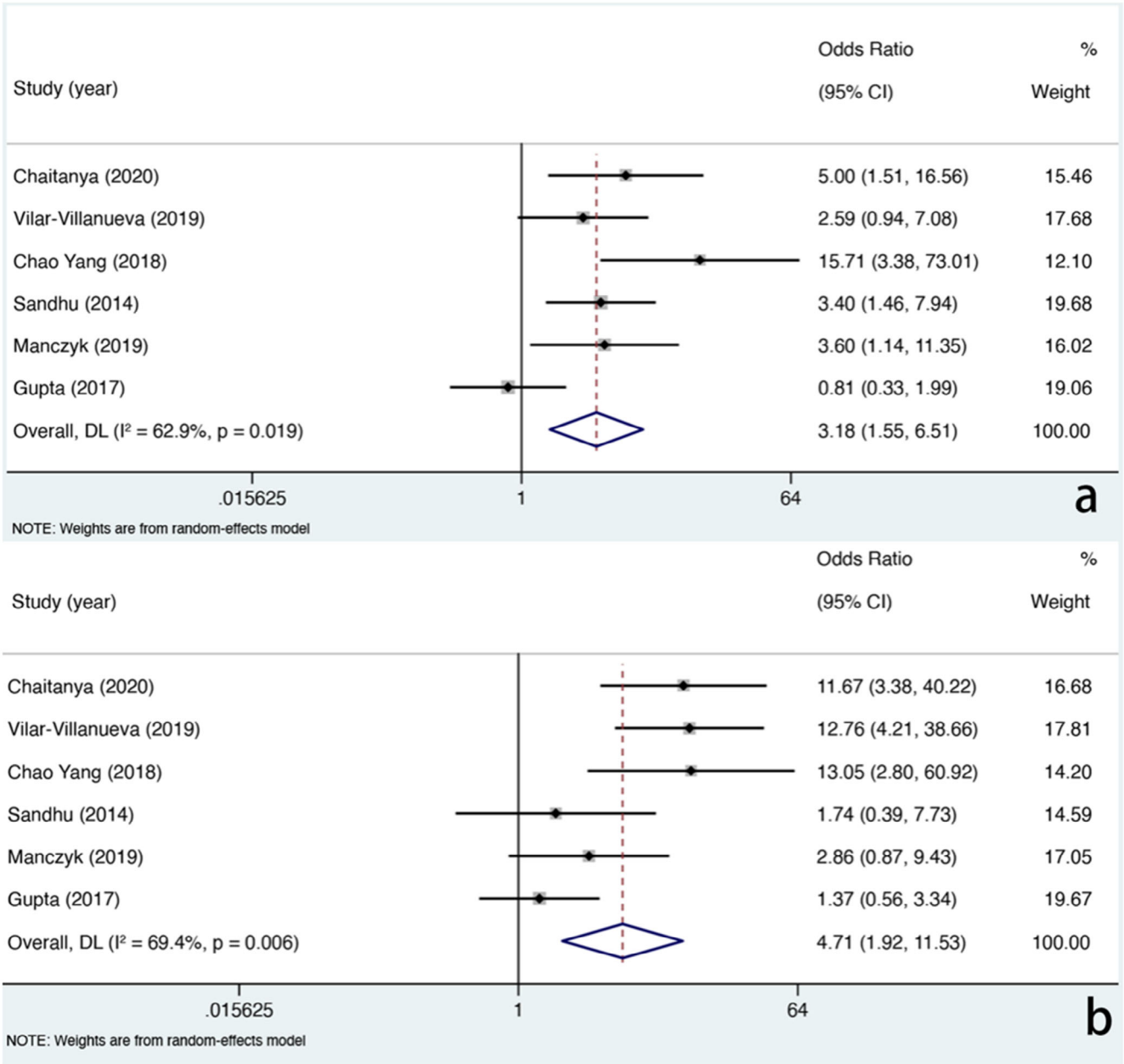

Fig. 2 Forest plot of the prevalence of anxiety in OLP patients and controls (a), forest plot of the prevalence of depression in OLP patients and controls (b).

Other psychological factors

Due to the lack of uniform and complete outcome indicators, we only carried out a descriptive analysis of the relationship of OLP with anger, personality characteristics and sleep disorders.

