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EDITED BY

Yuanjun Xie,
Fourth Military Medical University, China

REVIEWED BY

Zhidan Wang,
Jiangsu Normal University, China
Zhaowen Liu,
Massachusetts General Hospital and Harvard
Medical School, United States
Luis De Taboada,
Jelikalite, Inc., United States

*CORRESPONDENCE

Shuangchun Ai
✉ aishuangchun@163.com
Shuangyue Liu
✉ shuangyue_liu@hotmail.com

[†]These authors have contributed equally to this work and share first authorship

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Photobiomodulation improves depression symptoms: a systematic review and meta-analysis of randomized controlled trials

Qipei Ji^{1†}, Shichang Yan^{1†}, Jilin Ding^{2†}, Xin Zeng³, Zhixiang Liu¹, Tianqi Zhou¹, Zhuorao Wu¹, Wei Wei¹, Huaqiang Li¹, Shuangyue Liu^{2*} and Shuangchun Ai^{2*}

¹School of Health Preservation and Rehabilitation, Chengdu University of Traditional Chinese Medicine, Chengdu, China, ²Department of Rehabilitation, Mianyang Hospital of Traditional Chinese Medicine, Mianyang, China, ³Department of Endocrinology and Metabolism, The Affiliated Hospital of Southwest Medical University, Luzhou, China

Background: Depression is a common mental illness that is widely recognized by its lack of pleasure, fatigue, low mood, and, in severe cases, even suicidal tendencies. Photobiomodulation (PBM) is a non-invasive neuromodulation technique that could treat patients with mood disorders such as depression.

Methods: A systematic search of ten databases, including randomized controlled trials (RCTs) for depression, was conducted from the time of library construction to September 25, 2023. The primary outcome was depression. The secondary outcome was sleep. Meta-analysis was performed using RevMan (version 5.4) and Stata (version 14.0). Subgroup analyses were performed to identify sources of heterogeneity. The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Results: Three thousand two hundred and sixty-five studies were retrieved from the database and screened for inclusion in eleven trials. The forest plot results demonstrated that PBM alleviated depression (SMD = −0.55, 95% CI [−0.75, −0.35], $I^2 = 46\%$). But it is not statistically significant for patients' sleep outcomes (SMD = −0.82, 95% CI [−2.41, 0.77], $I^2 = 0\%$, $p > 0.05$). Subgroup analysis showed that s-PBM was superior to t-PBM in relieving symptoms of depression. The best improvement for t-PBM was achieved using a wavelength of 823 nm, fluence of 10–100 J/cm², irradiance of 50–100 mW/cm², irradiance time of 30 min, treatment frequency < 3/week, and number of treatments > 15 times. The best improvement for s-PBM was achieved using a wavelength of 808 nm, fluence ≤ 1 J/cm², irradiance of 50–100 mW/cm², irradiance time ≤ 5 min, treatment frequency ≥ 3/week, number of treatments > 15 times. All results had evidence quality that was either moderate or very low, and there was no bias in publication.

Conclusion: We conclude that PBM is effective in reducing depression symptoms in patients. However, the current number of studies is small, and further studies are needed to extend the current analysis results.

Systematic Review Registration: <https://www.crd.york.ac.uk/PROSPERO/>, CRD42023444677.

KEYWORDS

photobiomodulation, t-PBM, s-PBM, low-level laser therapy, depression, sleep, meta-analysis

1. Introduction

Depression is a common mental illness that is widely recognized by its lack of pleasure, fatigue, low mood, and, in severe cases, even suicidal tendencies (1). As reported in 2017 statistics released by the World Health Organization (WHO), 322 million people worldwide suffer from depression, with an overall prevalence rate of 4.4%, including 5.1% for women and 3.6% for men (2). Depression can be a significant burden on an individual's life, and those who suffer from it are more susceptible to developing cardiovascular disease, long-term diseases such as obesity, and other illnesses caused by lifestyle behaviors (e.g., smoking alcohol abuse) (3, 4). Furthermore, depression is a burden on society due to the 20 times higher than usual suicide rate (5, 6). Sleeping disorders, which are often caused by depression, are often positively correlated with mortality and have a negative impact on patients' quality of life as the disease progresses (7–9). Pharmacological treatments such as tricyclic antidepressant treatment are still the mainstay of treatment for depression today. However, with less than half of all patients worldwide receiving antidepressant treatment [possibly due to side effects and low patient compliance (10, 11)], treating depression remains difficult and challenging (12).

Photobiomodulation (PBM), also known as low-level laser therapy (LLLT), represents a device-based intervention employing visible and/or near-infrared (NIR) light emitted by lasers or light-emitting diodes (LEDs) to regulate physiological processes (13–16). Our review examines the impact of PBM on brain physiology, with a specific focus on its effects on depression and sleep. The research on PBM's influence on brain physiology can be broadly categorized by where the light is applied within the body: transcranial PBM (t-PBM) and systemic PBM (s-PBM) (15). t-PBM directly modulates brain physiology by delivering light to the brain (17). At the same time, s-PBM indirectly influences brain physiology by applying light to other body areas, such as acupoints or pain points, thereby inducing systemic physiological changes that subsequently affect brain physiology (13–16). The mechanism of action (MoA) for t-PBM has partially been elucidated - transcranial-delivered light is absorbed by mitochondria in brain cells, normalizing mitochondrial function and restoring energy homeostasis (18–20). Mitochondrial dysfunction has been linked to conditions such as depression (21), sleep disturbances (22), and cognitive impairment (23, 24). Under appropriate light irradiance and luminous flux, red and NIR photons (ranging from 600 nm to 1,164 nm), absorbed by cytochrome c oxidase (CCO) in brain cells, contribute to the normalization of mitochondrial function (25) and an increase in ATP synthesis (18, 26, 27). This, in turn, has beneficial effects on enhancing cognitive and emotional brain functioning (28–31). The precise mechanism (s) by which s-PBM could affect brain physiology is still unclear. However, the beneficial effects of s-PBM on neurons have been well established, even if it is applied to distant locations and not directly to neurons (32). s-PBM can activate circulating immune cells (13, 33–35) or stem cells (36), the mitochondria (37), and the cardiovascular or the lymphatic system, which then leads to an overall increase in the mitochondrial activity to increase (similar to direct stimulation with t-PBM), resulting in a neuroprotective effect (32). In summary, both t-PBM and s-PBM possess neuroprotective effects,

and when comparing the two, direct stimulation with t-PBM is more effective, at least in animal models of Parkinson's (38).

