SYSTEMATIC REVIEW

Treatment of periodontitis and C-reactive protein: A systematic review and meta-analysis of randomized clinical trials

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Abstract

Background: Systemic inflammation is implicated in the onset and progression of several chronic diseases. Periodontitis is a potential trigger of systemic inflammation.

Purpose: To comprehensively appraise all the evidence on the effects of the treatment of periodontitis on systemic inflammation assessed by serum C-reactive protein (CRP) levels.

Data Sources: Six electronic databases were searched up to 10 February 2022 to identify and select articles in English language only.

Study Selection: Twenty-six randomized controlled clinical trials reporting changes amongst 2579 participants about CRP levels at 6 months or more after treatment.

Data Extraction: Two reviewers independently extracted data and rated the quality of studies. Meta-analyses were performed using random and fixed effect models.

Risk of Bias: Risk of bias (RoB 2.0 tool) and quality of evidence (GRADEpro GDT tool) analyses were completed.

Data Synthesis: Treatment of periodontitis reduced CRP levels by 0.69 mg/L (95% confidence interval: −0.97 to −0.40) after 6 months, but limited evidence was retrieved from studies with longer follow-ups. Similar findings were observed in

participants with other co-morbidities in addition to periodontitis. Greatest reductions were observed in participants with concentrations of CRP >3 mg/L at baseline.

Limitations: High level of heterogeneity.

Conclusions: Treatment of periodontitis reduces serum CRP levels (up to 6 months follow-up) to a degree equivalent to that observed after traditional lifestyle or drug interventions. This evidence supports a causal association between periodontitis and systemic inflammation.

KEYWORDS
biomarkers, CRP, inflammation, meta-analysis, periodontitis

Clinical Relevance

Scientific rationale for study: Systemic inflammation drives several chronic diseases and periodontitis could be an unrecognized trigger.

Principal findings: Treatment of periodontitis reduces serum CRP levels consistently up to six months. This "anti-inflammatory" effect was confirmed across participants with or without other co-morbidities, with the greatest reductions in participants with CRP > 3 mg/L.

Practical implications: This evidence supports a causal association between periodontitis and systemic inflammation which could explain the excess risk of future other non-communicable diseases and their complications. Assessment and effective management of periodontitis could be part of routine medical care in a not-too-distant future.

1 | INTRODUCTION

Inflammation is the body's protective response to infection and/or trauma. It is governed by local cell-activation processes resulting in a systemic response (acute phase response) aimed at eliminating the insult and promoting tissue healing and homeostasis (Furman et al., 2019). The dynamics of this response is well described by the changes in circulating levels of biomarkers like C-reactive protein (CRP). A sharp rise in CRP occurs over the first week following the insult and it is then followed by a gradual reduction of the marker accompanying the clearance of the insult (Sproston & Ashworth, 2018). Low-grade inflammation has been however linked to several chronic diseases like cardiovascular diseases (CVDs), type II diabetes mellitus (T2DM), renal diseases (CKD), cancer and neurodegenerative disorders (Furman et al., 2019). Efforts to identify and, if possible, manage all possible causes of excess inflammation and their impact on systemic health outcomes have received greater attention over the last 10 years.

Periodontitis is amongst the most common inflammatory diseases of the adult population, and its incidence increases with age as it is usually detected only later in life when advanced signs are reported. Despite its multifactorial origin, the main cause of periodontitis remains the undisturbed presence of a dysbiotic dental biofilm, which we now understand is responsible not just for a local but also a systemic inflammatory response (Tonetti et al., 2007).

Current evidence suggests that untreated periodontitis causes systemic inflammation, and this could represent a key mechanism explaining the increased incidence of systemic health complications

observed in these populations (D'Aiuto et al., 2018; Machado et al., 2021). However, there is inconsistent evidence on the causal nature of the association and the effects of the treatment of periodontitis on systemic inflammation (Lockhart et al., 2012).

Few attempts to critically review the evidence on the relationship between periodontitis and serum levels of CRP have been performed to date (Ioannidou et al., 2006; Paraskevas et al., 2008; Freitas et al., 2012; Demmer et al., 2013; Baeza et al., 2020). Inconsistent methodologies, shorter study follow-ups and high level of heterogeneity of the studies reviewed, however, undermine the quality of the evidence and conclusions of those reviews. Our aim was therefore to produce the most up-to date systematic critical appraisal of all evidence regarding the effects of the treatment of periodontitis on systemic inflammation assessed through randomized controlled clinical trials.

2 | METHODS

2.1 | Protocol registration and reporting format

A research protocol was registered with PROSPERO (CRD42019150354 [Appendix 1]): URL: https://www.crd.york.ac.uk/prospero/ (Moher et al., 2009) following PRISMA 2020 guidelines (Appendix 2).

The focused research question posed was: *What is the effect of the treatment of periodontitis on circulating CRP levels compared to non-treatment or control intervention after at least 6 months?*

2.2 | Eligibility: Inclusion and exclusion criteria

The following PICO outline was used.

2.2.1 | Population

Individuals >18 years old.

2.2.2 | Intervention

Non-surgical periodontal therapy (NSPT) only, NSPT with or without the use of adjunctive therapy such as antiseptics and/or local antibiotics.

2.2.3 | Comparison

No treatment or control intervention for periodontitis including (a) oral hygiene instructions, (b) supragingival tooth cleaning or (c) community (non-specialist) dental care (CPT).

2.2.4 | Outcome

The primary outcome was the difference between groups in circulating CRP levels (after at least 6 months or beyond). Secondary outcomes included changes in levels of other inflammatory biomarkers (interleukin [IL]-6, 8, 10 and tumour necrosis factor α [TNF-α]); along with changes in periodontal measures of inflammation (bleeding on probing [BOP], gingival pocket probing depth [PPD] and clinical attachment levels [CAL]).

2.2.5 | Study design and duration

Only randomized controlled trials (RCTs) reporting CRP levels 6 months or more following periodontal therapy, in English language, were included in the process.

All other types of articles (controlled clinical trials, cohort studies, case control studies, cross-sectional studies, pilot studies, reviews, letter to the editor, etc.) and animal studies were excluded.

2.3 | Information sources and searches

Six electronic databases were searched up to the 10 February 2022 including Medline OVID SP, EMBASE OVID SP, Cochrane library, CINAHL Ebsco Host and Web of Sciences Core Collection, SIGLE (System for Information on Grey Literature in Europe) using detailed search strategies combined with screening of manual reference lists (full details in Appendix 3: T1).

2.4 | Study selection and data extraction

Titles and abstracts (when available) were independently screened by two reviewers (SL and SBH) for eligibility based on inclusion/exclusion criteria. Detailed reasons for exclusion of studies were recorded (Appendix 3: T2). Disagreements were resolved by discussion and if necessary, involving a third reviewer (MO). Full-text reports were obtained for included studies or for those with insufficient information in the title and abstract to make a clear decision. Great effort was devoted in contacting authors to retrieve any missing data. Evidence tables were generated for all studies and grouped based on the study design PICO.

2.5 | Risk of bias in individual studies

Quality assessment of included studies was undertaken independently and in duplicate by two reviewers (SL and MO). The Cochrane Handbook—RoB 2.0 (Sterne et al., 2019) tool was used to assess RCTs and studies were categorized as high, medium or low risk of bias. Further, the GRADEpro GDT tool (McMaster University, 2016) was used to assess the quality of evidence for intervention versus control studies. Independent evaluation of the quality of evidence (SL and SH) was performed against the GRADE system and any discrepancies were resolved through discussion with a third author (MO). The evidence for relevant outcomes was summarized in a 'Summary of findings' table, along with the number of participants and studies addressing the outcome, and the GRADE rating for the outcome.

2.6 | Summary measures

The main outcome variables were reported as mean difference (MD) and 95% confidence intervals (CI).