Anger

As only one study examined anger and OLP, only a descriptive analysis was carried out. Mehdipour *et al.* used the Anger Expression-In scale to determine the correlation between anger and OLP, which showed the OLP group (MD = 69.42) reported greater anger than the control group (MD = 59.00, $P = 0.005$).[38]

Personality Traits

Two studies used different scales to assess the correlation between OLP and personality characteristics.[36,39] Ivanovski *et al.* used the Minnesota Multiphasic Personality Inventory-202 to analyse the personality characteristics of 20 patients with erosive OLP, 20 patients with reticular OLP and 25 healthy controls. The results showed that, compared to the controls,

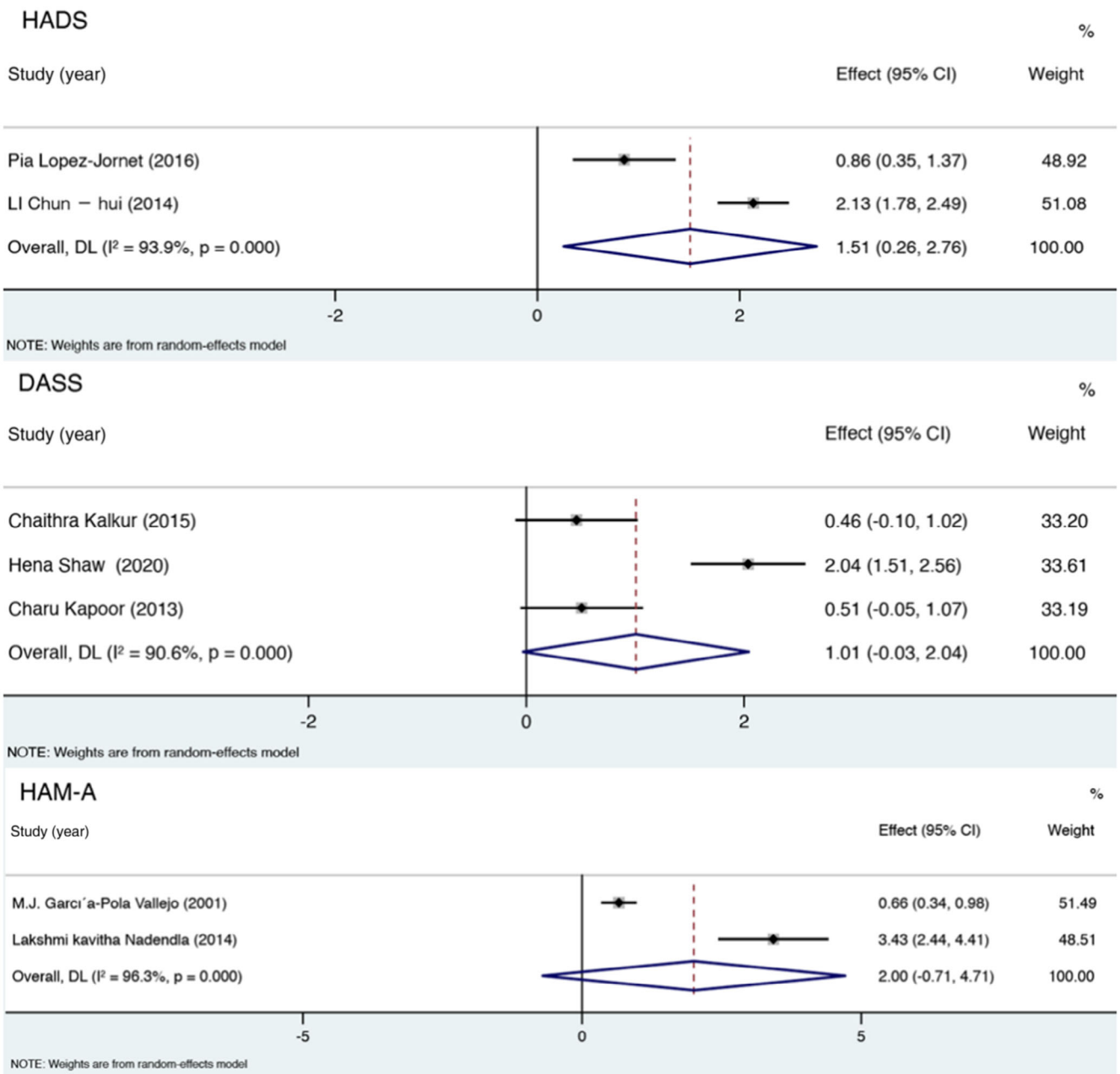

Fig. 3 Forest plot of anxiety in OLP patients and controls.

hypochondriasis, depression and hysteria were significantly higher in patients with these types of OLP ($P < 0.05$).[39] Fädler *et al.*[40] found a significant negative association between neuroticism and oral health-related quality-of-life in patients with OLP.