PBM is currently garnering considerable attention in neuropsychiatric disorders (39). Evidence indicates that t-PBM can ameliorate depressive symptoms (40), with potential mediation through enhanced cerebral blood flow (31). For instance, Schiffer et al. (31) found that people with major depressive disorder (MDD) complicated by anxiety experienced significant reductions in depression scores after 2 weeks of t-PBM treatment. Clinical studies have demonstrated that s-PBM irradiation of the back and thighs alleviates depressive symptoms in patients with low back pain (41). s-PBM irradiation of the neck and acupuncture points in patients with alcohol addiction also relieves depressive symptoms (42). The use of s-PBM has been shown to relieve depression in patients with low back pain.

The FDA has cleared PBM for peripheral pain, and it is gaining popularity as a neuromodulation technique (13). Specifically, PBM was utilized to target emotional disturbance in animal models and humans, and it was demonstrated to modify the neural inflammatory profile of rat brains (43–45).

Given the current global disease burden of depression and sleep disorders, few systematic review and Meta-analyses have explored the effects of PBM on depression (46, 47), and even fewer have explored the optimal dose of PBM. Therefore, we attempted to summarize the most compelling evidence from randomized controlled trials using meta-analysis to explore the feasibility of PBM for the treatment of depressive symptoms and to summarize the optimal dose of PBM for the treatment of depressive symptoms.

2. Methods

This study has been registered with PROSPERO, registration number CRD42023444677. It was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Supplementary Appendix 1) (48).

2.1. Search strategy

From their inception to September 25, 2023, two reviewers independently searched PubMed, Embase, the Cochrane Library, Web of Science, ScienceDirect, PsycInfo, CNKI, VIP, Sinomed, and Wanfang Database. Search terms included Low-Level Light Therapy, Photobiomodulation Therapy, transcranial photobiomodulation, near-infrared light, depression, and randomized controlled trials. In Supplementary Appendix 2, the search formula is displayed in detail. In addition, we manually checked all reference lists of the retrieved papers and questioned specialists to find any potential relevant research.

2.2. Inclusion and exclusion criteria

Studies were chosen if they met the following inclusion criteria: (1) the study design was either a randomized or crossover study; (2)

participants had depressive symptoms; (3) patients were being treated using PBM (t-PBM or s-PBM); (4) the studies used widely recognized depression and sleep scales, with a primary outcome of depression and the secondary outcome of sleep.

Excluded were studies that met the following criteria: (1) conference reports, abstracts, animal trials, and replicated research; (2) the experimental group received both PBM and other treatments; (3) the objective data was either missing or could not be extracted, and the full text was unavailable after contacting the corresponding author; (4) studies in which other nondepressive outcomes interfere with the observation of depression efficacy; (5) non-Chinese and English literature.

2.3. Study selection

Endnote 20 was utilized to manage the search record. Two reviewers independently screened titles and abstracts for potentially qualified studies based on the inclusion criteria after deleting duplicate results. They then read the full text of potentially eligible studies to identify the final included literature. In the event of a disagreement, a third reviewer is invited to discuss and make a decision.

2.4. Data collection and extraction

Two reviewers (Q-pJ and S-cY) used the data extraction form to extract the required data from the included studies. The data to be extracted includes first author, time of publication, irradiance, irradiation site, wavelength, fluence, light source, treatment frequency, number of treatments, time of intervention, and outcomes. A third reviewer was asked to discuss and make a judgment call in case of disagreement.

2.5. Risk-of-bias assessment

Using the Cochrane assessment of the risk of bias, two reviewers (Q-pJ and S-cY) independently evaluate the bias risk. The tool divides studies into three categories according to their risk of bias: low, high, or unclear. These categories are selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and staff), detection bias (blinding of the outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting bias), and other biases. In the event of a dispute, a third reviewer was brought in.

2.6. Certainty of the evidence

The rating of recommendations is grounded in the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology, in which the certainty of evidence is categorized as “very low,” “low,” “medium,” or “high” (49). The quality of randomized controlled trials is high, while the quality of observational studies is low. Research quality can be lowered by five factors: limitations, inconsistency, indirectness, imprecision, and publication bias (50).

2.7. Statistical analysis

The statistical significance threshold was set at $p < 0.05$, and the data was integrated with RevMan 5.4 and Stata 14.0. Results for this study were continuous variables, and for each effect size, the researchers calculated 95% confidence intervals (CIs). For outcomes assessed using the same scale, the data were pooled using the mean difference (MD), while for outcomes assessed using different scales, the standardized mean difference (SMD) was calculated. Statistical heterogeneity of the included studies was assessed using the chi-square test and the I^2 statistical measure. Low, medium, and high heterogeneity existed according to the I^2 statistic (25, 50, and 75%). A fixed-effects model was used when $p > 0.1$ or $I^2 < 50\%$. Otherwise, a random effects model was used. Forest plots are used to display the pooled estimations. The estimates were analyzed in subgroups based on age, light source, intervention duration, wavelength, irradiance time, irradiation site, fluence, irradiance, treatment frequency, and number of treatments. Sensitivity analyses for exploring the stability of the study results were present.

2.8. Publication bias

When there were more than ten included studies for the outcome, possible publication bias was assessed by funnel plot, Egger's regression, and Begg's regression ($p < 0.05$ indicates publication bias) (51, 52). If there was a significant publication bias, a Duval and Tweedie trim and fill method was used to provide possible missing trials.

