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The Influence of Psychological Stress and Stress-Related Disorders in the Treatment Outcome of Periodontitis: A Systematic Review and Meta-Analysis

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ABSTRACT

Background and Objective: In humans 16 years and above with periodontitis (Population), how do psychological stress and stress-related disorders (PSRD; Exposure) compared to those without PSRD (Comparison) affect clinical attachment level (CAL) upon periodontitis treatment (Outcome), as observed in experimental studies or descriptive pre–post studies (Study design)?

Methods: Five major databases were searched for pre–post studies, descriptive cohort and quasi-experimental or randomised controlled trials (RCTs). For meta-analysis, mean differences in CAL and bleeding on probing (BOP) were pooled with random-effects models. Risk of bias, study quality and certainty of evidence were assessed.

Results: Thirteen studies (eight prospective, two retrospective, two quasi-experimental and one pilot RCT) with 1610 participants were identified. PSRD (measured as stress in nine studies, depression in three studies and anxiety in one study) showed a negative influence on periodontitis treatment (steps 1 + 2: eight studies, steps 1 + 2 + 3 or 4: four studies, step 4: one study) outcomes. Meta-analysis of steps 1 + 2 treatment results revealed that patients with PSRD (exposure: stress)—compared to those without—had smaller reductions in CAL (three studies; $n = 170$; weighted mean difference (WMD) = 0.78 mm; $p = 0.01$) and probing pocket depth (PPD; three studies; $n = 170$; WMD = 1.02 mm; $p = 0.04$) following periodontitis treatment in studies.

Conclusion: PSRD adversely affected periodontitis treatment outcomes, particularly concerning CAL and PPD, even though our confidence in the effect estimate is limited in the case of CAL and very low in the case of PPD. This conclusion, based on small treatment cohorts and quasi-experimental studies following steps 1 + 2 of periodontitis treatment over a 3–6-month period, warrants validation through rigorously designed studies.

1 | Introduction

Periodontitis is an inflammatory disease that causes an irreversible loss of periodontal tissues. According to the global burden of disease studies, one in eight people worldwide suffered from severe periodontitis in 2021, and this number is projected to increase by 44%, affecting over 1.5 billion people by 2050 (Nascimento et al. 2024). The disease is a major cause of tooth

loss, contributing to reduced oral function and oral health-related quality of life (OHRQoL) (Gerritsen et al. 2010). Reciprocal associations between periodontitis and other systemic diseases are increasingly recognised as significant contributors to the overall disease burden.

Poor oral hygiene, smoking and diabetes increase periodontitis risk (Timmerman and van der Weijden 2006; Van Dyke and

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Dave 2005). Mounting evidence suggests that periodontitis is associated not only with non-oral systemic inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease, but also with stress-related pathology (Otomo-Corgel et al. 2012; Sanz et al. 2020; Neupane et al. 2022). Psychological stress and stress-related disorders (PSRD) such as depression, anxiety, bipolar disorder and traumatic stress disorders are also commonly reported. In the context of the COVID-19 pandemic in recent years, high prevalence has been reported in adults for depression (28.0%), anxiety (27%), post-traumatic stress symptoms (24%), stress (37%), psychological distress (50.0%) and sleep problems (28%) (Nochaiwong et al. 2021). Furthermore, chronic and overwhelming psychological stress causes alterations to the hypothalamic–pituitary–adrenal (HPA) axis, leading to a dysregulated stress–response system (Jurruena et al. 2021), facilitating increased susceptibility to and worsening of the periodontitis pathology (Decker et al. 2021; Lee et al. 2023).

Indeed, findings suggesting periodontitis to be closely associated with psychological stress (Coelho et al. 2020; Castro et al. 2020) are supported in several reviews documenting clinically consistent associations between PSRD and periodontitis (Aggarwal et al. 2022; Badia et al. 2022; Castro et al. 2020; Decker et al. 2020; Halawany et al. 2015; Liu et al. 2018; Zheng et al. 2021; Hajishengallis and Chavakis 2021). One could suggest that susceptibility to periodontitis and its progression among PSRD patients may be explained by poor or inadequate oral hygiene (Kisely et al. 2016), host immunity alterations, or both.

The interrelationship between periodontitis and PSRD holds significant clinical and preventive relevance, as the management of one condition may enhance outcomes in the other. A few recently published studies indicate that psychological stress may negatively influence outcomes following steps 1 or 2 of periodontal treatment, showing inferior results in clinical attachment level (CAL) reduction (Marruganti et al. 2023), bleeding on probing (BOP) reduction (Petit, Anadon-Rosinach, Rettig, et al. 2021; Romano et al. 2023) and probing pocket depth (PPD) reduction (Petit, Anadon-Rosinach, Rettig, et al. 2021; Marruganti et al. 2023). These clinically relevant findings underscore the need for further investigation and warrant a comprehensive evaluation of the existing body of scientific evidence on the topic. However, no systematic review on this topic has been performed so far. Therefore, we developed the following PECOS question for this systematic review and meta-analysis: ‘In humans 16 years and above with periodontitis (Population), how do psychological stress and stress-related disorders (PSRD; Exposure) compared to those without PSRD (Comparison) affect CAL upon periodontitis treatment (Outcome), as observed in experimental studies or descriptive pre–post studies (Study design)?’

2 | Materials and Methods

The protocol for this study was preregistered in PROSPERO (CRD42022380477) and is available online. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Page et al. 2021).

The following focused (PECOS) question was considered:

In humans 16 years and above with periodontitis (Population), how do psychological stress and stress-related disorders (PSRD; Exposure) compared to those without PSRD (Comparison) affect clinical attachment level (CAL) upon periodontitis treatment (Outcome), as observed in experimental studies or descriptive pre–post studies (Study design)?

2.1 | Population, Exposure, Comparison, Outcome and Study Design (PECOS) Components

2.1.1 | Population

Humans, 16 years and above with periodontitis undergoing periodontitis treatment.

2.1.2 | Exposure

Diagnosis of PSRD or classified as having high levels of psychological stress.

2.1.3 | Comparison

Patients without PSRD diagnoses or classified as having low levels of psychological stress.

2.1.4 | Outcome

2.1.4.1 | Primary Outcome. Changes in clinical attachment level (CAL-c).

2.1.4.2 | Secondary Outcomes. Changes in bleeding on probing (BOP-c), change in probing pocket depth (PPD-c), oral health-related quality of life (OHRQoL), change in radiographic bone loss (RBL-c), change in full-mouth plaque score (FMPS-c), recurrent periodontal disease and tooth loss.

2.1.5 | Study Design

Descriptive cohort or pre–post studies, or experimental studies including quasi-experimental or randomised controlled trials (RCTs).