Sleep Disorder

Sleep disorders, as one of the physical disorders related to psychological factors, are inextricably related to OLP. The results of two studies that assessed sleep quality in OLP patients using the ESS and PSQI reported the prevalence of poor sleep quality was significantly higher in OLP patients compared with controls. Poor sleep quality is one of the risk factors for the occurrence and development of OLP.[18,34]

DISCUSSION

OLP is a multifaceted disease with a complex aetiology that is related to the environment, genes, systemic diseases and life factors.[1] Many recent studies have shown that the occurrence and development of OLP, especially the deterioration and recurrence of the

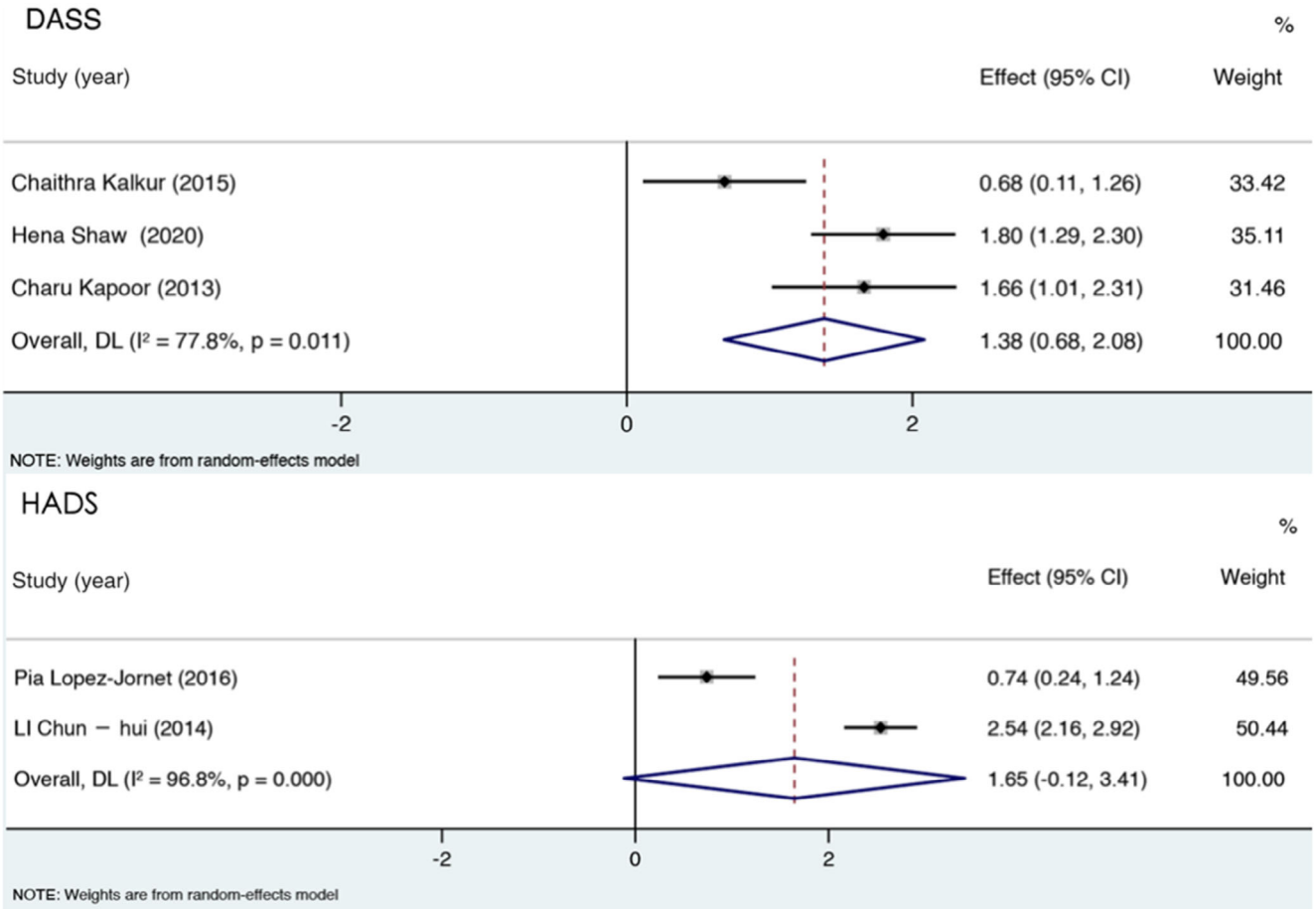

Fig. 4 Forest plot of anxiety in OLP patients and controls.

disease, are accompanied by psychological problems (e.g. stress, anxiety and depression) that can impair quality-of-life, physical and mental health of patients.[41] Furthermore, the malignant potential of OLP could increase their psychological burden. Although there are some psychological studies of OLP patients, the causal relationship between OLP and mental health has been inconclusive. In addition, previous studies have only carried out descriptive analyses of the psychological status of patients with OLP. The quantitative results of our study clearly show that patients with OLP have higher levels of anxiety, depression and stress than healthy controls do.

All the included studies, except three, found that anxiety, depression and stress play an important role in the occurrence and development of OLP. Given that OLP is a long-term chronic inflammatory disease and there is no ideal treatment for it, OLP can also affect the quality of life and physical condition of patients. Worrying about potential malignant changes in OLP might cause anxiety and depression. Therefore, the mental health of patients with OLP should not be ignored.

Anxiety and depression (as measured by the DASS and HADS) appear to be the most common comorbidities in OLP patients. This meta-analysis showed that patients with OLP had higher levels of anxiety than normal controls, and deterioration of the disease was associated with episodes of anxiety, which is consistent with the results of previous studies.