3. Results

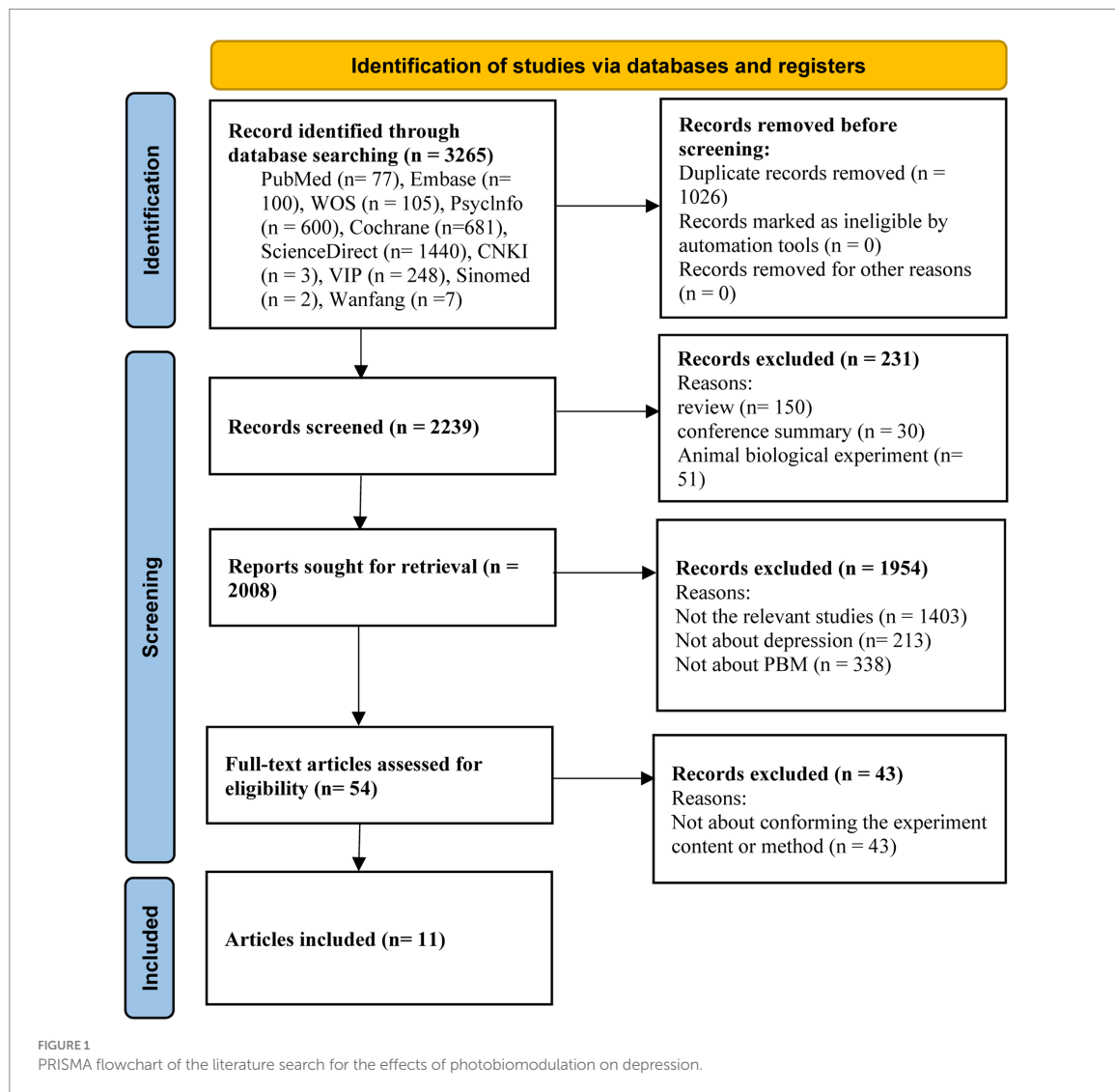
3.1. Selection and inclusion of studies

An initial search of 3,265 studies was conducted through ten databases. Eleven research studies (53–63) were identified for meta-analysis through multiple screening steps, such as excluding duplicates, selecting the type of literature, systematically reviewing title and abstract contents, and reviewing the full text (Figure 1).

3.2. Characteristics of included studies

Table 1 presents the characterization of the included trials. A total of eleven studies met our inclusion and exclusion criteria. The study areas were mainly in the United States, Australia, and Turkey, and most participants suffered from varying degrees of depression or other mood-affecting disorders. The participants totaled 407, including 200 in the experimental group and 207 in the control group. Most of the participants were between 30 and 50 years old.

Among the eleven studies, the light interventions differed in light source, Irradiation site, intervention duration, Irradiance, wavelength, fluence, treatment frequency, and number of treatments. The light source was LED in 5 studies (53, 54, 56, 57, 60, 61) and laser in 6 (55, 58, 59, 61–63). Regarding the duration of the interventions, five



studies (53, 54, 56, 61, 62) were within 4 weeks, five studies (53–55, 57, 63) were within 6–8 weeks, and one study was within 9–12 weeks (60). The wavelengths of the light ranged from 808 nm to 1,064 nm. By irradiating site, PBM can be categorized into t-PBM and s-PBM, where five studies (53, 54, 56, 60, 61) treated the brain directly (t-PBM) exposing the DIPFC, three (57–59) treated at a tender acupoint, and three in different acupoint (55, 62, 63). Based on treatment frequency, six (53–57, 60) studies treated <3/week and five studies ≥3/week (58, 59, 61–63). Based on the number of treatments, six (55–57, 60–62) studies treated ≤15 times and five studies >15 (53, 54, 58, 59, 63). Regarding the fluence, two studies were within ≤1 J/cm² (62, 63), three studies within 1–10 J/cm² (57–59), four studies within 10–100 J/cm² (53, 54, 56, 60), and two study within 100–1,000 J/cm² (55, 61). For the irradiance, four studies were within ≤50 mW/cm² (53, 54, 58, 59), five were within 50–100 mW/cm² (57, 60–63), and one was 250 mW/cm² (56).