Recurrent periodontitis was defined as the progression of periodontitis after previous successful treatment. We adopted any operationalisations applied in the original publications that reported this outcome.

2.2 | Search Strategy and Eligibility Criteria

Records were searched in the databases Embase (Ovid), Medline (Ovid), Cochrane Library, Scopus and PsycInfo published up to 3 July 2024. We evaluated published articles including online-only and pre-publication versions. Hand searches were also conducted in Google Scholar to identify relevant non-indexed publications and grey literature. No restrictions were made for the publication year or the language of publication. For periodontitis, we used

the following MeSH terms: periodontal disease, aggressive periodontitis, chronic periodontitis, periodontal abscess and periodontal pocket. Full details of the search strategy are available in Appendix S1.

2.2.1 | Inclusion Criteria

Studies evaluating subjects 16 years and above were considered. The minimum age of 16 years was chosen to capture studies with samples that may have included young adult populations with a lower age range. Studies to be included could consist of any modality of periodontitis treatment but should have reported one pre- and post-treatment measure of periodontal parameters or a measure of the change in score in those parameters. Studies were eligible if they assessed the presence or absence of stress-related disorders, which were operationalised broadly using DSM-5 diagnoses (American Psychiatric Association 2013) related to stress, and subcategories of the medical subject headings thereof, including the following diagnoses: (a) Depressive disorders (b) Anxiety Disorders (c) Bipolar & Related Disorders and (d) Trauma- and Stressor-Related Disorders. Studies that reported on the level of stress at baseline, or any time before treatment completion, were also eligible. Any type of longitudinal studies including RCTs, descriptive cohort, quasi-experimental, and any pre-post studies were eligible. Both experimental and observational designs were considered.

2.2.2 | Exclusion Criteria

Cross-sectional studies, prevalence studies or studies not reporting on the periodontal parameters as main outcomes were excluded. We considered a minimum of 6 weeks between pre- and post-measures as essential to demonstrate a treatment effect; therefore, study durations shorter than 6 weeks were deemed ineligible. Qualitative studies and case reports/series (subjects, $n \leq 5$), opinion articles/letters to the editor with no empirical data, conference proceedings and reviews were excluded. Non-human studies and studies including subjects under 16 years of age were also excluded.

2.3 | Screening and Study Selection

The selection of studies comprised a two-step process: title and abstract screening, followed by full-text review. The authors independently screened the title and abstract of each search result. Studies subject to full-text analysis were either discarded with reason for exclusion, included for data extraction or considered for contacting authors of relevant publications with missing data. Both authors performed independent full-text review of the papers passing the screening step using the Covidence systematic review platform (Covidence Systematic Review Software 2024). Any disagreements at any stage of literature review were resolved through discussion.

2.4 | Data Extraction, Synthesis and Quality Assessment

We extracted variables from each included article covering the main study characteristics and treatment-outcome variables in

Covidence, which were subsequently exported to a spreadsheet and tabulated. For studies included in the meta-analyses, we extracted the values of periodontal parameters at baseline and at treatment completion, as well as change in the levels from baseline to final assessment, whenever available (Table 4). Data consistency and completeness were assessed by the second reviewer. Although we included studies lasting a minimum of 6-week-long therapy, longer treatment periods might be necessary to evaluate outcomes of surgery (step 3) and maintenance (step 4). Therefore, results from every type of periodontal therapy were considered independently and presented according to the treatment time horizon. Quality assessment of the cohort studies was performed by using the Newcastle–Ottawa scale (NOS; Wells et al. 2000). We used the Cochrane risk-of-bias (RoB) 2.0 tool for RCTs (Sterne et al. 2019) and ROBINS-I for non-randomised trials (Sterne et al. 2016). Quality assessment was also performed according to guidelines for pre-post studies (NHLBI 2014), which enabled quality assessment across different study designs. The level of certainty of evidence was reported according to the GRADE approach, with collaborative assessment undertaken for risk of bias, indirectness, inconsistency, imprecision and publication bias, as well as the upgrade dimensions: large magnitude of effect; dose-response gradient; plausible confounding that would reduce a demonstrated effect (Hultcrantz et al. 2017; Guideline Development Tool, n.d.). The accompanying summary-of-findings (SoF) table is presented, and a full GRADE Evidence Profile Table is appended in Supporting Information.

2.5 | Meta-Analysis

Our main outcome of interest was the relative difference in the periodontal outcomes between groups with and without PSRD. When at least two studies evaluated similar periodontitis therapy modality and PSRD exposure, with reporting of both pre and post mean values per group or directly reported the mean differences per outcome, a meta-analysis was conducted. We used the pre and post values to calculate mean differences across groups. Standard deviations around the mean differences were used if the original studies reported those values. Because of the unavailability of data regarding the correlations between pre and post values of the periodontal parameters, we estimated the standard deviation of the changes by imputing a fixed conservative estimation of the correlation coefficient of $r=0.7$ as recommended by Rosenthal (1993) into the following formula, as used in previous publications (Papadopoulos et al. 2020; Yagiz et al. 2022):

$$SD_{\text{change}} = \sqrt{SD_{\text{pre}}^2 + SD_{\text{post}}^2 - (2 \times r \times SD_{\text{pre}} \times SD_{\text{post}})}$$

where SD_{pre} and SD_{post} represent the standard deviations of the group means of the respective treatment outcome at baseline and post treatment, respectively. One study (Varadhan et al. 2019) was subjected to this estimation. Finally, meta-analysis was performed using the mean differences and the 95% confidence intervals from Review Manager 5.4 (The Cochrane Collaboration 2020). Random-effects models were used because of the expected variations in sampling, treatment and follow-up duration. The weighted mean difference (WMD) of the pre-post changes in periodontal outcomes between groups with and without PSRD was calculated

and visualised using forest plots. Heterogeneity was assessed using the I^2 statistic. Funnel plots are presented for visual inspection of publication bias. Because of the small number of studies included in the meta-analysis, no formal tests were performed for publication bias or meta-regression.

3 | Results

The systematic search returned 3641 unique references. After title and abstract screening, 76 papers were selected for full-text review. The screening procedure entailed 79% agreement between the two reviewers, with a kappa value of 0.57. The final analysis included 13 unique studies based on 15 publications. The PRISMA flow chart of the search results and study selection is provided as Figure 1. The reason for exclusion of studies following full-text review is available as Appendix S2.

The SoF table summarises the main findings for the primary and secondary outcomes, including effect estimates and certainty

of evidence as assessed using the GRADE approach. For transparency, a full GRADE Evidence Profile Table is provided in Appendix S6.