[8,20,24] Alves *et al*. found state anxiety and trait anxiety scores were higher in patients with OLP; state anxiety differed significantly between the OLP and control groups, but there was no significant difference in trait anxiety between the two groups. The authors suggested the OLP group simply had a higher anxiety response to the situation than the control group did, but did not show any somatic symptoms of anxiety.[30] Zucoloto *et al*.[35] found increased anxiety was related to disease deterioration. Most studies have found that the stress, depression and anxiety of patients with erosive OLP were all associated with severe, symptomatic oral involvement. The possible mechanism is that changes in OLP oral or intestinal microbiota indirectly affect the oral and intestinal microecological balance.[42] The most important problem is that neuroimmune

regulation of the microbiome contributes to the onset or manifestation of the underlying signs and symptoms of neurodegenerative and behavioural disorders, such as autism spectrum disorder, anxiety and depression by acting on the brain-gut axis.[43] These findings indicate psychotherapy might be necessary for patients with OLP.

Depression is one of the leading causes of disability, globally,[44] and it is a consistent risk factor for many oral mucosal diseases, including OLP.[41] One study found the prevalence rate of depression in patients with OLP was 64.6%, which was higher than that of the healthy controls (11.6%).[26] Another study found patients with OLP had higher mean depression scores than a healthy control group (patients without mucosal disease) but had very similar depression scores to a control group with burning mouth syndrome (BMS), which typically includes facial pain and myofascial pain dysfunction syndrome.[45] Rojo-Moreno *et al.*[46] found depression was more prominent in patients with erosive OLP. However, in order to avoid depression and anxiety, which are considered to be secondary factors due to the pain symptoms of OLP patients, some studies have only included asymptomatic OLP patients; yet, these studies indicated that asymptomatic OLP patients had higher levels of anxiety and depression compared with healthy controls.[15] These findings were consistent with the results of previous studies and could support the view that anxiety and depression contributed not only to the development of OLP but also to worsen it.[46] To summarize, depressive symptoms might trigger OLP oral lesions and also be the cause of repeated relapses.