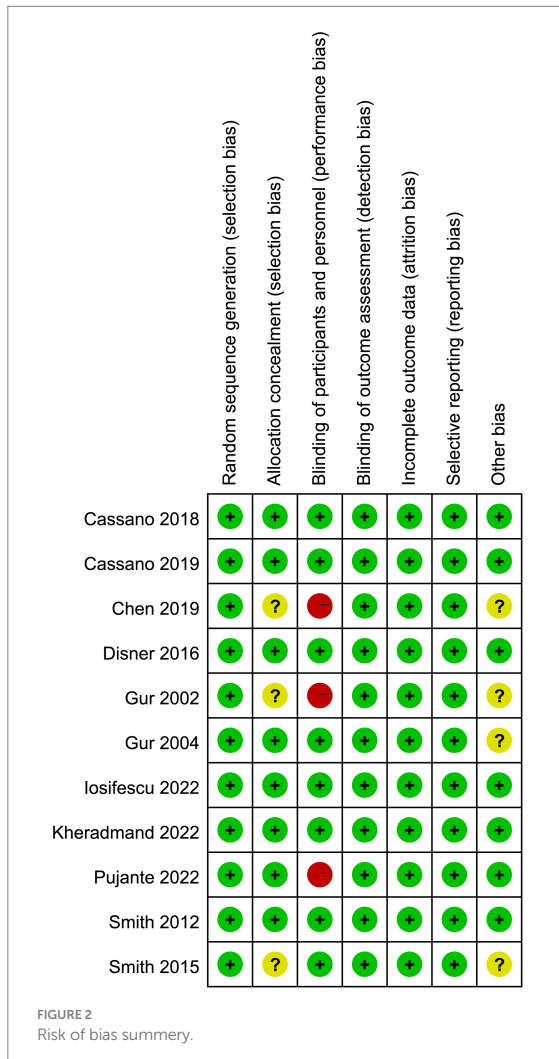
3.3. Risk of bias in studies

The risk of bias graph for each inclusion study is shown in Figure 2, and the percentages for each study are shown in Figure 3. Of the eleven included studies, all mentioned random sequence generation. Regarding allocation concealment, three studies were assessed as having some problems because details of assignment concealment were not mentioned, and eight studies reported details of allocation concealment. Nine studies mentioned blinding in their studies. Although the studies used different types of interventions, participants and staff were not informed whether they were in the experimental or control group. Three studies did not mention blinding of participants and staff. In addition, incomplete outcome data and selective reporting were not mentioned in any of the studies. Regarding other biases, seven studies were considered to be at low risk, and the remaining four were considered to have some problems.

TABLE 1 Characteristics of included studies.

Study (year)	Country	Participants (n)	Mean age	Irradiation site	Irradiance	time	wavelength	treatment frequency	number of treatments	Fluence	Light source	Duration	Outcomes
Gur 2002	Türkiye	Fibromyalgia (n = 50)	EG:30.36 CG:28.52	tender point (s-PBM)	11.2 mW/cm ²	3 min	904 nm	14/week	28	2 J/cm ²	Laser	2 weeks	HDRS
Turkey 2004	Turface	MPS (n = 50)	EG:32.24 CG:30.92	tender point (s-PBM)	11.2 mW/cm ²	3 min	904 nm	14/week	28	2 J/cm ²	Laser	2 weeks	BDI
Smith 2012	Australia	MDD (n = 44)	EG:40.8 CG:36.27	acupoint (s-PBM)	100 mW/cm ²	10s	808 nm	3/week	12	1 J/cm ²	Laser	4 weeks	HAMD
Smith 2005	Australia	MDD (n = 30)	EG:38.9 CG:38.1	acupoint (s-PBM)	100 mW/cm ²	10s	808 nm	3/week	24	0.5 J/cm ²	Laser	8 weeks	BDI
Cassano 2018	America	MDD (n = 20)	EG:47.3 CG:50.7	DIPFC (t-PBM)	36.2 mW/cm ²	30 min	823 nm	2 /week	16	65.2 J/cm ²	LED	8 weeks	HAMD
Cassano 2019	America	SD (n = 21)	EG:45.0 CG:50.7	DIPFC (t-PBM)	33.2 mW/cm ²	30 min	823 nm	2 /week	16	65.2 J/cm2	LED	8 weeks	HAMD
Chen 2019	China	Sleep disorders (n = 25)	EG:52.69 CG:52.17	acupoint (s-PBM)	NA	15 min	808 nm	2 /week	10	540 J/cm ²	Laser	5 weeks	HADS, PSQI
Kheradmand 2022	Iran	Schizophrenia (n = 32)	EG:50.24 CG:49.47	DIPFC (t-PBM)	100 mW/cm ²	15 min	810 nm	3/week	6	144 J/cm ²	Laser	2 weeks	PANSS
Pujante 2022	Spain	Xerostomia (n = 53)	EG:65.4 CG:67.8	tender point (s-PBM)	83.3 mW/cm ²	2 min	810 nm	1/week	6	6 J/cm ²	LED	6 weeks	HADS, PSQI
Iosifescu 2022	America	MDD (n = 49)	EG:37.2 CG:42.8	DIPFC (t-PBM)	54.8 mW/cm ²	4 min	830 nm	2/week	12	65.8 J/cm ²	LED	12 weeks	HDRS
Disner 2016	America	MDD (n = 32)	EG:18.72 CG:20.33	DIPFC (t-PBM)	250 m W/cm ²	4 min	1,064 nm	2/week	4	60 J/cm ²	LED	2 weeks	CES-D

EG, experimental group; CG, control group; NA, not available; PBM, photobiomodulation; t-PBM, transcranial PBM; s-PBM, systemic PBM; Min, minutes; s, second; LED, light-emitting diodes; HDRS, the Hamilton Depression Rate Scale; BDI, Beck depression Inventory; HAMD, Hamilton Depression Rating Scale; PSQI, the Pittsburgh Sleep Quality Index; HADS, the Hospital Anxiety and Depression Scale; CES-D, Center for Epidemiologic Studies- Depression Scale; PANSS, Positive and Negative Syndrome Scale; MPS, myofascial pain syndrome; MDD, major depressive disorder; SD, sexual dysfunction; DIPFC, dorsolateral prefrontal cortex.



3.4. Results of the meta-analysis

3.4.1. Depression

A total of eleven trials (53–63) reported on 407 patients with depression. Meta-analysis of fixed effects showed that PBM improved patients' depressive symptoms compared with controls (SMD = -0.55, 95% CI [-0.75, -0.35], $I^2 = 46\%$; Figure 4). Sensitivity analyses showed that exclusion of each study did not affect the stability of our trial (Figure 5).