3.1 | General Study Characteristics and Study Quality

Study details are shown in Table 1. Thirteen studies (eight prospective, two retrospective, two quasi-experimental and one pilot randomised control parallel study) were included, encompassing 1610 study subjects (range: 25–697 subjects, female samples ranging from 0% to 72.5%). Periodontitis treatment included steps 1, 2, 3 and 4 of therapy, with one study involving antibiotics and none reporting the use of chlorhexidine or other adjuncts. The reporting of PSRD varied: from the diagnosis of stress-related disorders (three studies) and saliva measures of cortisol (two studies) to standardised questionnaires (seven studies) and non-structured interviews (one study). Altogether, nine studies determined stress, three

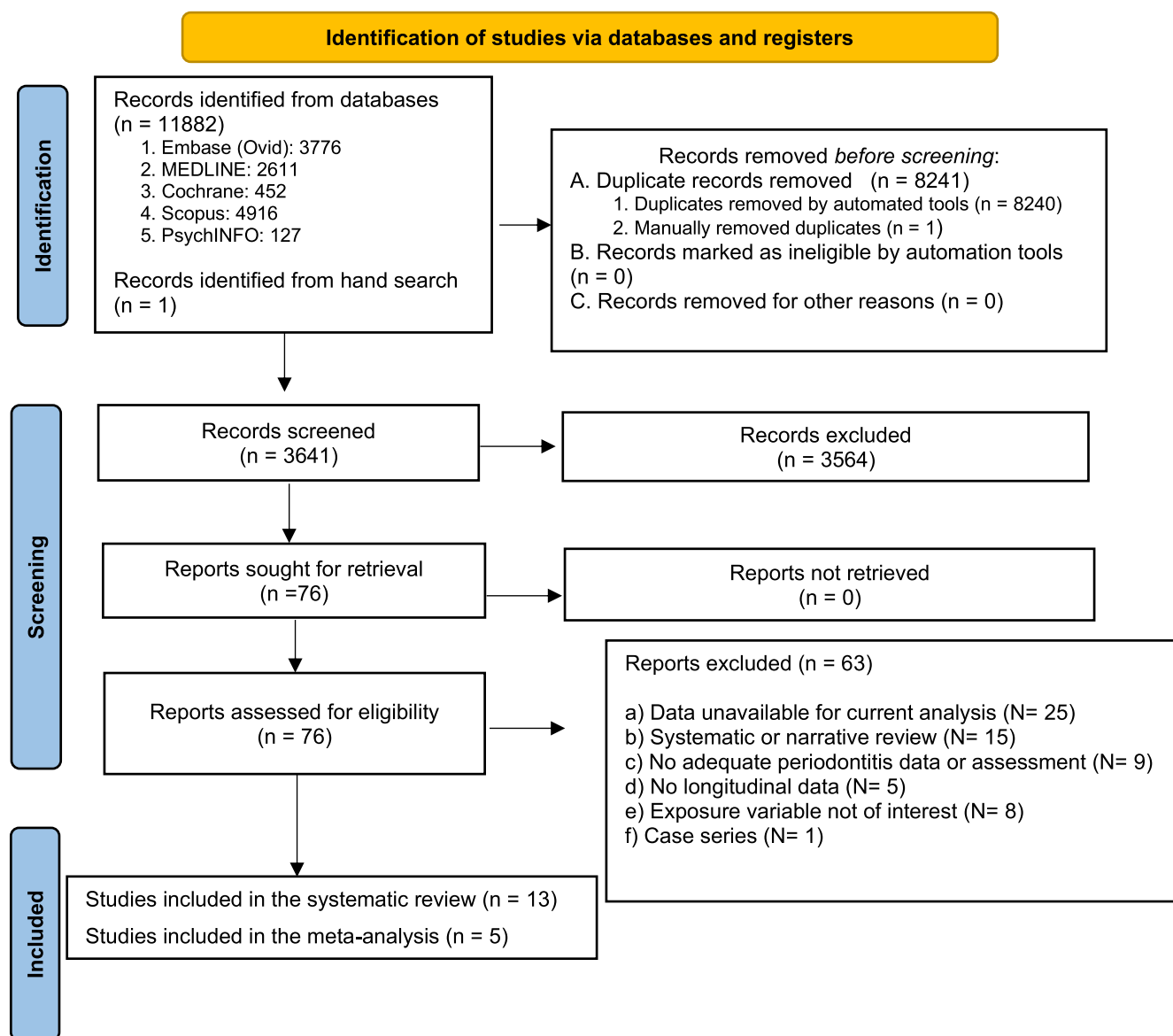


FIGURE 1 | Preferred reporting items for systematic reviews and meta-analysis flow diagram for the current study.

TABLE 1 | Characteristics of the studies included in the systematic review.

First author (year)	Country	Sample size and age (mean ± SD)	Female (%)	Study design and setting	Study outcome measures	Mental disorder diagnosis/PSRD reporting	'Cut off' for being stressed	Periodontal diagnosis	Periodontal treatment	Follow-up duration
Discepoli et al. (2022)	Italy	N = 126; (52.2 ± 10.1) years	58.7	Pre-post quasi-experimental design; University Unit of Periodontics	PPD, BOP, FMPS	Brief-IPQ, emotional response	Linear (11-point scale)	Stage I/II/III/IV	Steps 1, 2	3 months
Petit, Anadon-Rosinach, Tuzin, et al. (2021), Petit, Anadon-Rosinach, Rettig, et al. (2021)	France	N = 54; 51.2 years	56.0	Prospective study, University Periodontology department	PPD, BOP, CAL, FMPS	DASS-42, binary (y/n)	DASS-stress: ≥ 14	Stage III/IV	Steps 1, 2	6 months
Costa et al. (2020)	Brazil	N = 124; depressed (n = 35) and non-depressed (n = 89)	51.6	Prospective study, Private dental clinic	PPD, BOP, CAL, FMPS	Diagnosis of depressive disorder, APA by psychiatrist (y/n)	Binary (y/n) diagnosis of depressive disorder	Stage II/III/IV	Step 4	6 years
Bertoldi et al. (2018)	Italy	N = 40; 35.4 years	72.5	Prospective study, Private practice	PPD, BOP, FMPS	Clinical interview; self-rating anxiety state (AS) and self-rating depression scale (DS).	Linear scale used in analysis	Stage I/II/III	Steps 1, 2, 4	18 months
Varadhan et al. (2019)	India	N = 60; 30–55 years	0%	Pilot randomised RCT; University periodontology unit; participants were members of border security Force	PPD, CAL, BOP	Derogatis stress profile (DSP), Saliva analysis of Cortisol	<0.72 unstressed, 0.72–0.90 stressed, > 0.90 severely stressed	Stage III/IV	Steps 1, 2	3 months

(Continues)

TABLE 1 | (Continued)