2.7 | Data analysis and synthesis of results

Descriptive statistics was performed to present the evidence retrieved using dedicated R software using the metafor package for building fixed and random effects models. MD and standard error (SE) estimates of treatment of periodontitis on serum CRP levels in randomized trials with 6 months or longer follow-up were calculated. Means and standard deviation (SD) or means and SE or median and interquartile range (IQR) are reported in tables, where appropriate (e.g., Appendix T3). Heterogeneity was assessed by the Cochran's test and the I^2 statistics including adjustments for random effects model (DerSimonian and Laird method); the level of statistical significance was decided as 5% ($p < .05$). Sensitivity analyses were performed in (a) studies defined as of high and medium–low RoB scores, (b) based on the presence of co-morbidities, (c) based on different treatment modalities, (d) on disease severity and (e) according to baseline CRP values, and (f) use of antibiotics. Fixed effect models (inverse variance

method) were used if less than three studies were identified. Forest plots and random effect models were generated. The negative values for CRP levels favour the experimental group versus control group. Possible publication bias was assessed by means of funnel plots using Egger's test (Egger et al., 1997). A supplemental descriptive analysis was performed to describe the baseline levels of serum CRP reported in all included studies (combining means and variances from both groups included in each trial) (Appendix 4: F1).

2.8 | Risk of bias across studies: Publication bias

Egger's test and funnel plots for included studies were used to assess publication bias.

3 | RESULTS

3.1 | Study selection

The combined electronic search identified 12,988 articles. After removal of duplicates ($n = 180$) and irrelevant abstracts ($n = 12,577$), 231 manuscripts were eligible for full text screening. Two hundred and five studies were excluded (Appendix 3: T2). Twenty-six studies (Tonetti et al., 2007; Higashi et al., 2009; Katagiri et al., 2009; Offenbacher et al., 2009; Pinho Mde et al., 2009; Chen et al., 2012; López et al., 2012; Caúla et al., 2014; Kapellas et al., 2014; Koromantzos et al., 2012; Fang et al., 2015; Hada et al., 2015; Geisinger et al., 2016; Deepti et al., 2017; Mizuno et al., 2017; Wang et al., 2017, 2020; Zhou et al., 2017; D'Aiuto et al., 2018; Grubbs et al., 2020; Lobo et al., 2020; Matern et al., 2020; Montero et al., 2020; Nguyen et al., 2021; Rapone et al., 2021; Vachhani & Bhavsar, 2021) met the inclusion criteria and were included in the descriptive analysis. Evidence tables were generated according to the study design and in chronological order (Appendix 3: T3).

3.2 | Description of studies

Twenty-six RCTs were conducted in 14 different countries across five different continents and included varied ethnicities (Appendix 3: T4).

A total of 2941 participants aged between 24 and 68 years were retrieved from single- and multi-centre studies. As data required to convert the values to mean (SE) from median and IQR could not be obtained for five studies, these studies were excluded from the meta-analyses. Twenty-three studies evaluated CRP values at 6 months (two of these also reported data at 12 months), while only six studies evaluated CRP values at 12 months or more. Nineteen studies with data in mean (SD/SE) at 6 months and four studies at 12 months or more were finally included in two separate meta-analyses (Table 1 and 2) (Figure 1—PRISMA flow chart). Baseline CRP values were reported as categorical variable as ≤1 mg/L in three studies, between

1 and 3 mg/L in eight studies and as ≥3 mg/L in the remaining 15 studies. Two studies recruited participants suffering only from periodontitis (Tonetti et al., 2007; Zhou et al., 2017) while the rest included patients with T2DM ($N = 11$ studies), CVD ($N = 4$ studies) and CKD ($N = 2$). One study included patients with periodontitis and polycystic ovary syndrome, two studies included rheumatoid arthritis (RA) and further three trials included metabolic syndrome as co-morbidities. Data from these latter studies could not be combined for quantitative analyses. Seventeen studies included as test treatment NSPT compared with delayed NSPT at 6 months, three studies compared NSPT versus CPT at 6 months, one compared it at 12 months, while three studies compared NSPT versus CPT at 12 months. Three studies compared NSPT + adjunctive versus NSPT with placebo, however data were not available. Four studies evaluated CRP values in patients with moderate periodontitis, 11 studies with mild, moderate to severe periodontitis and 11 studies including moderate, severe and advanced periodontitis.

IL-6 levels were assessed in 11 studies, IL-8 in three, IL-10 in two studies and IL-1β in one study. TNF-α was evaluated in five studies. White blood counts (WBC) were reported in four studies. Fibrinogen, erythrocyte sedimentation rate (ESR) and E-selectin were reported in three studies, while intra-cellular adhesion molecules (ICAM-3) and asymmetric dimethylarginine (ADMA) were reported in two studies each. The treatment of periodontitis reduced the levels of several inflammatory biomarkers (WBC, fibrinogen, ICAM-3, ADMA, TNF-α, E-selectin, IL-6, IL-8 and IL-10). Indeed, seven of the 11 studies reported a decrease in IL-6 levels after treatment (Higashi et al., 2009; Kapellas et al., 2014; Fang et al., 2015; Geisinger et al., 2016; Zhou et al., 2017; Grubbs et al., 2020; Wang et al., 2020), while two studies reported no difference (Tonetti et al., 2007; Montero et al., 2020) and one an increase in the biomarker (D'Aiuto et al., 2018). Inconclusive evidence was found on the effects of the treatment of periodontitis on IL-8 (Geisinger et al., 2016; D'Aiuto et al., 2018; Montero et al., 2020) and IL-10 (Geisinger et al., 2016; D'Aiuto et al., 2018). Four studies reported a decrease in TNF-α levels (Chen et al., 2012; Fang et al., 2015; Geisinger et al., 2016; Montero et al., 2020) while one study initially reported an increase at 6 months and no difference from baseline value at 12 months after treatment (D'Aiuto et al., 2018). A consistent decrease in E-selectin (Tonetti et al., 2007; Geisinger et al., 2016; D'Aiuto et al., 2018), ICAM-3 (Geisinger et al., 2016; D'Aiuto et al., 2018) and ESR (Pinho Mde et al., 2009; Caúla et al., 2014; Nguyen et al., 2021) was reported after the treatment of periodontitis. Two studies reported a decrease in total WBC levels (Tonetti et al., 2007; Hada et al., 2015), while one clinical trial reported no change after treatment (Montero et al., 2020). A reduction in IL-1β levels was reported in a single trial (Montero et al., 2020). Data were not available for assessment of two studies reporting on fibrinogen levels after treatment of periodontitis (López et al., 2012; Lobo et al., 2020).

Most studies (21 of 26) reported changes in BOP as percentage (BOP%) while PPD and CAL changes in millimetres were reported in 15 and 13 studies, respectively. All studies reported a decrease in BOP% (Katagiri et al., 2009; Offenbacher et al., 2009; Pinho Mde

TABLE 1 Studies showing the effect of periodontal therapy on serum C-reactive protein (CRP) levels at 6 months