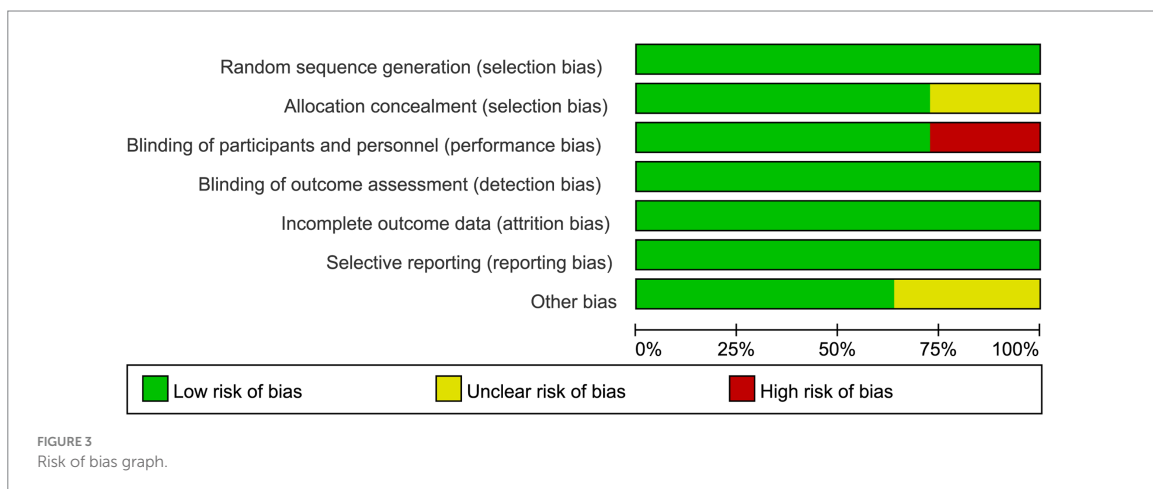
3.4.1.1. Subgroup analysis

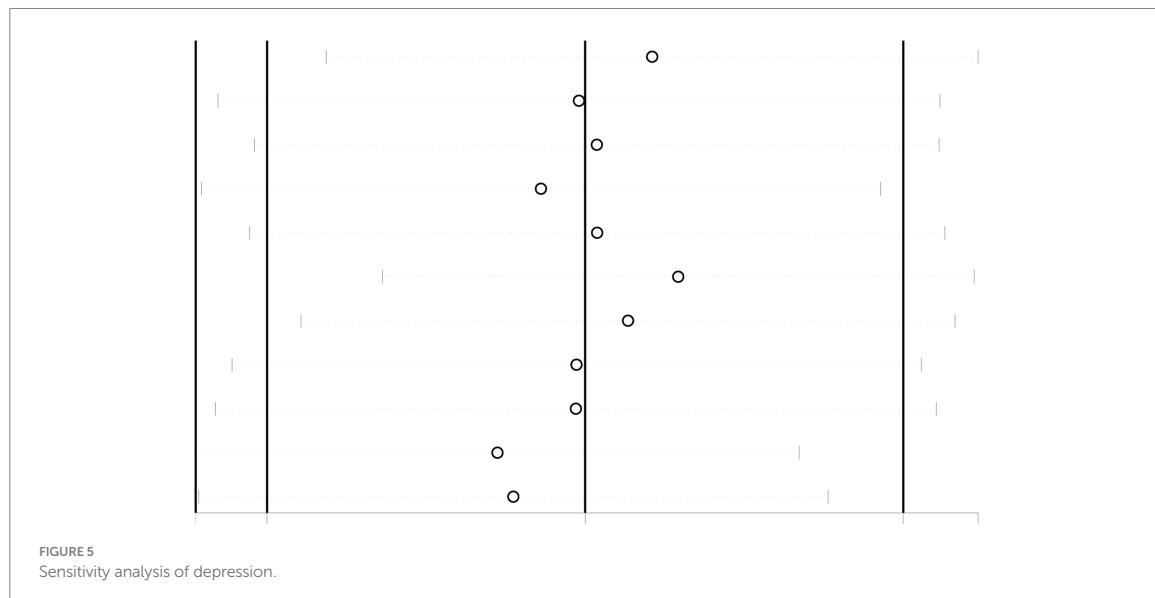
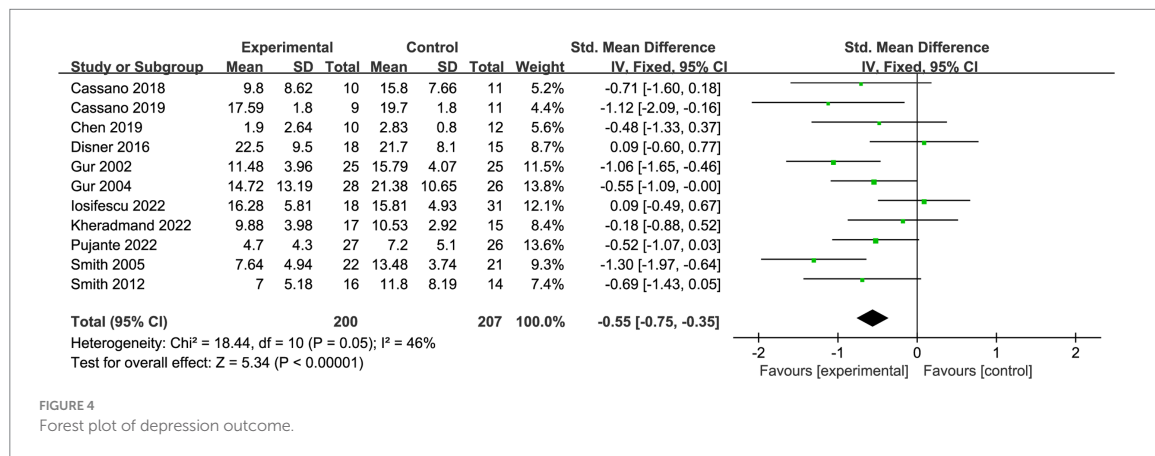
Subgroups were analyzed as shown in Table 2 (supplementing the forest plot in Appendix 4). The light was broadly categorized according to where it was applied in the body: transcranial PBM (t-PBM) and systemic PBM (s-PBM). In terms of improvement in depression, s-PBM was superior to t-PBM. A subgroup analysis of the efficacy of t-PBM on depression showed that adults under 40 years of age showed more significant improvement in depression than adults over 40 years of age; the light source was more effective with LED than with a laser; and an irradiance time of 30 min provided the best improvement in depression; Light with a wavelength of 823 nm is best; fluence of 10–100 J/cm² is better than 100–1,000 J/cm² for depression; irradiance ≤50 mW/cm² is best; treatment frequency <3/week is best; number of treatments >15 times is the best.