First author (year)	Country	Sample size and age (mean $\pm$ SD)	Female (%)	Study design and setting	Study outcome measures	Mental disorder diagnosis/PSRD reporting	'Cut off' for being stressed	Periodontal diagnosis	Periodontal treatment	Follow-up duration
Fardal and Linden (2008), Fardal et al. (2016)	Norway	N=81; refractory ($n=27$, 48.5 years) and controls ($n=54$, 48.1 years)	63.0	Retrospective, Private specialist practice. Patients refractory to treatment categorised as cases and normal responders as controls	Tooth loss, refractory cases	Interview	Binary (y/n) report of high stress level	Stage III/IV	Steps 1, 2, 3, 4	13.4 years
Bakri et al. (2013)	UK	N=45; stressed ($n=16$, 49.8 years) and unstressed ($n=29$, 44.6 years)	64.4	Quasi-experimental study, Public Periodontology unit	PPD, BOP, CAL	Salivary cortisol	Salivary cortisol levels: Stressed: > 10 ng/mL (am), > 2.5 ng/mL (pm)	Stage II/III	Steps 1, 2	6 months
Vettore et al. (2005)	Brazil	N=66; initial disease ($n=20$; stressed $n=6$, 45.9 years) Moderate disease ($n=26$; $n=12$, 46.4 years); severe disease ($n=20$; stressed $n=5$, 46.1 years)	40.9	Prospective case-control study, University setting	PPD, BOP, CAL, FMPS	Stress symptoms inventory (SSI)	Binary according to SSI score, cut-off not reported	Classified according to PPD categories: < 4 mm 4–6 mm > 6 mm	Steps 1, 2	3 months
Kamma and Baehni (2003)	Greece	N=25; 34.4 years.	56.0	Prospective study, private practice	PPD, BOP, CAL, FMPS	Modified and perceived stress (MAPS, Linn 1986)	Experience of stressful social events (y/n) according to MAPS	Stage III/IV	Steps 1, 2, 3, 4 (AB, $n=11$)	5 years

(Continues)

TABLE 1 | (Continued)

First author (year)	Country	Sample size and age (mean $\pm$ SD)	Female (%)	Study design and setting	Study outcome measures	Mental disorder diagnosis/PSRD reporting	'Cut off' for being stressed	Periodontal diagnosis	Periodontal treatment	Follow-up duration
Elter et al. (2002)	USA	N = 697; depressed (n = 85) and non-depressed (n = 614); 48.5 years	49.8	Retrospective cohort study, medical/dental records from dental care programme	PPD, Sub-median and Supra-median treatment outcomes based on PPD	DSM-IV, depression	Presence of depression diagnosis	Stage II/III/IV	Steps 1, 2, 3, 4	1 year
Marruganti et al. (2023)	Italy	N = 120; 58.8 ($\pm$ 11.2)	31.7	Prospective study, University setting	PPD, BOP, CAL, FMPS	PSS (Cohen 1983)	> 13 (moderate/high PSS)	Stage II/III	Steps 1, 2	3 months
Piedra-Hernández et al. (2023)	Costa Rica	N = 82; 48.3 years	61.0	Prospective study, University setting	OHRQoL (OHIP-14)	MDAS	Anxiety score; normal/slight vs. moderate and extreme	Stage I/II/III/IV	Steps 1, 2	n/a
Romano et al. (2023)	Italy	N = 63 (minor stress, age 55.4 years) N = 27 (major stress, age 57.1 years)	58.9	Prospective study, University setting	PPD, BOP, CAL, FMPS	PSS-10	$\geq$ 20 (major stress)	Stage III/IV	Steps 1, 2	3 months

Abbreviations: AB, antibiotic usage; BOP, bleeding on probing; Brief-IPQ, the Brief Illness Perception Questionnaire; CAL, clinical attachment level; DASS-42, Depression Anxiety and Stress Scale; FMPS, full-mouth plaque score; MDAS, Modified Corah's Dental Anxiety Scale; NSPD, non-surgical periodontal treatment; PPD, pocket probing depth; PSS, perceived stress score; REC, recession.

studies determined depression and one study determined anxiety. Seven studies used dichotomised PSRD based on a questionnaire; only two studies were based on clinical diagnosis of depression. Two studies used three categories of PSRD, and the remaining two studies used the level of psychological stress as exposure variable. The follow-up duration ranged from 3 months to 13.4 years (median: 9 months). Reporting of confounders considered in the analysis from the different studies is available in Appendix S4.

Quality assessment of the included studies is presented in Tables 3a–3c, with details in Appendix S5. Half of the studies were assessed to be of poor quality, three studies had good quality and two studies had fair quality. No study included in the meta-analysis was assessed to be of good quality.

3.2 | Treatment Outcomes of Periodontitis and the Role of PSRD

The main findings of the studies included in the systematic review are summarised in Table 2. All seven studies assessing CAL-c found stress-related disorders to influence CAL-c negatively following the treatment. Ten studies evaluated PPD-c, nine of which found PSRD to influence PPD-c negatively; one reported a negative or neutral effect of PSRD on PPD-c depending on PPD severity. Three of five studies found stress-related disorders to negatively influence BOP-c. Two studies showed a neutral relationship.

Two studies reporting tooth loss had long follow-up of 6 and 13.4 years. Both identified PSRD as a predictor of recurrent periodontitis, which in Costa et al. (2020) was defined as having PPD > 4 mm and CAL > 3 mm and BOP or suppuration, while Fardal and Linden (2008), Fardal et al. (2016) used the classification suggested by Hirschfeld and Wasserman (1978), where assignment to downhill (losing 4–9 teeth) or extreme downhill (losing 10 teeth or more) was classified as recurrent periodontitis. Five of seven studies reporting FMPS-c (absolute changes over time) found a neutral effect following periodontitis treatment.

OHRQoL was reported in one study, showing that low anxiety resulted in a lowered OHIP-14 score.

Changes in radiographically measured bone levels were not reported in any of the included studies.

3.3 | Sub-Group Analyses According to Periodontitis Therapy, Type of PSRD and Study Design

3.3.1 | Type of Periodontitis Therapy

Seven of the included studies (Bakri et al. 2013; Discepoli et al. 2022; Marruganti et al. 2023; Petit, Anadon-Rosinach, Tuzin, et al. 2021; Petit, Anadon-Rosinach, Rettig, et al. 2021; Romano et al. 2023; Varadhan et al. 2019; Vettore et al. 2005) reported results after steps 1 and 2 of treatment. These studies had a median follow-up period of 3 months (range: 3–6 months). Six studies reported CAL change, and all six studies found PSRD

to negatively influence CAL reduction. Seven studies reported PPD change, all showing inferiority of PPD reduction in the presence of PSRD. Five studies reported on BOP change, where three found inferiority of BOP in the presence of PSRD (Petit, Anadon-Rosinach, Tuzin, et al. 2021; Petit, Anadon-Rosinach, Rettig, et al. 2021; Romano et al. 2023; Varadhan et al. 2019), while two studies reported no difference (Marruganti et al. 2023; Vettore et al. 2005).