S no	Author (year)	Country	Total participants	Health status	Procedure — Treatment group	Procedure — Control group	CRP levels at difference at 6 months (mean ± SD/mean [SE]) Hs-CRP (mg/L) — Treatment group	Control group
1.	Vachhani and Bhavsar (2021)	India	80	CKD and PDD	NSPT	OHI, delayed NSPT	BL: 6.59 ± 17.25 6 months: 3.03 ± 3.20	BL: 4.80 ± 4.22 6 months: 6.79 ± 6.49
2.	Wang et al. (2020)	Hong Kong	58	T2DM and PDD	NSPT	OHI, delayed NSPT	BL: 1.78 ± 0.29 6 months: 1.39 ± 0.28	BL: 1.55 ± 0.41 6 months: 1.53 ± 0.37
3.	Montero et al. (2020)	Spain	63	Met S and PDD	OHI, NSPT + antibiotic	OHI, CPT + placebo	BL: 3.9 ± 2.9 6 months: 2.9 ± 0.4	BL: 3.9 ± 3.4 6 months: 4.0 ± 0.8
4.	D'Aiuto et al. (2018)	United Kingdom	165	T2DM and PDD	NSPT + sup PT every 3 months + surgery	CPT (supragingival scaling and polishing) + delayed NSPT (patients received any additional PT)	BL: 3.8 ± 6.8 6 months: 2.9 ± 4.2	BL: 2.6 ± 2.6 6 months: 4.4 ± 10.4
5.	Mizuno et al. (2017)	Japan	37	T2DM and PDD	OHI + NSPT	OHI, delayed NSPT	BL: 4.287 ± 1.048 6 months: 5.472 ± 2.444	BL: 5.153 ± 1.780 6 months: 5.554 ± 2.493
6.	Wang et al. (2017)	Hong Kong	18	T2DM and PDD	OHI + NSPT	OHI, delayed NSPT	BL: 2.32 ± 2.72 6 months: 1.95 ± 2.27	BL: 3.46 ± 3.54 6 months: 2.75 ± 3.53
7.	Deepti et al. (2017)	India	51	PCOS and PDD	NSPT + myo-inositol	OHI + myo-inositol	BL: 3.42 ± 0.86 6 months: 1.45 ± 0.65	BL: 3.21 ± 0.75 6 months: 2.22 ± 0.49
8.	Zhou et al. (2017)	China	107	Prehypertension and PDD	OHI + NSPT + local-minocycline ointment	OHI + CPT (supragingival scaling and polishing)	BL: 3.20 ± 1.70 6 months: 2.35 ± 0.91	BL: 3.37 ± 1.60 6 months: 3.59 ± 1.59
9.	Geisinger et al. (2016)	United States	475	T2DM and PDD	NSPT + sup PT	OHI, delayed NSPT	BL: 4.98 ± 5.88 6 months: 0.65 ± 5.16	BL: 5.09 ± 6.64 6 months: −0.02 ± 4.68
10.	Hada et al. (2015)	India	55	CHD and PDD	NSPT	OHI, delayed NSPT	BL: 5.10 ± 2.00 6 months: 6.30 ± 7.53	BL: 3.62 ± 2.31 6 months: 4.94 ± 2.04
11.	Fang et al. (2015)	China	97	ESRD and PDD	NSPT + extractions (supragingival prophylaxis at 3 months)	OHI, delayed NSPT	BL: 3.65 ± 2.81 6 months: 2.56 ± 1.64	BL: 3.8 ± 2.8 6 months: 3.96 ± 2.82
12.	Caúla et al. (2014)	Brazil	64	T2DM and PDD	NSPT	Delayed NSPT	BL: 1.03 ± 0.79 6 months: 0.54 ± 0.31	BL: 0.9 ± 0.35 6 months: 1.22 ± 0.33
13.	Chen et al. (2012)	China	83	T2DM and PDD	TG-NSPT at baseline + subgingival scaling at 3 months	Delayed NSPT	BL: 3.21 ± 4.45 6 months: 1.58 ± 1.31	BL: 2.81 ± 4.05 6 months: 3.16 ± 5.45
14.	Koromantzos et al. (2012)	Greece	60	T2DM and PDD	OHI + NSPT + extractions + sup PT	OHI + CPT at baseline + delayed NSPT	BL: 0.42 (0.19) 6 months: 0.08 (0.26)	BL: 0.29 (0.25) 6 months: 0.37 (0.19)
15.	Pinho Mde et al. (2009)	Brazil	30	RA and PDD	NSPT	Delayed NSPT	BL: 0.90 ± 1.06 6 months: 0.63 ± 0.54	BL: 0.61 ± 0.19 6 months: 0.81 ± 1.10

(Continues)

TABLE 1 (Continued)

S no	Author (year)	Country	Total participants	Health status	Procedure		CRP levels at difference at 6 months (mean ± SD/mean [SE]) Hs-CRP (mg/L)	
					Treatment group	Control group	Treatment group	Control group
16.	Offenbacher et al. (2009)	United States	303	CHD and PDD	OHI + NSPT + extractions	OHI + extractions + community dental care	BL: 3.17 (0.39) 6 months: 3.12 (0.38) 12 months: 3.41 (0.78)	BL: 3.18 (0.36) 6 months: 3.53 (0.45) 12 months: 2.79 (0.71)
17.	Higashi et al. (2009)	Japan	48	CVD and PDD	OHI + NSPT	No treatment	BL: 2.7 ± 1.9 6 months: 1.8 ± 0.9	BL: 2.6 ± 2.2 6 months: 2.5 ± 2.1
18.	Katagiri et al. (2009)	Japan	49	T2DM and PDD	NSPT	OHI only	BL: 1.858 ± 2.531 6 months: 1.38 ± 1.6	BL: 2.278 ± 2.593 6 months: 2.92 ± 6.9
19.	Tonetti et al. (2007)	United Kingdom	120	Healthy and PDD	OHI + NSPT + extractions + local antibiotics	OHI + CPT	BL: 2.5 ± 2.7 6 months: 2.69 ± 4.85	BL: 3.8 ± 5.5 6 months: 2.96 ± 3.44

Abbreviations: BL, baseline; CHD, coronary heart disease; CKD, chronic kidney disease; CPT, community dental treatment; CVD, cardiovascular disease; ESRD, end stage renal disease; Met S, metabolic syndrome; NSPT, non-surgical periodontal therapy; OHI, oral hygiene instruction; PDD, periodontal disease; RA, rheumatic arthritis; T2DM, type 2 diabetes mellitus; TG, treatment group.

TABLE 2 Studies showing the effect of periodontal therapy on serum C-reactive protein (CRP) levels at 12 months or more

S no	Author(year)	Country	Total participants	Health status	Procedure		CRP levels at difference at 12 months or more (mean ± SD/mean [SE]) Hs-CRP (mg/L)	
					Treatment group	Control group	Treatment group	Control group
1.	Matern et al. (2020)	Germany	80	Obesity and PDD	OHI, NSPT + systemic antibiotic/placebo	OHI, NSPT + systemic antibiotic/placebo	BL: 4.7 ± 8.4 27.5 months: 1.7 ± 2.1	BL: 2.0 ± 2.1 27.5 months: 1.2 ± 1.5
2.	D'Aiuto et al. (2018)	United Kingdom	165	T2DM and PDD	NSPT + sup PT every 3 months + surgery	CPT (supragingival scaling and polishing) + delayed NSPT (patients received any additional PT)	BL: 3.8 ± 6.8 12 months-2.6 ± 3.4	BL: 2.6 ± 2.6 12 months-3.2 ± 4.6
3.	Kapellas et al. (2014)	Australia	273	Multiple Co-morbidities and PDD	NSPT	Delayed NSPT	BL: 4.68 ± 5.41 12 months: 5.28 ± 6.46	BL: 4.84 ± 6.18 12 months: 4.25 ± 4.38
4.	Offenbacher et al. (2009)	United States	303	CHD and PDD	OHI + NSPT + extractions	OHI + extractions + community dental care	BL: 3.17 (0.39) 12 months: 3.41 (0.78)	BL: 3.18 (0.36) 12 months: 2.79 (0.71)

Abbreviations: BL, baseline; CHD, coronary heart disease; CPT, community dental treatment; NSPT, non-surgical periodontal therapy; OHI, oral hygiene instruction; PDD, periodontal disease; T2DM, type 2 diabetes mellitus.

et al., 2009; Chen et al., 2012; Koromantzos et al., 2012; Caúla et al., 2014; Kapellas et al., 2014; Fang et al., 2015; Hada et al., 2015; Geisinger et al., 2016; Deepti et al., 2017; Mizuno et al., 2017; Wang et al., 2017, 2020; Zhou et al., 2017; D'Aiuto et al., 2018; Grubbs et al., 2020; Montero et al., 2020; Nguyen et al., 2021; Rapone et al., 2021), PPD (Katagiri et al., 2009; Offenbacher et al., 2009; Pinho Mde et al., 2009; Chen et al., 2012; Caúla et al., 2014; Kapellas et al., 2014; Geisinger et al., 2016; Deepti et al., 2017; Mizuno et al., 2017; D'Aiuto et al., 2018; Grubbs et al., 2020; Montero et al., 2020; Wang et al., 2020; Nguyen et al., 2021; Rapone et al., 2021) and an improvement in CAL levels after the delivery of treatment (Offenbacher et al., 2009; Chen et al., 2012; Caúla et al., 2014; Fang et al., 2015; Hada et al., 2015; Geisinger et al., 2016; Deepti et al., 2017; Mizuno et al., 2017; Grubbs et al., 2020; Montero et al., 2020; Wang et al., 2020; Nguyen et al., 2021; Rapone et al., 2021).

Ten studies were categorized as of low risk of bias while additional eight studies as of some concern and eight studies as of high risk of bias (Appendix 3: T5). The randomization process, the blinding of participants/personnel and the loss to follow-up were the main factors affecting bias.

3.3 | Quantitative analyses

Evidence for a statistically significant reduction of CRP after 6 months of treatment was confirmed in 19 studies (MD of -0.69 mg/L, 95% CI: -0.97 to -0.40, $p < .0001$, $I^2 = 66\%$, $p = .001$) (Figure 2). No treatment effect was instead observed in the four studies assessing CRP levels at 12 months or beyond (Figure 3).