Subgroup analyses of the efficacy of s-PBM on depression showed that s-PBM improved depression better in adults under 40 years old; irradiation site was more effective at the acupoint than at the tender point; light source was more effective at the laser; and irradiance time was best when it was ≤5 min; Wavelength of 808 nm is best for depression; fluence at ≤1 J/cm² best improves depression; irradiance of 50–100 mW/cm² is best; treatment frequency ≥3/week is best; number of treatments >15 times is best.

3.4.1.2. Publication bias

As shown in Figure 6, publication bias was examined by funnel plot and Egger's and Begg's tests. The funnel plot showed basic symmetry with $p = 0.547$ in Egger's test and $p = 0.533$ in Begg's test, indicating no publication bias ($p > 0.05$).





3.4.2. Sleep

A total of two trials (55, 57) with 75 patients reported sleep. Meta-analysis of fixed effects showed no statistically significant difference in patient sleep in the PBM (s-PBM) group compared to the control group (SMD = -0.82, 95% CI [-2.41, 0.77], $I^2 = 0\%$; $p > 0.05$; Figure 7).

3.5. Certainty of the evidence

The GRADE results are presented in Supplementary Appendix 3. The level of evidence certainty was rated as “moderate” for depression and ‘very low’ for sleep. The leading causes of the sample size of the included study were too small, and the confidence interval was too broad.

4. Discussion

4.1. The effect of PBM on depression and sleep

A total of eleven randomized controlled trials was included in this meta-analysis, and the combined data suggest that PBM may be an efficacious depression treatment. Neurophysiological studies have confirmed that important pathological causes of depression include neuroinflammation, reduced levels of monoamine neurotransmitters, and mitochondrial dysfunction (64–67). PBM has been increased for the treatment of depression, and it stimulates neuronal processes in the brain as well as CCO, the excitation of which leads to an increase in neuronal ATP synthesis (68). These low-level lasers can modulate nitric oxide (NO) release (68, 69) thereby increasing brain oxygenation and blood

TABLE 2 Subgroup analyses of depression outcome (t-PBM and s-PBM).

Outcome or subgroup	Number of studies	Patients (E/C)	Overall effect size (95% CI) <i>p</i>		Heterogeneity <i>I</i> ² <i>p</i>	
t-PBM						
Overall	5	72/83	−0.21 [−0.54, 0.11]	0.20	38%	0.17
Age						
≤40	2	36/37	−0.09 [−0.36, 0.56]	0.70	0%	1.00
>40	3	36/37	−0.56 [−1.04, −0.09]	0.02	22%	0.28
Light source						
LED	4	55/68	−0.22 [−0.59, 0.14]	0.23	53%	0.09
Laser	1	17/15	−0.18 [−0.88, −0.52]	0.61	-	-
Irradiance time						
≤5 min	2	36/46	0.09 [−0.36, 0.53]	0.70	0%	1.00
15 min	1	17/15	−0.18 [−0.88, 0.52]	0.61	-	-
30 min	2	19/22	−0.90 [−1.55, −0.25]	0.007	0%	0.54
Wavelength						
810 nm	1	17/15	−0.18 [−0.88, 0.52]	0.61	-	-
823 nm	2	19/22	−0.90 [−1.55, −0.25]	0.007	0%	0.54
830 nm	1	18/31	0.09 [−0.49, 0.67]	0.77	-	-
1,064 nm	1	18/15	−0.09 [−0.60, 0.77]	0.80	-	-
Fluence						
10–100 J/cm ²	4	55/68	−0.22 [−0.59, 0.14]	0.23	53%	0.09
100–1,000 J/cm ²	1	17/15	−0.18 [−0.88, 0.52]	0.61	-	-
Irradiance						
≤50 mW/cm ²	3	37/53	−0.35 [−0.78, 0.09]	0.12	62%	0.07
50–100 mW/cm ²	2	35/30	−0.04 [−0.53, 0.44]	0.86	0%	0.59
Treatment frequency						
< 3/week	4	55/68	−0.22 [−0.59, 0.14]	0.23	53%	0.09
≥ 3/week	1	17/15	−0.18 [−0.88, −0.52]	0.61	-	-
Number of treatments						
≤ 15	3	53/61	0.01 [−0.36, 0.38]	0.96	0%	0.82
> 15	2	19/22	−0.90 [−1.55, −0.25]	0.007	0%	0.54
s-PBM						
Overall	6	128/124	−0.76 [−1.02, −0.50]	<0.00001	6%	0.38
Age						
≤40	4	91/86	−0.88 [−1.19, −0.57]	<0.00001	17%	0.31
>40	2	37/38	−0.51 [−0.97, −0.05]	0.03	0%	0.93
Irradiation site						
tender point	3	80/77	−0.69 [−1.01, −0.37]	<0.0001	4%	0.35
acupoint	3	47/48	−0.89 [−1.32, −0.46]	<0.0001	25%	0.26
Light source						
LED	1	27/26	−0.52 [−1.07, 0.03]	0.06	-	-
Laser	5	101/98	−0.83 [−1.12, −0.54]	<0.0001	8%	0.36
Irradiance time						
≤5 min	5	118/112	−0.79 [−1.06, −0.52]	<0.0001	17%	0.31

(Continued)

TABLE 2 (Continued)