Three studies reported results after steps 1, 2, 3 and 4 of therapy. Elter et al. (2002) found a negative influence on PPD reduction and a neutral effect on FMPS. Kamma and Baehni (2003) reported a negative influence on CAL reductions. Finally, PSRD predicted being refractory to treatment and more tooth loss (Fardal et al. 2016; Fardal and Linden 2008).

Costa et al. (2020) found that CAL, PPD and tooth loss were negatively influenced by PSRD following step 4 of therapy over 5 years, while BOP showed a neutral relationship.

3.3.2 | Type of PSRD

3.3.2.1 | Stress. We included nine studies with stress as the PSRD exposure, whereas the outcome measures were CAL and PPD (seven studies each), BOP (five studies) and tooth loss (one study). All studies of CAL (Bakri et al. 2013; Costa et al. 2020; Kamma and Baehni 2003; Marruganti et al. 2023; Petit, Anadon-Rosinach, Tuzin, et al. 2021; Petit, Anadon-Rosinach, Rettig, et al. 2021; Romano et al. 2023; Varadhan et al. 2019) and PPD (Bakri et al. 2013; Discepoli et al. 2022; Marruganti et al. 2023; Petit, Anadon-Rosinach, Tuzin, et al. 2021; Petit, Anadon-Rosinach, Rettig, et al. 2021; Romano et al. 2023; Varadhan et al. 2019; Vettore et al. 2005) found stress to negatively affect their changes. Effects on BOP reduction were either negative (Petit, Anadon-Rosinach, Tuzin, et al. 2021; Petit, Anadon-Rosinach, Rettig, et al. 2021; Romano et al. 2023; Varadhan et al. 2019) or neutral (Marruganti et al. 2023; Vettore et al. 2005). Fardal and Linden (2008) found that being stressed is a predictor of more tooth loss.

3.3.2.2 | Depression. Three studies reported depression as the PSRD exposure. One study found inferior CAL reduction in the presence of depression (Costa et al. 2020). Both studies reporting on PPD change showed inferior PPD reduction in the presence of depression (Costa et al. 2020; Elter et al. 2002). Bertoldi et al. (2018) found inferior BOP reduction, while Costa et al. (2020) reported a neutral relationship, which also showed more tooth loss among depressed patients.

3.3.2.3 | Anxiety. One study used anxiety as the PSRD exposure. This study found inferior OHRQoL outcome following periodontitis treatment in patients expressing anxiety (Piedra-Hernández et al. 2023).

We did not find any studies investigating the role of other PSRD, such as bipolar disorder or post-traumatic stress disorder (PTSD).

3.3.2.4 | Study Design. The review did not find differing tendencies of PSRD's impact on the measured outcomes depending on the study design.

TABLE 2 | Main findings summarising the effects of psychological stress and related disorders (PSRD) on the treatment outcome of periodontitis.

Study	Outcome measure(s)	Main results	Main effects of psychological stress and related disorders (PSRD) on periodontal parameters
Discepoli et al. (2022)	PPD, FMPS	Emotional response (anxiety, stress) predicted lower probability of achieving closed pockets (regression).	Negative effect on PPD reduction, Neutral effect on FMPS
Petit, Anadon-Rosinach, Tuzin, et al. (2021), Petit, Anadon-Rosinach, Rettig, et al. (2021)	BOP, PPD, FMPS, CAL	Increasing STAI-YA negatively influenced BOP and PPD reduction following NSPT. STAI-YB was negatively associated with BOP reduction Increasing DASS stress negatively influenced BOP reduction in multivariable analysis DASS stress was associated with lower mean PPD reduction Increasing BDI showed no association with BOP outcome Increasing BDI negatively influenced FMPS DASS depression and DASS stress negatively influenced FMPS change following treatment DASS anxiety positively influenced FMPS change BDI significantly influences PPD change > 3 mm Increasing BDI negatively influenced CAL reduction following treatment DASS stress negatively influenced mean CAL following treatment.	Neutral effect on BOP change (BDI), Negative effect on BOP reduction (STAI) Negative effect on POP reduction and PPD reduction (DASS stress) Negative effect on FMPS (DASS-depression, DASS stress) Positive effect on FMPS (DASS anxiety) Negative effect on PPD-change (STAI-YA, DASS stress) Negative effect on CAL reduction (DASS stress, BDI)
Costa et al. (2020)	BOP, PPD, FMPS, CAL, tooth loss	DD (depression diagnosis): Increase in BOP 3.9%, none DD (NDD): increase in BOP 1.9% DD (depression diagnosis): Increase in mean PPD 1.7 mm; non-DD: increase in mean PPD 1.0 mm (difference 0.7 mm) DD: Increase plaque score mean 5.5%, NDD: Increase in plaque score mean 2.7%, DD: mean CAL increase 0.9 mm, non-DD: mean CAL increase 0.2 mm (difference 0.7 mm) DD: mean tooth loss in follow up 0.9, non-DD mean tooth loss 0.2 (difference 0.7).	Negative effect on PPD reduction, CAL reduction and FMPS and tooth loss
Bertoldi et al. (2018)	BOP, FMPS	BOP after treatment was correlated with depression score.	Negative effect on BOP, Neutral effect on FMPS
Varadhan et al. (2019)	BOP, PPD, CAL	Patients with chronic stress showed least improvement in BOP, PPD and CAL measures upon treatment completion. Stressed participants received either stress reduction therapy (SRT) as adjunct to non-surgical periodontal therapy (NSPT) or NSPT only. Mean reduction in PPD levels (2.3 unstressed group vs. 1.9 stressed group receiving SRT + NSPT vs. 0.3 stressed group receiving NSPT only) Mean reduction in CAL levels (1.2 unstressed group vs. 1.2 stressed group receiving SRT + NSPT vs. 0.2 stressed group receiving NSPT only) Mean reduction in BOP levels (2.7 unstressed group vs. 2.8 stressed group receiving SRT + NSPT vs. 1.1 stressed group receiving NSPT only).	Negative effect on PPD and CAL

(Continues)

TABLE 2 | (Continued)