3.3.1 | Sensitivity analysis based on risk of bias

The positive effect of the treatment of periodontitis was confirmed at 6 months in the 14 studies with low and medium risk of bias (MD of -0.68 mg/L, 95% CI: -1.07 to -0.29, $p = .00067$, $I^2 = 78\%$, $p = 0$) (Appendix 4: F2: A). Greater reductions of CRP levels were noted in the five studies with high risk of bias (MD of -0.75 mg/L, 95% CI: -1.03 to -0.46, $p < .00001$, $I^2 = 0\%$, $p = .54$) (Appendix 4: F2: B).

3.3.2 | Sensitivity analysis in patients with co-morbidities

Treatment of periodontitis in otherwise systemically healthy patients (Tonetti et al., 2007; Zhou et al., 2017) resulted in a statistically significant reduction of -1.09 mg/L in circulating CRP (95% CI: -1.56 to -0.63, $p < .00001$, $I^2 = 72\%$, $p = .061$) (Figure 4a), but one of the two studies accounted for over 90% weight in total. Similar trend but not significant reductions in CRP after 6 months of treatment was noted in studies including participants with comorbid CVD (Higashi et al., 2009; Offenbacher et al., 2009; Hada et al., 2015) (MD of

-0.49 mg/L, 95% CI: -1.19 to 0.22, $p = .175$, $I^2 = 0\%$, $p = .44$). Statistically significant reductions were observed in patients with T2DM at 6 months (Katagiri et al., 2009; Chen et al., 2012; Koromantzos et al., 2012; Caúla et al., 2014; Geisinger et al., 2016; Mizuno et al., 2017; Wang et al., 2017, 2020; D'Aiuto et al., 2018) (MD of -0.44 mg/L, 95% CI: -0.84 to -0.04, $p = .033$, $I^2 = 38\%$, $p = .13$) (Figure 4b,c). Even greater reduction in CRP levels was observed in patients with comorbid CKD (MD of -1.77 mg/L, 95% CI: -2.61 to -0.92, $p = <.0001$, $I^2 = 75\%$, $p = .047$) but there was high level of heterogeneity, and one study heavily overweighed the other (84%) (Figure 4d). Limited evidence was identified on the effects of treating periodontitis on CRP levels in patients with T2DM after 12 months (Figure 4e) (Kapellas et al., 2014; D'Aiuto et al., 2018).

3.3.3 | Sensitivity analysis based on treatment methodologies

Delivering NSPT resulted in a statistically significant reduction of CRP levels of -0.62 mg/L (95% CI: -0.99 to -0.24, $p = .0013$, $I^2 = 65\%$, $p = .013$) after 6 months when compared with delayed treatment. A similar statistically significant reduction of CRP of -0.67 mg/L (95% CI: -1.26 to -0.07, $p = .029$, $I^2 = 50\%$, $p = .076$) was observed when compared with CPT at 6 months as compared with 12 months (-0.41 [95% CI: -1.31 to 0.49, $p = .369$, $I^2 = 0\%$, $p = .334$]) (Appendix 4: F3: A–C). The weight of one amongst the two studies included, however, was five times greater than the other one (85% vs. 15%).

3.3.4 | Sensitivity analysis based on severity of periodontitis

Similar statistically significant reductions of CRP after 6 months of treatment were observed (a) in patients with moderate to severe periodontitis (MD of -0.78 mg/L, 95% CI: -1.27 to -0.29, $p = .0018$, $I^2 = 5\%$, $p = .426$) and (b) in patients with mild, moderate and severe/advanced periodontitis (MD of -0.79 mg/L, 95% CI: -1.17 to -0.41, $p < .0001$, $I^2 = 75\%$, $p = .001$), but not in those with moderate periodontitis (MD of 0.0 mg/L, 95% CI: -1.18 to 1.19, $p = .996$, $I^2 = 77\%$, $p = .01$) (Appendix 4: F4: A–C).

3.3.5 | Sensitivity analysis based on initial CRP levels

When grouping studies according to the baseline values of CRP (Appendix 4: F5: A–C), greater reductions in the biomarker were observed in participants with >3 mg/L (MD of -0.83 mg/L, 95% CI: -0.29 to -1.38, $p = .003$, $I^2 = 79\%$, $p = .002$) when compared with those who had values between 1 and 3 mg/L (MD of -0.66 mg/L, 95% CI: -1.25 to -0.07, $p = .03$, $I^2 = 25\%$, $p = .335$), and those with values <1 mg/L (MD of -0.49 mg/L, 95% CI: -0.84 to -0.15,
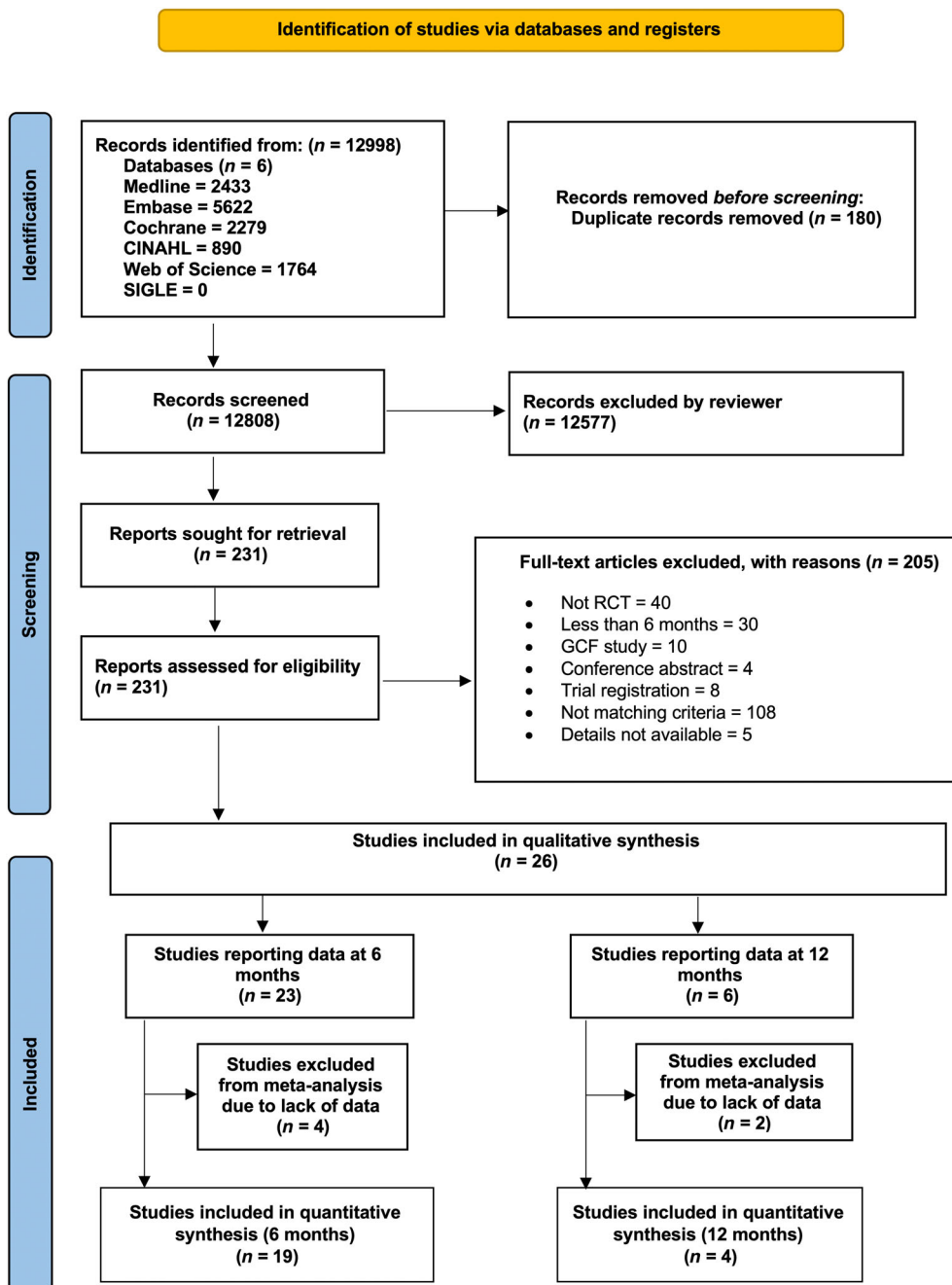
FIGURE 1 PRISMA flow chart. Flow chart of the study selection process. The systematic search yielded 12,998 reports. After removal of duplicates and the application of inclusion and exclusion criteria, 26 studies were included in the quantitative analysis; meta-analyses were carried out with 19 studies for 6 months, and four studies for 12 months after treatment. Medline, Embase, Cochrane, CINAHL and Web of Science, and manual search strategies were used. GCF, gingival crevicular fluid; RCT, randomized controlled trial

$p = .005$, $I^2 = 46\%$, $p = .171$). For analysis of studies with CRP levels <1 mg/L, one of the three studies contributed for 58% of the overall weight.