Outcome or subgroup	Number of studies	Patients (E/C)	Overall effect size (95% CI) <i>p</i>		Heterogeneity <i>I</i> ² <i>p</i>	
15 min	1	10/12	−0.48 [−1.33, 0.37]	0.27	-	-
Wavelength						
808 nm	3	48/47	−0.89 [−1.32, −0.46]	<0.0001	25%	0.26
810 nm	1	27/26	−0.52 [−1.07, 0.03]	0.06	-	-
904 nm	2	53/51	−0.78 [−1.18, −0.38]	0.0001	35%	0.21
Fluence						
≤ 1 J/cm ²	2	38/35	−1.03 [−1.53, 0.54]	<0.0001	31%	0.23
1–10 J/cm ²	3	80/77	−0.69 [−1.02, −0.36]	<0.0001	4%	0.35
Irradiance						
≤ 50 mW/cm ²	2	53/51	−0.78 [−1.18, −0.38]	0.0001	35%	0.21
50–100 mW/cm ²	3	65/61	−0.80 [−1.17, −0.44]	<0.0001	39%	0.19
Treatment frequency						
< 3/week	2	37/38	−0.51 [−0.97, −0.05]	0.03	0%	0.93
≥ 3/week	4	91/86	−0.88 [−1.19, −0.57]	<0.00001	17%	0.31
Number of treatments						
≤ 15	3	53/52	−0.56 [−0.95, −0.17]	0.005	0%	0.92
> 15	3	75/72	−0.92 [−1.26, −0.58]	<0.00001	40%	0.19

LED, light-emitting diodes; PBM, photobiomodulation; t-PBM, transcranial PBM; s-PBM, systemic PBM; Min, minute; nm, nanometer.
 Bold value means *p* < 0.05.

flow. In addition to this, PBM modulates neurotransmitter metabolism, reduces neuroinflammation and oxidative stress, and thus acts as a neuroprotective agent (70). Many clinical trials have shown that PBM can be effective in alleviating depressive symptoms. Schiffer et al. (31) used the t-PBM to treat MDD patients suffering from anxiety disorders and traumatic stress disorders, and the research showed a significant improvement in depression and anxiety in the second and fourth weeks.

Regarding the sleep aspect, the results of this study showed no statistically significant effect of PBM on sleep. Therefore, more randomized controlled trials may be needed to determine the role of PBM in sleep. The current study suggests that PBM may improve PSQI scores and sleep quality by modulating the circadian rhythm of cortisol levels (71, 72). Several studies have also reported that PBM improves sleep quality in patients, but the exact mechanism is still under investigation (73–75).

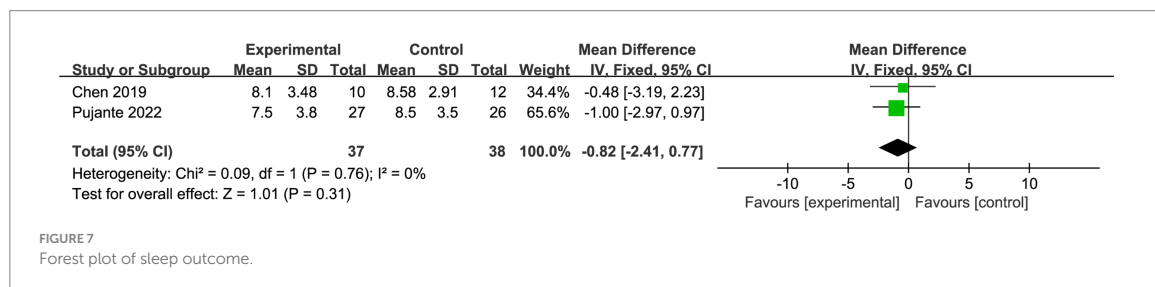
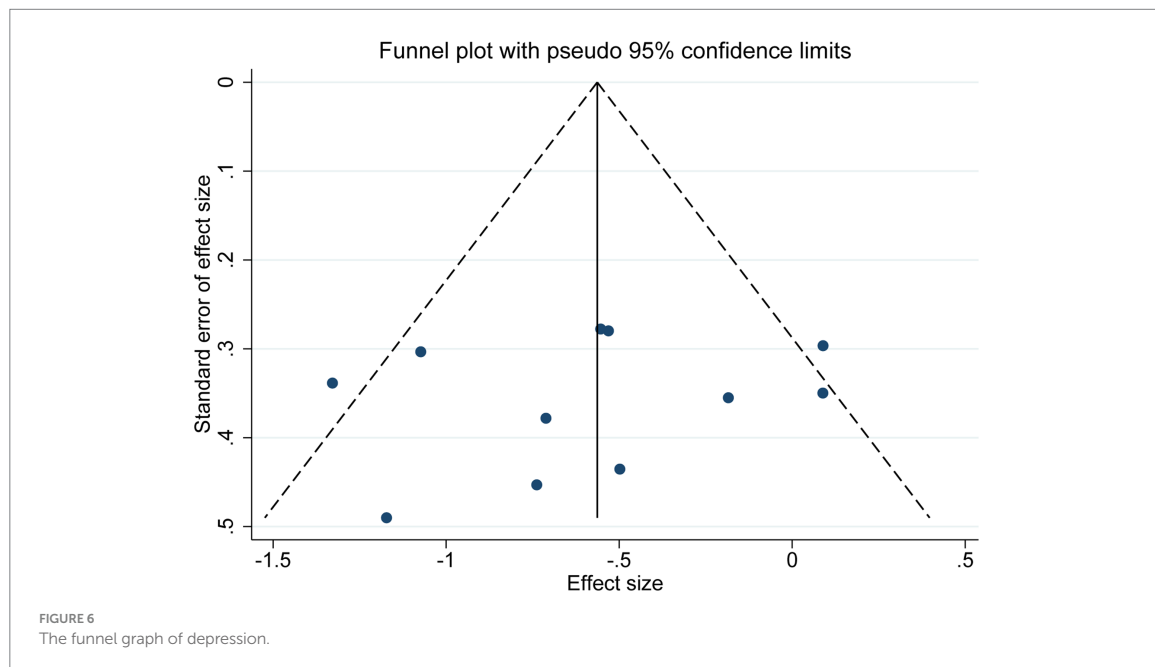
4.2. The prognosis of PBM for the treatment of depression

According to subgroup analyses, t-PBM and s-PBM showed opposite effects on the improvement of depression in terms of age. t-PBM showed better effects in patients aged 40 years or older; the opposite was true for s-PBM. Previous studies have shown that t-PBM affects prefrontal cortical CCO, which plays a key role in mitochondrial respiration (76). Whereas changes in CCO increase with age, older adults may benefit more from t-PBM treatment, which is consistent with our findings (77). Interestingly, s-PBM appeared to be more beneficial for younger participants in our study. This may be because fewer studies included middle-aged and

older patients. Few studies have focused on the effects of PBM on depressed patients of different ages, so more research is needed to validate this finding.