Study	Outcome measure(s)	Main results	Main effects of psychological stress and related disorders (PSRD) on periodontal parameters
Fardal and Linden (2008), Fardal et al. (2016)	Tooth loss	Being stressed increased risk of being refractory to periodontal treatment, significant also when adjusted for smoking. Refractory cases lost more teeth (10.3 teeth lost, SD 3.5) compared to controls (0.3 teeth lost, SD 0.57). The chance of identifying a non-responding patient based on stress was 32.4% (better prediction than smoking and family history).	Negative effect on treatment outcome measured by refractory cases, negative effect on tooth loss
Bakri et al. (2013)	PPD, CAL	1.0 mm less PPD reduction in stressed compared to non-stressed participants in deep bleeding sites 1.2 mm less CAL reduction in stressed compared to non-stressed participants in deep bleeding sites 0.4 mm less PPD reduction in stressed compared to non-stressed in deep non-bleeding sites 0.2 mm less CAL reduction in stressed compared to non-stressed in deep non-bleeding sites.	Negative effect on PPD reduction and CAL reduction
Vettore et al. (2005)	BOP, PPD, FMPS	Stressed subjects had significant BOP reductions, so had non-stressed subjects. Stressed subjects showed a non-significant change in relative frequencies of pockets between baseline and follow-up, compared to significant change for non-stressed. Evident for PPD categories 4-6 mm and > 6 mm. FMPS was reduced significantly in stressed as well as non-stressed participants.	Neutral effect on BOP and FMPS, negative effect on PPD change
Kamma and Baehni (2003)	CAL	Stress significantly ($p=0.03$) influenced CAL when evaluated together with number of lost teeth, smoking and acute episodes of periodontal infection.	Negative effect on CAL
Elter et al. (2002)	PPD, FMPS	Sub-median treatment-outcome in terms of open pockets after treatment were more present among depressed. No significant difference in FMPS between depressed and non-depressed participants.	Negative effect on PPD reduction, neutral effect on FMPS
Marruganti et al. (2023)	PPD, BOP, CAL, FMPS	Moderate/high PSS was associated with lower PPD change and CAL change compared to patients with lower PSS.	Negative effect on mean PPD reduction Neutral effect on reduction of PPD > 6 mm Negative effect on CAL change Neutral effect on BOP change
Piedra-Hernández et al. (2023)	OHIP-14	Patients with slight anxiety had a significant reduction in OHIP-14 score, while patients with moderate and high anxiety had a non-significant reduction in OHIP-14 score.	Negative effect on OHRQoL change
Romano et al. (2023)	PPD, BOP, CAL, FMPS	Patients with major stress level had significantly lower reduction in BOP, PPD and CAL following NSPT. No significant difference was observed for FMPS.	Negative effect on BOP reduction, PPD reduction and CAL reduction. Neutral effect on FMPS change

Abbreviations: BOP, bleeding on probing; Brief-IPQ, The Brief Illness Perception Questionnaire; CAL, clinical attachment level; FMPS, full-mouth plaque score; NSPT, non-surgical periodontal treatment; PPD, pocket probing depth; PSS, perceived stress score; STAI-YA, State Anxiety Inventory; STAI-YB, Trait Anxiety.

TABLE 3a | Quality assessment of the included studies using the Newcastle-Ottawa Quality Assessment tool for Cohort studies.

Criteria	Petit, Anadon- Rosinach, Tuzin, et al. (2021), Petit, Anadon- Rosinach, Rettig, et al. (2021)	Costa et al. (2020)	Bertoldi et al. (2018)	Fardal and Linden (2008), Fardal et al. (2016)	Vettore et al. (2005)	Kamma and Baehni (2003)	Elter et al. (2002)	Marruganti et al. (2023)	Piedra- Hernández et al. (2023)	Romano et al. (2023)
A. Selection (maximum of four stars)										
1. Representativeness of the exposed cohort	☆	☆	☆	☆	☆	☆	★	☆	☆	☆
2. Selection of the non-exposed cohort	★	★	★	★	★	★	★	★	★	★
3. Ascertainment of exposure	★	★	☆	☆	☆	☆	★	★	★	★
4. Demonstration that outcome of interest was not present at start of study (no bone disease at start of study)	★	★	★	☆	★	★	☆	★	★	★
B. Comparability (maximum of two stars)										
1. Comparability of cohort on the basis of the design or analysis	★★	★★	★★	★★	★★	☆	★★	★★	★★	★
C. Outcome (maximum of three stars)										
1. Assessment of outcome	☆	☆	☆	★	★	☆	★	★	☆	☆
2. Was follow-up long enough for outcomes to occur?	★	★	★	★	★	★	★	★	☆	★

(Continues)

TABLE 3a | (Continued)

Criteria	Petit, Anadon- Rosinach, Tuzin, et al. (2021), Petit, Anadon- Rosinach, Rettig, et al. (2021)	Costa et al. (2020)	Bertoldi et al. (2018)	Fardal and Linden (2008), Fardal et al. (2016)	Vettore et al. (2005)	Kamma and Baehni (2003)	Elter et al. (2002)	Marruganti et al. (2023)	Piedra- Hernández et al. (2023)	Romano et al. (2023)
	★	☆	☆	☆	☆	☆	☆	★	☆	★
3. Adequacy of follow-up of cohorts	6	5	4	4	5	3	7	7	5	6
Total (maximum of nine stars)										
Overall quality	Good	Poor	Poor	Poor	Fair	Poor	Good	Good	Poor	Fair

Note: comparability of cohorts on the basis of analysis does not necessarily reflect adjustment for the relevant confounders of the role of stress or related disorders in periodontal treatment outcome; thus, a single star is allotted to the relevant studies.

3.4 | Meta-Analysis

Meta-analyses were performed for the outcomes CAL and PPD on three studies including 73 PSRD subjects and 97 non-PSRD subjects (Figure 2), all evaluating outcomes after steps 1 and 2 of periodontitis treatment and using stress as PSRD exposure. For the primary outcome (CAL), it was shown that patients with PSRD compared to those without PSRD have inferior outcomes following treatment of periodontitis (weighted mean difference; WMD = 0.78 mm; 95% CI = 0.17–1.40; $p = 0.01$; $I^2 = 65\%$). Our confidence in the effect estimate in the case of CAL is limited. Similar effects of PSRD were found in terms of PPD (WMD = 1.02 mm; 95% CI = 0.03–2.00; $p \leq 0.04$; $I^2 = 92\%$). We have very little confidence in the effect estimate for the impact of PPD; the true effect may be substantially different from these values.

As indicated by the I^2 values, heterogeneity was found to be high for PPD but low to modest for CAL. Funnel plots are presented for visual inspection of publication bias evident in the small number of studies included (Figure S1, Appendix S3).

According to the GRADE approach, the certainty of the evidence was rated as moderate for both outcomes subject to meta-analysis.