3.3.6 | Sensitivity analysis based on use of antibiotics

Three studies that used either systemic or local antibiotics showed statistically significant reductions in CRP (MD of 1.10 mg/L, 95% CI: −1.34 to −0.86, $p = .0173$, $I^2 = 0\%$, $p < .0001$), and one study contributed to 73% of the total weight. Sixteen studies that did not report

any antibiotic use showed reductions in CRP of lower magnitude (MD of −0.58 mg/L, 95% CI: −0.86 to −0.31, $p = .022$, $I^2 = 44\%$, $p < .0001$) (Figure 5a,b). Reductions observed amongst three studies that did not include use of antibiotics at 12 months were not statistically significant (MD of 0.22 mg/L, 95% CI: −0.96 to 1.39, $p = .129$, $I^2 = 52\%$, $p = .716$) (Appendix 4: F6).

3.4 | Publication bias

No evidence of publication bias in studies with 6 months follow-up was observed when using Egger's test ($p = .872$) and visual

Forest plot for difference in CRP levels post treatment at 6 months

All data (6 months)	Treatment N	mean (SD)	Control N	mean (SD)	Mean difference (95% CI)	Weight (%)	Mean difference (95% CI)
Vachhani et al.(2021)	47	3.03 (3.20)	33	6.79 (6.49)		1.55	−3.76 (−5.90 to −1.62)
Montero et al.(2020)	32	2.90 (0.40)	31	4.00 (0.80)		11.37	−1.10 (−1.38 to −0.82)
Wang et al.(2020)	29	1.39 (1.51)	29	1.53 (1.99)		5.54	−0.14 (−1.05 to 0.77)
D'Aiuto et al.(2019)	133	2.90 (4.20)	131	4.40 (10.40)		1.89	−1.50 (−3.41 to 0.41)
Mizuno et al.(2017)	20	5.47 (2.44)	17	5.55 (2.49)		2.54	−0.08 (−1.68 to 1.51)
Wang et al.(2017)	11	1.95 (2.27)	6	2.75 (3.53)		0.99	−0.80 (−3.54 to 1.94)
Deepti et al.(2017)	26	1.45 (0.65)	25	2.22 (0.49)		11.04	−0.77 (−1.09 to −0.45)
Zhou et al.(2017)	53	2.35 (0.91)	54	3.59 (1.59)		9.25	−1.24 (−1.73 to −0.75)
Geisinger.et al (2016)	240	5.63 (5.16)	235	5.07 (4.68)		5.70	0.56 (−0.33 to 1.45)
Hada et al.(2015)	30	6.30 (7.53)	25	4.94 (2.04)		0.81	1.36 (−1.68 to 4.40)
Fang et al.(2015)	48	2.56 (1.64)	49	3.96 (2.82)		5.46	−1.40 (−2.32 to −0.48)
Caula et al.(2014)	32	0.54 (0.31)	32	1.22 (0.33)		12.32	−0.68 (−0.84 to −0.52)
Chen Lei et al.(2012)	42	1.58 (1.31)	41	3.16 (5.45)		2.30	−1.58 (−3.28 to 0.12)
Koromantzos et al.(2012)	30	0.08 (1.04)	30	0.37 (1.42)		7.84	−0.29 (−0.92 to 0.34)
Pinho et al.(2009)	15	0.63 (0.54)	15	0.81 (1.10)		7.95	−0.18 (−0.80 to 0.44)
Offenbacher et al.(2009)	126	3.12 (5.05)	102	3.53 (3.84)		3.95	−0.41 (−1.60 to 0.78)
Higashi et al.(2009)	24	1.80 (0.90)	24	2.50 (2.10)		5.50	−0.70 (−1.61 to 0.21)
Katagiri et al.(2009)	32	1.38 (1.60)	17	2.92 (6.90)		1.18	−1.54 (−4.03 to 0.95)
Tonetti et al.(2007)	61	2.96 (3.44)	59	2.69 (4.85)		2.80	0.27 (−1.23 to 1.77)
Overall (95% CI)	**1031**		**955**			**100.00**	**−0.69 (−0.97 to −0.40)**

−6 −5 −4 −3 −2 −1 0 1 2 3 4 5
Favours treatment — Favours control

Heterogeneity: *p*-value = .001 , *I*^{2} = 66%
Test for overall effect: *p*-value < 0.0001
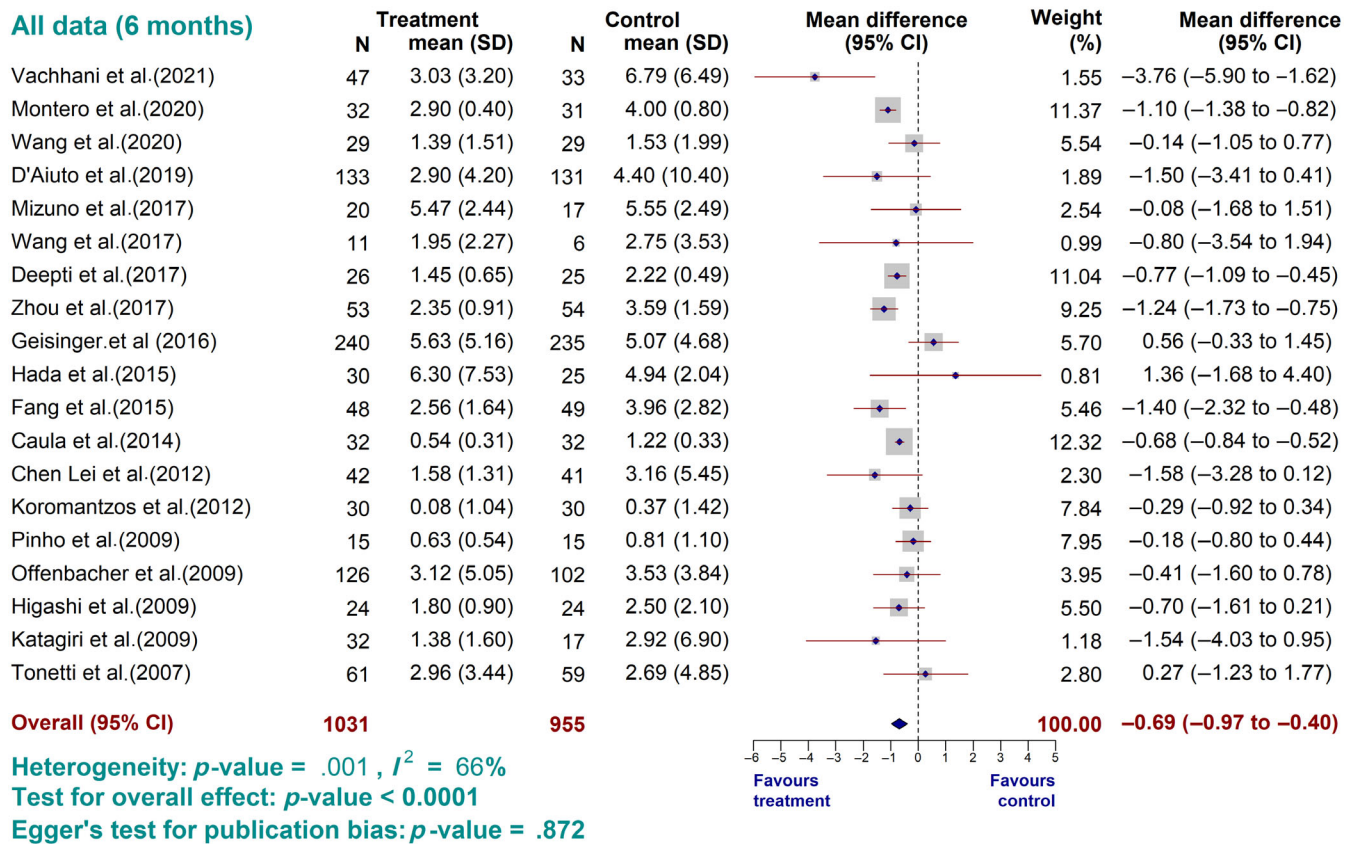**Egger's test for publication bias: *p*-value = .872**