Quantitative analysis of six of the included studies on OLP showed that stress factors are one of the risk factors for OLP. The characteristics of stress easily contribute to tension, irritability, being upset or depressed (negative impact) and the tendency to react excessively to stressful events.[9] An earlier study that examined stress before the onset/extension of OLP found a stressful environment, especially family stressors, appeared to play a part in the occurrence and expansion of OLP injuries[9]; in 10–68% of patients with OLP, stressful life events occur before the onset of the disease.[47] Other studies have shown that a longer duration of subjective symptoms was positively related to a poorer quality of life; the greater the perceived stress was, the more serious the lesions of OLP were, creating a vicious cycle leading to recurrent attacks.[41,47] The activation of neurohormones by psychological stress mainly occurs through the hypothalamus–pituitary–adrenal (HPA) axis, and then key stress hormones (such as corticotropin-releasing hormone, ACTH and glucocorticoids) are upregulated. Through these stress-related hormones, along with additional stress response mediators (e.g. neuropeptides or neurotrophic factors), the immune response undergoes profound changes.[46] Therefore, special attention should be paid to changes in patients' mental stress in OLP management.

Some studies have shown that anger and personality traits can influence the process or the treatment outcomes of patients with OLP. Gabriella *et al.* found that the personality traits of these patients predict their attitudes about disease management and might affect treatment outcomes. Conscientiousness and extroversion personality traits are especially likely to have a significant impact on the treatment outcomes for patients with OLP who need long-term drug treatment.[50] Personality traits affect disease-management behaviour, particularly compliance, as well as subjective awareness of the influence of disease on the quality of life of patients with oral mucosal diseases. As OLP is a chronic disease that requires long-term treatment, it is important to evaluate personality traits, such as neuroticism, extroversion, openness, affinity and responsibility, to predict patients' behavioural management of OLP.[36,39]

Sleep is essential to health and quality of life, and sleep disorders (insomnia and drowsiness) can lead to subhealthy states and even a number of chronic inflammatory conditions, such as autoimmune diseases.[18] Studies have found that sleep disorders often precede or accompany mental illnesses, most notably depression and anxiety.[34] Two of the included studies that assessed sleep using the PSQI or ESS indicated the level of sleep quality in OLP patients was significantly lower than that of normal people, and sleep disturbances could cause anxiety and depression, which should be one of the risk factors for screening OLP.[18,34] Therefore, it is necessary to emphasize the role of sleep disorders in the onset of OLP and the possibility of their causing other mental disorders; clinically, OLP patients with sleep disorders should be actively counselled.

Some studies suggest that common oral mucosal diseases, such as recurrent oral ulcer (ROU), BMS and OLP might be influenced by psychological factors because the oral mucosa is very sensitive to mental stimulation, and oral diseases are the direct expression of emotions or the indirect result of psychological changes.[44] One possible mechanism might be that changes in acute or chronic psychological stress lead to significant changes in innate or adaptive immune responses, as changes in the immune response are mediated by neuroendocrine mediators of the HPA axis and the sympathetic adrenal axis. Stress increases the Th2 response by altering the balance of Th1/Th2 cytokines, thereby altering and promoting immune dysregulation, which enhances OLP immune dysregulation.[42] This situation suggests that psychobiological mechanisms might contribute to the pathogenesis of

OLP and psychiatric comorbidities might enhance the immune response of OLP.

Although the studies in this meta-analysis indicate a link between OLP and psychological problems, they do not elucidate whether OLP is caused by psychological problems, whether psychological problems are caused by the clinical symptoms of OLP or whether fear of cancer leads to increased emotional distress. Furthermore, most studies used self-report psychological assessment scales. Future research needs to use objective evaluations of psychological factors, instead of self-report measures and reduce confounding variables. The precise etiological mechanism by which psychological disorders influence OLP also needs to be addressed further.

Limitations

This study has the following limitations: few case-control studies, small sample sizes, heterogeneity in the results, the use of different scales, and the different clinical types of OLP studied. These factors should be considered in future research in this area.

CONCLUSION

OLP is a common chronic inflammatory disease that has a great effect on the quality of life of patients. The meta-analyses in this study indicate anxiety, depression and stress influence the occurrence and development of OLP. Certain specific personality traits also appear to influence the treatment of OLP, such as neuroticism and responsible willfulness. Overall, these results support that negative emotional and psychological states might play a role in the pathogenesis, development and relapses of OLP. Therefore, psychological and psychiatric examinations should be carried out routinely for patients with OLP to improve their psychological state and effectively promote their recovery and improve the prognosis of the disease.

DECLARATION OF INTEREST

The authors declare no potential conflicts of interest.

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