4 | Discussion

This systematic review and meta-analysis investigated the effect of PSRD on the treatment outcome of periodontitis, as reported in the updated literature. While the reporting of PSRD was done in terms of several measures, most studies reported the same periodontal parameters. Nonetheless, a clear trend emerged from the data presented in the included studies. Our primary outcome measure, CAL, was negatively affected by the presence of PSRD. The systematic review found seven studies reporting on CAL change, all of which reported inferior treatment outcomes in the presence of PSRD. Meta-analysis confirmed the finding, with robust effect in studies investigating steps 1 and 2 of periodontitis treatment and stress as PSRD exposure. Also, 9 of 10 studies showed inferior PPD reductions in the presence of PSRD, which was also confirmed in the meta-analysis. The results for BOP change and tooth loss were reported in fewer and more heterogeneous studies. Collectively, these results support the notion that PSRD negatively influence periodontitis treatment outcomes. However, the certainty of evidence was evaluated to be limited in the case of CAL and very low in the case of PPD, whereas it was uncertain in the case of the outcomes BOP, tooth loss, OHRQoL, FMPS and radiographic bone loss.

The present clinical results warrant the attention of clinicians; PSRD are not only a risk factor for the presence and onset of periodontitis but also influence treatment outcomes negatively. The observed differences seem to be influenced by other factors than the plaque level alone, which has traditionally been the major emphasis in periodontal therapy (Axelsson et al. 2004; Lindhe and Nyman 1975; Löe et al. 1965). The present results indicate that PSRD adversely affect healing upon periodontitis treatment.

TABLE 3b | Quality assessment of the included experimental studies using the ROBINS-I and RoB 2 tools.

ROBINS-I tool	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias across domains
Discepoli et al. (2022)	Moderate risk	Low risk	Low risk	Some concerns	Low risk	Some concerns	Some concerns	Moderate risk
Bakri et al. (2013)	Moderate risk	Serious risk	Moderate risk	Low risk	Moderate risk	Serious risk	Low risk	Serious risk
Cochrane risk of bias tool (RoB 2)	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias across domains		
Varadhan et al. (2019)	Low risk	Low risk	Some concerns	Low risk	Some concerns	Moderate risk		

Several studies have documented the presence of PSRD as inducing a systemic alteration of immunological activity (Glaser and Kiecolt-Glaser 2005; Hänsel et al. 2010; Schmidt et al. 2010), increasing host reactivity and negatively influencing oral and systemic health. This is documented for C-reactive protein, several cytokines and immunological modulators, linking periodontal diseases and stress-related disorders closely together (Lu et al. 2014; Neupane et al. 2022). PSRD-associated increase in the risk of periodontitis pathology and its progression may be biologically mediated or through the indirect effect of PSRD on health-related behaviours such as poor dental hygiene practices, poor nutrition and smoking (Warren et al. 2014). In the long-term studies included in the review, tooth loss and recurrent periodontal disease were documented (Costa et al. 2020; Elter et al. 2002; Fardal and Linden 2008). These findings suggest that the effects of stress may have long-term detrimental effects on the periodontium. Although several biological mechanistic explanations exist for the associations between stress pathology and accompanying periodontitis, more empirical evidence is required (Neupane et al. 2022).

A recent publication drew attention to periodontitis treatment outcomes related to lifestyle factors (Marruganti et al. 2023). Also, host-modulating therapy in periodontal disease has received great attention. Such efforts include dietary supplements (i.e., fatty acids, vitamins, fruits), TNF- α inhibitors, humanised monoclonal antibody therapy and the use of probiotics, all of which have shown promising effects (Balta et al. 2021). Recently, several studies have investigated stress reduction as an adjunct to periodontal therapy, and this may be of relevance for the clinician. Yoga has been found to improve periodontal treatment outcomes significantly (Sudhanshu et al. 2017), and stress-coping interventions have also been suggested to improve the treatment outcome for participants enrolled in a comprehensive stress coping programme (Varadhan et al. 2019).

It should be noted that only 13 studies were identified, of which only 3 provided the data for the meta-analysis. According to the GRADE approach, moderate certainty implies that we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different. Except for the studies included in the meta-analysis, the identified studies are heterogeneous in terms of PSRD exposure, periodontitis treatment performed, study design and follow-up time. The studies do not adhere to the suggested EFP guidelines (Herrera et al. 2023) of periodontal treatment. Therefore, the results should be interpreted with caution and considered preliminary.

Moreover, we did not account for baseline levels of periodontal parameters when evaluating the changes in stress parameters. This was due to inadequate data and the risk of over-correction with extracted or imputed standard deviation of the means. Pre-post meta-analysis of non-randomised samples may be subject to biased results (Cuijpers et al. 2017). However, in the absence of substantial data, we provide an up-to-date summary of the state of the art in this research area. When designing future studies, methodological rigour should be central with a larger sample size and careful selection of more homogenous groups of participants. In particular, there is a further need for controlled

TABLE 3c | Evaluation of study quality according to guidelines for pre-post studies (NHLBI 2014).

Study	1. Was the question or objective clearly stated?	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	4. Were all eligible participants that met the prespecified entry criteria enrolled?	5. Was the sample size sufficiently large to provide confidence in the findings?	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided <i>p</i> values for the pre-to-post changes?	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Score	Overall study quality rating
Discepoli et al. (2022)	1	0	1	1	1	1	1	0	1	1	0	0	8	Good
Petit, Anadon-Rosinach, Tuzin, et al. (2021), Petit, Anadon-Rosinach, Rettig, et al. (2021)	1	1	1	0	1	1	1	1	0	1	0	0	8	Good
Costa et al. (2020)	1	1	1	0	1	0	0	1	0	1	0	0	6	Poor
Bertoldi et al. (2018)	1	1	0	0	0	1	1	0	0	1	0	0	5	Poor
Varadhan et al. (2019)	1	1	0	0	0	1	1	1	1	1	0	0	7	Fair
Fardal and Linden (2008), Fardal et al. (2016)	1	0	1	0	1	1	1	0	0	0	0	0	5	Poor
Bakri et al. (2013)	1	1	0	1	0	1	1	0	1	1	0	0	7	Fair

(Continues)

TABLE 3c | (Continued)

Study	1. Was the study question or objective clearly stated?	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	4. Were all eligible participants that met the prespecified entry criteria enrolled?	5. Was the sample size sufficiently large to provide confidence in the findings?	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	10. Did the statistical methods examine changes in outcome measures from before to after the intervention?	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Score	Overall study quality rating
Vettore et al. (2005)	1	1	1	0	0	1	1	1	0	1	0	0	7	Fair
Kamma and Baehni (2003)	1	0	1	0	0	1	1	0	0	1	0	0	5	Poor
Elter et al. (2002)	1	1	1	1	1	1	1	0	0	1	0	0	8	Good
Marruganti et al. (2023)	1	0	1	1	1	1	1	0	1	1	0	0	8	Good
Piedra-Hernández et al. (2023)	1	1	1	0	1	0	1	0	1	1	0	0	7	Fair
Romano et al. (2023)	1	1	0	0	1	1	1	1	0	1	0	0	7	Fair