FIGURE 2 Forest plot for difference in C-reactive protein (CRP) levels after treatment at 6 months. Summary forest plot for association between periodontal treatment (non-surgical periodontal therapy [NSPT] and community dental treatment/delayed NSPT) and changes in CRP levels 6 months after treatment in randomized control trials. Summary forest plot for mean difference (95% confidence interval [CI]). The random effects model was used, and the relative size of the data markers indicates the weight of the sample size from each study. The data markers indicate: N, sample size for treatment or control groups; mean (SD)

Forest plot for difference in CRP levels post treatment at 12 months or more

All data (at least 12 months)	Treatment N	mean (SD)	Control N	mean (SD)	Mean difference (95% CI)	Weight (%)	Mean difference (95% CI)
Matern et al.(2020)	40	1.70 (2.10)	40	1.20 (1.50)		37.02	0.50 (−0.30 to 1.30)
D'Aiuto et al.(2019)	133	2.60 (3.40)	131	3.20 (4.60)		31.06	−0.60 (−1.57 to 0.37)
Kapellas et al.(2014)	138	5.28 (6.46)	135	4.25 (4.38)		22.19	1.03 (−0.28 to 2.34)
Offenbacher et al.(2009)	12	3.41 (2.70)	25	2.79 (3.55)		9.73	0.62 (−1.66 to 2.90)
Overall (95% CI)	**323**		**331**			**100.00**	**0.29 (−0.49 to 1.06)**

−6 −5 −4 −3 −2 −1 0 1 2 3 4 5
Favours treatment — Favours control

Heterogeneity: *p*-value = .191 , *I*^{2} = 42%
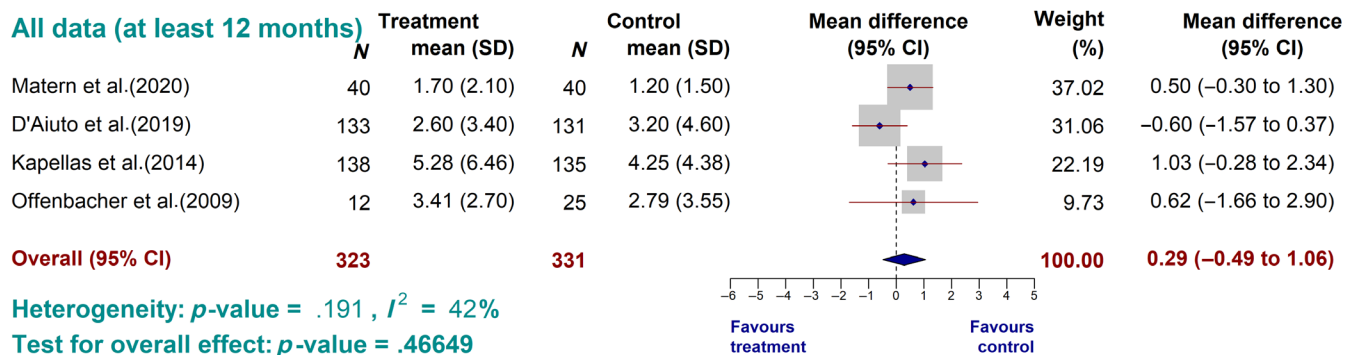**Test for overall effect: *p*-value = .46649**

FIGURE 3 Forest plot for difference in C-reactive protein (CRP) levels after treatment at 12 months or more. Summary forest plot for association between periodontal treatment (non-surgical periodontal therapy [NSPT] and community dental treatment/delayed NSPT) and changes in CRP levels 12 months or more after treatment in randomized control trials. Summary forest plot for mean difference (95% confidence interval). The random effects model was used, and the relative size of the data markers indicates the weight of the sample size from each study. The data markers indicate: N, sample size for treatment or control groups; mean (SD)
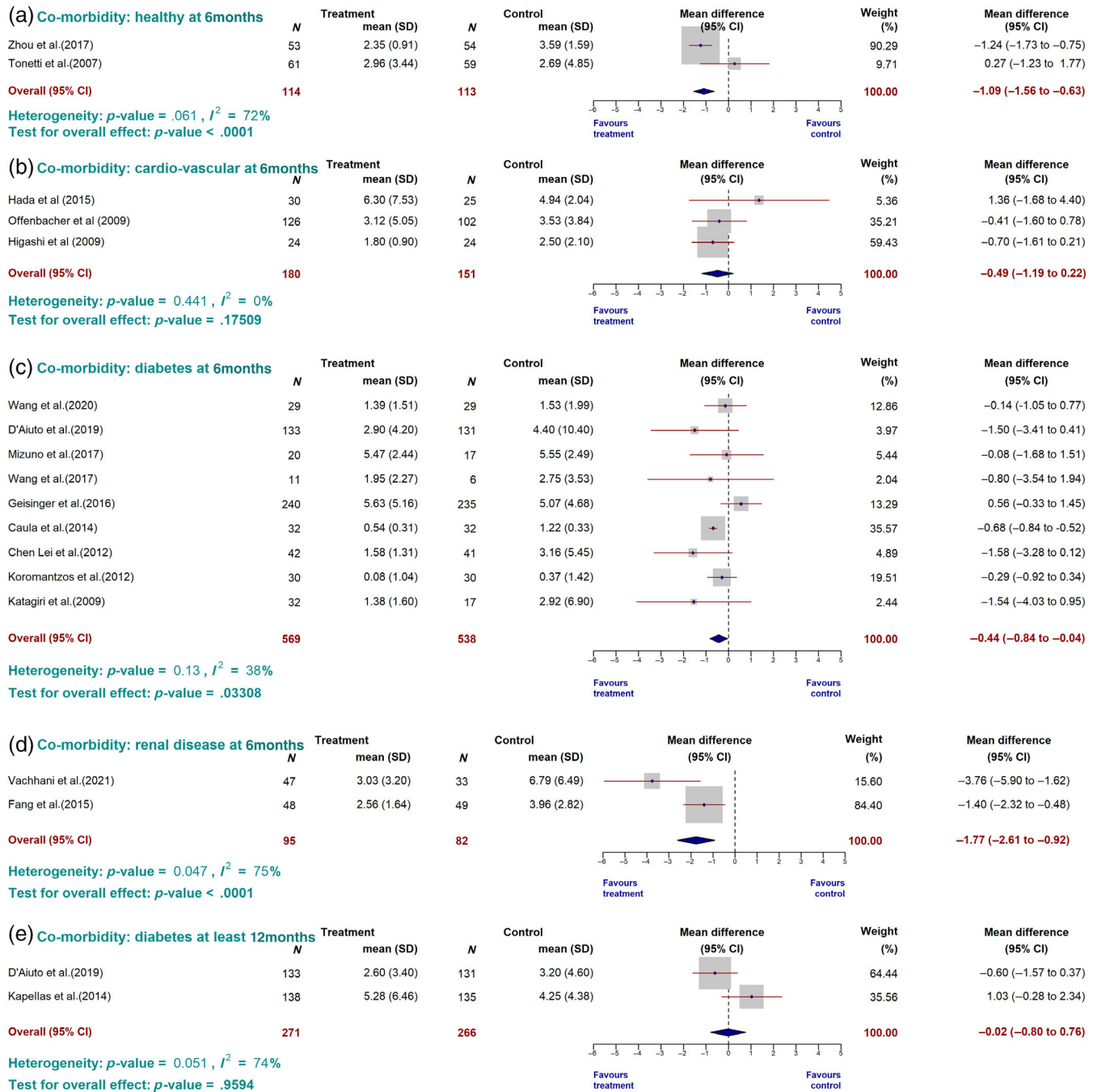
Forest plots for CRP value as per co-morbidities

FIGURE 4 (a–e) Forest plots for C-reactive protein (CRP) value as per co-morbidities. Summary forest plot for association between periodontal treatment (non-surgical periodontal therapy [NSPT] and community dental treatment/delayed NSPT) and changes in CRP levels 6 months after treatment in-(a)-healthy cohort, (b) cardiovascular disease, (c) diabetes at 6 months, (d) renal diseases at 6 months and (e) diabetes at 12 months. The fixed effect model was used for analysis (a, d and e). Random effects model was used (b and c); the relative size of the data markers indicates the weight of the sample size from each study. The data markers indicate: N, sample size for treatment or control groups; mean (SD); CI, confidence interval

assessment of the funnel plot (Appendix 4: F7). Treatment of periodontitis reduced CRP levels after 6 months with *high* overall *certainty* of evidence and moderate level of heterogeneity ($I^2 = 66\%$, $p < .0001$) (Balshem et al., 2011) (Appendix 3: T6).