PBM has started experimenting with different light sources (laser and LED). Our findings suggest that s-PBM has more dramatic improvements in depression with laser as the light source. This may be because lasers have greater penetration and irradiance than LEDs (78). t-PBM was best with LEDs as a light source, but the effect was insignificant. Although it is debated whether lasers are superior to LEDs, there is evidence that LEDs are comparable to lasers (15) and are safer and less costly (79, 80). t-PBMs are typically available at wavelengths in the 600–1,164 nm region, and wavelengths in this range can stimulate CCO activity more (81). Our results validate this theory, and subgroup analysis showed that PBM at 823 nm and 808 nm wavelengths showed the best improvement in depression. Several studies have confirmed that t-PBM at 808 nm is superior to t-PBM at other wavelengths regarding brain tissue penetration (82). However, according to Mie's theory, light at 1064 nm scatters more, penetrates more, and may excite more CCOs than at 600–900 nm (82, 83). Therefore, more research is needed to explore the PBM wavelengths most suitable for treating depression.

It has been indicated that depression is associated with the metabolism of the ventral-lateral and dorsal-medial prefrontal cortex (84). In our included study, t-PBM could irradiate the DLPFC region in F3 F4 on the patient's scalp. This suggests that DLPF may be associated with mechanisms that modulate antidepressant effects. At the same time, s-PBM may have systemic anti-inflammatory, antioxidant, and pro-metabolic effects (85, 86). In our study, s-PBM irradiated patients' acupoints and tender points. A case-control trial mentioned the possible antidepressant effect of s-PBM on the back and thighs of patients with low back pain combined with depression



(41). It is difficult to establish a causal relationship when pain and depression coexist because chronic low back pain may lead to depression, and somatic pain is a common symptom of depression (87). In this trial, five patients with LBP comorbid with depression were treated with physical therapy and s-PBM and retrospectively matched with five control patients who received physical therapy alone. Depression scores decreased significantly more in the s-PBM group than in the control group after treatment. This case-control study demonstrated that s-PBM possesses antidepressant effects. It has been proposed that the systemic effects of s-PBM through the mechanism of blood irradiation can also ultimately be neuroprotective in the brain (88). The brain will benefit from PBM's ability to down-regulate pro-inflammatory factors and to increase anti-inflammatory cytokines irrespective of the site of treatment (88).

4.3. The dose-dependent effects of PBM

Longer treatment times and higher irradiance PBMs may lead to longer-lasting results (74). In our study, t-PBM with irradiance time of 30 min, treatment frequency < 3/week, and number of treatments > 15 times showed the best improvement in depressive symptoms, which is

consistent with the above findings; however, subgroup analysis of s-PBM showed that s-PBM was best at irradiance time ≤ 5 min, treatment frequency ≥ 3 /week, and number of treatments > 15 times. This may be related to the biphasic dose response of PBM, i.e., PBM regimens based on excessive energy density (J/cm^2), excessive irradiance (mW/cm^2), or excessive number of repetitions with longer duration are significantly less effective than t-PBM regimens based on lower doses (89, 90). The biphasic response has been demonstrated several times in PBM studies (91, 92). Fluence-based subgroup analyses suggest that t-PBM ($10\text{--}100 J/cm^2$) and s-PBM ($1\text{--}10 J/cm^2$) may have higher antidepressant effects. This may be because most of the photons of t-PBM are absorbed or dispersed by the scalp, skull, and cerebrospinal fluid, and only a small portion may reach the neural tissues (93). Thus, a greater fluence is required to achieve an antidepressant effect. t-PBM at $0\text{--}50 mW/cm^2$ possesses a more substantial antidepressant effect than t-PBM at $50\text{--}100 mW/cm^2$, which the biphasic response of the PBM can also explain. The biphasic response of PBM has been verified in various *in vitro* and *in vivo* studies and animal models (94). This phenomenon suggests that excessive irradiance and excessively long irradiation times may have inhibitory effects. Various studies have shown that low to moderate doses of PBM promote cell growth, whereas high intensities counteract the beneficial effects of PBM on various cell types (90).

In summary, the dose of t-PBM can be considered: irradiance time of 30 min, fluence of 10–100 J/cm², irradiance ≤ 50 mW/cm², treatment frequency < 3 /week, number of treatments > 15 times; Dose of s-PBM can be considered: irradiance time ≤ 5 min, fluence of ≤ 1 J/cm², irradiance of 50–100 mW/cm², treatment frequency ≥ 3 /week, number of treatments > 15 times. However, due to the limited number of studies, the optimal regimen and potential influences of PBM for depression have not been determined, and more rigorously designed randomized controlled trials are needed to address these issues.

4.4. Limitations of this study

There are some potential limitations of our study. Firstly, the small sample size of the included studies may affect the accuracy of the results. Second, some of the included studies did not explicitly report the blinding method, which may present a risk of bias. Finally, significant heterogeneity may result from the different locations, doses, and wavelengths of PBM irradiation in the studies we included.

5. Conclusion

In conclusion, we conclude that PBM effectively improves depression in patients. Although it is not possible to determine the specific parameters for obtaining the best results, the following can be considered in this study: t-PBM wavelength selection 823 nm, fluence selection 10–100 J/cm², irradiance selection 50–100 mW/cm², irradiance time selection 30 min, treatment frequency < 3 /week, number of treatments > 15 times; s-PBM wavelength selection 808 nm, fluence selection ≤ 1 J/cm², irradiance selection 50–100 mW/cm², irradiance time ≤ 5 min, treatment frequency ≥ 3 /week, number of treatments > 15 times. However, the current number of studies is low, and further studies are needed to extend the current analysis. More rigorous randomized controlled trials are used to understand PBM's physiological mechanisms and beneficial effects on depression.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

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Author contributions

QJ: Writing – original draft, Writing – review & editing. SY: Writing – review & editing. JD: Writing – review & editing. XZ: Writing – review & editing. ZL: Writing – original draft. TZ: Writing – review & editing. ZW: Writing – review & editing. WW: Writing – review & editing. HL: Writing – review & editing. SL: Writing – review & editing. SA: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1267415/full#supplementary-material>

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