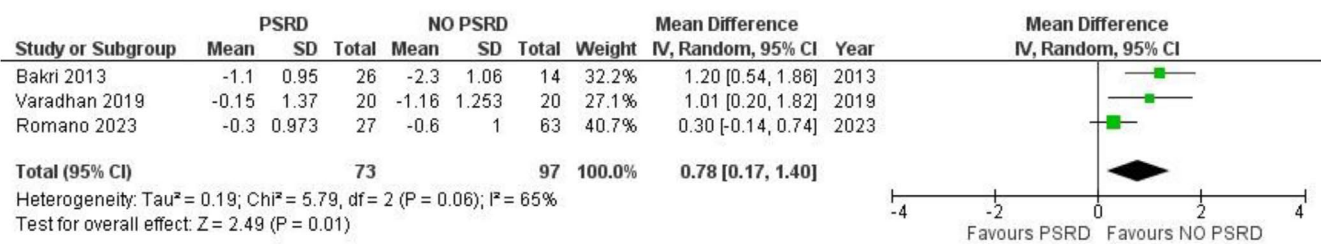
Note: Responses corresponding to NR (not reported), CD (cannot determine) or NA (not applicable) were coded as 0 for totalling the consensus score. Study quality reported as 'good', 'fair' and 'poor' was based on overall evaluations of possible sources of bias in each study.

TABLE 4 | Pre- and post-values along with mean changes for the study variables considered in the meta-analyses, according to stress-level categories.

Parameter	Study	Comparison	Stressed group				Non-stressed group			
			Mean (SD) pre-level	Mean (SD) post-level	Change mean (SD)	N	Mean pre-level	Mean post-level	Change mean (SD)	N
CAL	Bakri et al. (2013)	Stressed vs. non-stressed participants	8.10 ± 1.15	7.00	-1.10 ± 0.95	26	8.60 ± 0.99	6.30	-2.30 ± 1.06	14
		Stressed participants w/wo stress reduction intervention	3.73 ± 1.74	3.61 ± 1.79	-0.12 ± 1.37	20	3.67 ± 1.67	2.47 ± 1.42	-1.16 ± 1.25	20
	Romano et al. (2023)	Major stress levels vs. minor stress levels	4.70 ± 1.3	4.40 ± 1.20	-0.30 ± 0.97	27	4.40 ± 1.40	3.80 ± 1.00	-0.60 ± 1	63
PPD	Bakri et al. (2013)	Stressed vs. non-stressed participants	6.80 ± 0.68	5.40	-1.40 ± 0.93	26	6.80 ± 0.70	4.40	-2.40 ± 0.76	14
		Stressed participants w/wo stress reduction intervention	6.98 ± 1.34	6.70 ± 1.54	-0.28 ± 1.13	20	5.38 ± 1.63	3.43 ± 1.20	-2.32 ± 1.38	20
	Romano et al. (2023)	Major stress levels vs. minor stress levels	4.00 ± 0.60	3.30 ± 0.50	-0.70 ± 0.44	27	3.30 ± 0.50	2.90 ± 0.50	-0.90 ± 0.66	63

Note: Bakri et al.'s (2013) study reported the baseline and change from baseline to 6 months data as means and SD, without providing the post-treatment CAL or PPD levels. Thus, respective SD values of means for post-treatment CAL and PPD are left empty for this study.

CAL



PPD

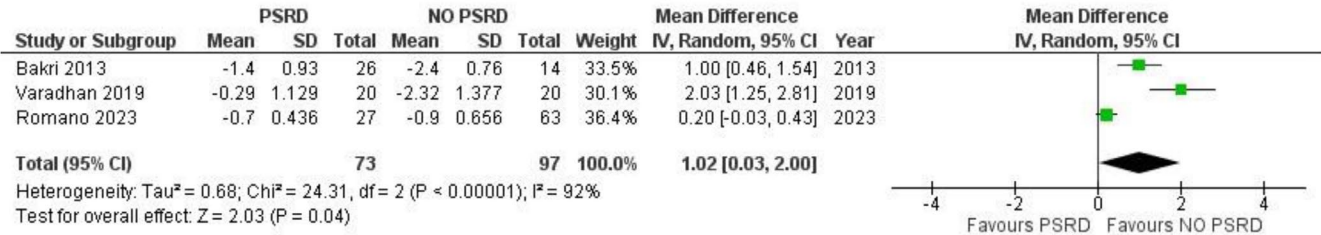


FIGURE 2 | Forest plots of effect sizes for the periodontal outcomes clinical attachment level (CAL) and probing pocket depth (PPD). Negative mean values indicate net reduction in the average levels of the respective parameter from baseline to the final assessment.

studies into this matter where intervention includes the component of actively targeting psychological stress. Another limitation is that studies included in the meta-analysis defined stress and related conditions using different criteria and assessment instruments and included diagnoses that do not necessarily relate to periodontitis uniformly. Future studies should include the use of standardised measures of stress and/or stress-related disorders that enable investigating the effect specific to the type and severity of PSRD. For example, investigating the biological effectors of periodontal outcomes should discriminate between depressive/anxiety state and trait (Solis et al. 2004; Hashioka et al. 2019). Furthermore, relevant confounders of the treatment outcomes such as smoking, alcohol consumption, systemic diseases and medications used should be accounted for (Natto et al. 2018). The limited number of studies identified in the literature precluded meta-regression or subgroup analysis. The analysis also identified several of the included studies to be of moderate/high risk of bias due to confounding, selection of participants and missing data, which should be acknowledged by the reader when interpreting these findings.

5 | Conclusions

The available evidence showed PSRD to adversely affect reductions in CAL and PPD following periodontitis treatment, as confirmed by meta-analysis. The certainty of evidence was rated as low in the case of CAL and very low in the case of PPD. Thus, the true effect of PSRD on CAL may be substantially different from the estimates we reported; it is likely to be substantially different from our estimates of the effect of PSRD on PPD. Furthermore, there is insufficient evidence to conclude on the possible effects of PSRD on the treatment outcome of periodontitis in terms of tooth loss, OHRQoL, FMPS and radiographic bone loss. The evidence base in this field is dominated by relatively small treatment cohorts and quasi-experimental

studies after steps 1 and 2 of periodontitis treatment followed for 3–6 months. Thus, the results from this study should be validated through original studies employing more rigorous pre-post designs, with standardised measurements and assessments of psychological stress or diagnoses of stress-related disorders, involving more homogeneous periodontal therapy and uniform treatment durations.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supporting information.