4 | DISCUSSION

This review confirms that periodontitis causes systemic inflammation, and its treatment is accompanied by a reduction in CRP serum

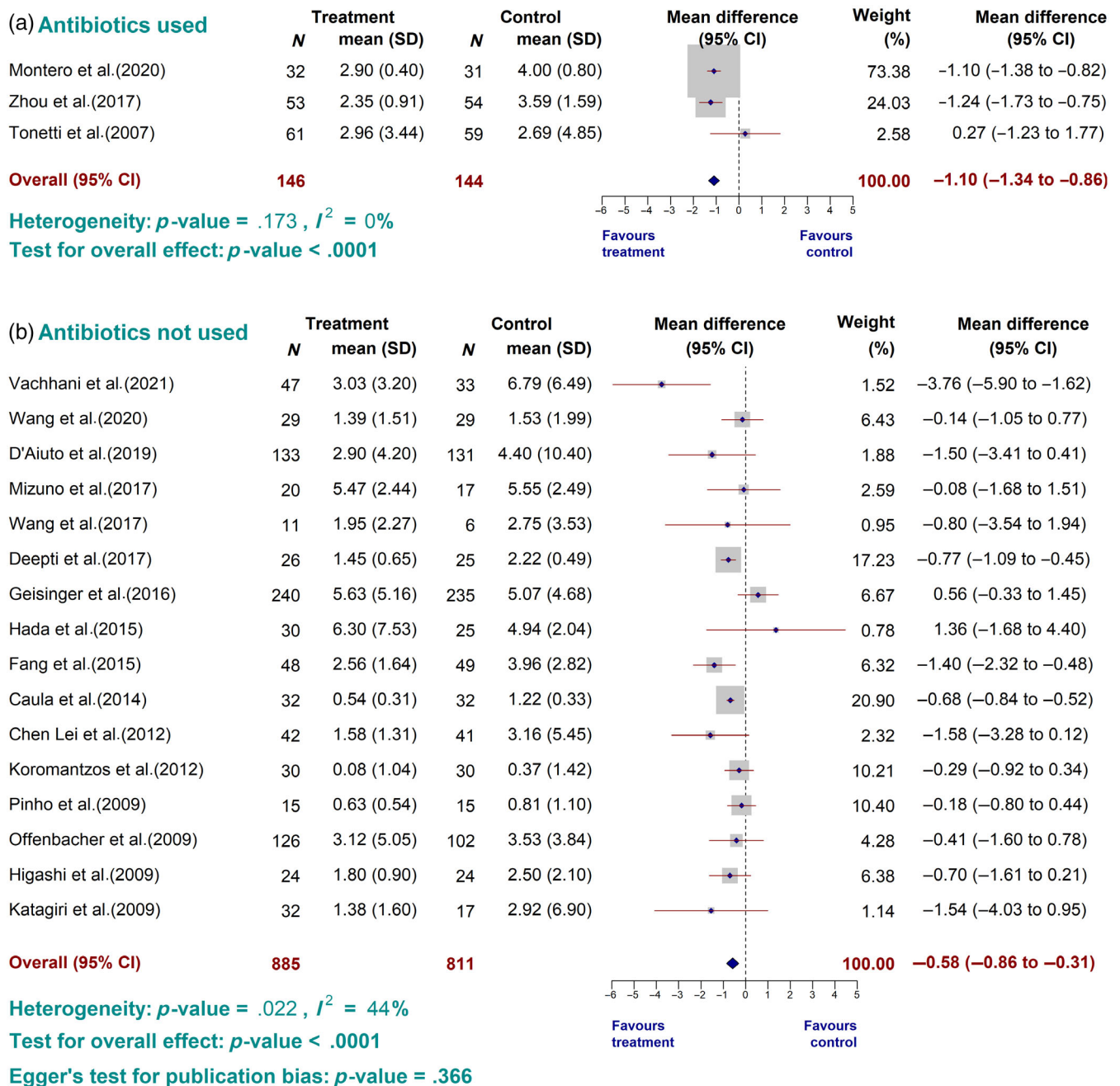## Forest plots investigating antibiotics use at 6 months

(a) Antibiotics used

	Treatment N	mean (SD)	Control N	mean (SD)	Mean difference (95% CI)	Weight (%)	Mean difference (95% CI)
Montero et al.(2020)	32	2.90 (0.40)	31	4.00 (0.80)		73.38	−1.10 (−1.38 to −0.82)
Zhou et al.(2017)	53	2.35 (0.91)	54	3.59 (1.59)		24.03	−1.24 (−1.73 to −0.75)
Tonetti et al.(2007)	61	2.96 (3.44)	59	2.69 (4.85)		2.58	0.27 (−1.23 to 1.77)
Overall (95% CI)	**146**		**144**			**100.00**	**−1.10 (−1.34 to −0.86)**

Favours treatment / Favours control

Heterogeneity: *p*-value = .173 , I^2 = 0%
Test for overall effect: *p*-value < .0001

(b) Antibiotics not used

	Treatment N	mean (SD)	Control N	mean (SD)	Mean difference (95% CI)	Weight (%)	Mean difference (95% CI)
Vachhani et al.(2021)	47	3.03 (3.20)	33	6.79 (6.49)		1.52	−3.76 (−5.90 to −1.62)
Wang et al.(2020)	29	1.39 (1.51)	29	1.53 (1.99)		6.43	−0.14 (−1.05 to 0.77)
D'Aiuto et al.(2019)	133	2.90 (4.20)	131	4.40 (10.40)		1.88	−1.50 (−3.41 to 0.41)
Mizuno et al.(2017)	20	5.47 (2.44)	17	5.55 (2.49)		2.59	−0.08 (−1.68 to 1.51)
Wang et al.(2017)	11	1.95 (2.27)	6	2.75 (3.53)		0.95	−0.80 (−3.54 to 1.94)
Deepti et al.(2017)	26	1.45 (0.65)	25	2.22 (0.49)		17.23	−0.77 (−1.09 to −0.45)
Geisinger et al.(2016)	240	5.63 (5.16)	235	5.07 (4.68)		6.67	0.56 (−0.33 to 1.45)
Hada et al.(2015)	30	6.30 (7.53)	25	4.94 (2.04)		0.78	1.36 (−1.68 to 4.40)
Fang et al.(2015)	48	2.56 (1.64)	49	3.96 (2.82)		6.32	−1.40 (−2.32 to −0.48)
Caula et al.(2014)	32	0.54 (0.31)	32	1.22 (0.33)		20.90	−0.68 (−0.84 to −0.52)
Chen Lei et al.(2012)	42	1.58 (1.31)	41	3.16 (5.45)		2.32	−1.58 (−3.28 to 0.12)
Koromantzos et al.(2012)	30	0.08 (1.04)	30	0.37 (1.42)		10.21	−0.29 (−0.92 to 0.34)
Pinho et al.(2009)	15	0.63 (0.54)	15	0.81 (1.10)		10.40	−0.18 (−0.80 to 0.44)
Offenbacher et al.(2009)	126	3.12 (5.05)	102	3.53 (3.84)		4.28	−0.41 (−1.60 to 0.78)
Higashi et al.(2009)	24	1.80 (0.90)	24	2.50 (2.10)		6.38	−0.70 (−1.61 to 0.21)
Katagiri et al.(2009)	32	1.38 (1.60)	17	2.92 (6.90)		1.14	−1.54 (−4.03 to 0.95)
Overall (95% CI)	**885**		**811**			**100.00**	**−0.58 (−0.86 to −0.31)**

Favours treatment / Favours control

Heterogeneity: *p*-value = .022 , I^2 = 44%
Test for overall effect: *p*-value < .0001
Egger's test for publication bias: *p*-value = .366

FIGURE 5 (a and b) Forest plots for C-reactive protein (CRP) value as per use of antibiotics. Summary forest plot for association between periodontal treatment (non-surgical periodontal therapy [NSPT] and community dental treatment/delayed NSPT) and changes in CRP levels 6 months after treatment (a) when antibiotics were used, (b) when no antibiotics were used

concentrations up to 6 months after treatment even without the initial use of antibiotics as adjunct. This finding is dependent on the initial level of systemic inflammation but also on the severity of periodontitis while it is independent of other co-morbidities like CVD, CKD and diabetes. Limited and inconclusive evidence was however gathered on the sustained effect of treating periodontitis on systemic inflammation beyond 6 months of follow-up.

4.1 | Results in relation to previous evidence

This is not the first systematic review on this topic, indeed our findings are in line with those reported in previous reviews (Paraskevas et al., 2008; Freitas et al., 2012), including populations of participants suffering from other non-communicable diseases such as diabetes, CKD and CVD (Teeuw et al., 2014; Artese et al., 2015; Delbove

et al., 2021). This is however the most up to date critical appraisal on the effects of the treatment of periodontitis on serum CRP levels and evaluation of its clinical relevance. The findings from this review are the most up to date comprehensive evaluation of the current evidence from only randomized controlled clinical trials. CRP is used as a clinical marker of inflammation and elevated serum levels are independent predictors of CVD even in otherwise healthy individuals (Libby et al., 2018). This is further confirmed by the dose-dependent stratification and risk increase based on initial CRP levels (<1 mg/L low risk; between 1 and 3 mg/L medium; and >3 mg/L with high risk) (Pearson et al., 2003). Systemic inflammation as assessed by high CRP levels raises the future risk of chronic diseases and their complications like diabetes, renal and CVDs (Libby et al., 2018; Furman et al., 2019). There is evidence that non-modifiable factors such as ethnicity (Kornman, 2020) and social gradient (increasing poverty and non-White populations) (Nazmi & Victora, 2007) are associated with elevated CRP levels and this could in part explain their role in future diseases risk. Reductions in CRP levels can be instead achieved by lifestyle interventions that promote better overall health (Furman et al., 2019). A landmark clinical trial (JUPITER) used rosuvastatin for middle-aged men and women with high levels of low-density lipoprotein (LDL) and residual inflammation as assessed by CRP. The results after 12 months of 20 mg rosuvastatin daily versus placebo showed a reduction of 50% lower median LDL cholesterol levels ($p < .001$) and 37% lower median CRP levels ($p < .001$), this was accompanied by a statistically significant reduction in the risk of any major cardiovascular events (Ridker et al., 2008). A 50% reduction in CVD risk has been documented when lowering CRP from 1 to 3 mg/L to less than 1 mg/L (Salazar et al., 2014). The CANTOS (Ridker et al., 2017) trial was the first large intervention study confirming that a reduction of CRP levels to less than 2 mg/L lowered the risk of cardiovascular death by one-third independent of any other cardiovascular risk factors in a sample of 10,000 patients with established CVD. This was also not an isolated finding as a similar reduction of CVD risk linked to reduction of inflammation was reported in the COLCOT trial when participants were given low-dose colchicine (a standard anti-inflammatory drug) (Tardif et al., 2019). Further evidence came from the CIRT trial, confirming that when using low dose of methotrexate but not producing changes in upstream systemic inflammation, no benefits in terms of reduction of CVD events were observed (Ridker et al., 2018). Collectively this evidence suggests that an intervention aimed at reducing systemic inflammation could be a valid tool in both primary and secondary CVD prevention. Treatment of periodontitis could well influence the residual inflammatory risk related to CVD.

4.2 | Potential mechanisms

Periodontitis is a chronic inflammatory disease triggered by a dysbiotic dental biofilm rich in gram-negative bacteria. It has been established that bacteria and their by-products may contribute to the pathogenesis of inflammatory conditions like RA and atherosclerosis (Libby et al., 2018). The exact mechanisms linking periodontitis to systemic inflammation however are yet to be fully understood. Dental plaque harbour pathogens and endotoxins, which in presence of reduced permeability at the gingival level, could result in short-term bacteraemia and affect the entire vasculature and existing atherosclerotic plaque deposits (Schenkein et al., 2020). An increased bacterial burden could represent a plausible mechanism for increases in white blood cell counts (Luthra et al., 2019), release of proinflammatory cytokines (interleukins) and then resulting in sustained release of acute phase proteins such as CRP (Tonetti et al., 2007; Orlandi et al., 2020) (Figure 6). An alternative novel mechanism could involve epigenetic changes occurring in the bone marrow haemopoietic progenitor cells and a derailment of the host immune response (Hajishengallis & Chavakis, 2021).
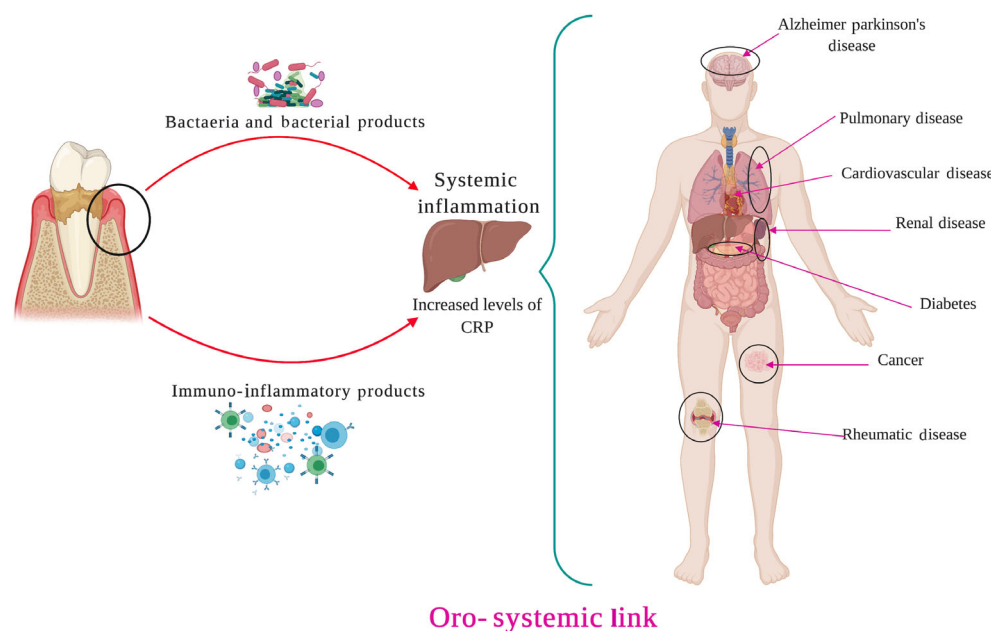
Bactaeria and bacterial products

Systemic inflammation

Increased levels of CRP

Immuno-inflammatory products

Alzheimer parkinson's disease

Pulmonary disease

Cardiovascular disease

Renal disease

Diabetes

Cancer

Rheumatic disease

Oro- systemic link

FIGURE 6 Oro-systemic inflammatory link. Putative pathways through which oral infection and inflammation can increase the risk of biosynthesis of C-reactive protein (CRP) and add to systemic health risk

4.3 | Clinical and public health implications and future recommendations

CRP is a common biomarker of systemic inflammation along with being an independent and consistent predictor of future CVDs and events. Periodontitis is the sixth most common global disease (Kassebaum et al., 2014) and is an overlooked source of systemic inflammation. Treatment of periodontitis results in reduction of both local and systemic inflammation. This review highlights an important anti-inflammatory effect of the treatment of periodontitis consistently across participants with clear medical history and those already suffering from other co-morbidities. A meta-analysis demonstrated that (a) the association between periodontitis and systemic inflammation is causal in nature, (b) a simple non-pharmacologic intervention (dental plaque removal and teeth cleaning) reduces systemic inflammation to a degree equivalent to that achieved by drug trials for the management of residual cardiovascular risk and (c) periodontitis could impact on the onset and development of complications of other co-morbidities (i.e., CVDs and diabetes). Future interventional trials with longer follow-up are warranted to demonstrate that indeed managing periodontitis will result in improved general health outcomes. Treatment of periodontitis could be implemented in health care systems to promote better oral and systemic health, especially in those individuals suffering from other co-morbidities with an established inflammatory pathogenesis.

4.4 | Limitations and strengths

This review has few limitations that should be highlighted. First, our search focused only on English language databases. Second, large variations in study designs and small sample sizes with large SEs were observed in most of the studies retrieved. Third, a variable level of heterogeneity was observed in most of the analyses depending on the different case definitions as inclusion criteria, the method of delivery of NSPT. Additionally, the limited data from RCTs with longer follow-ups (12 months or more) did not allow drawing definitive results over 6 months following treatment. However, a detailed protocol, the robust methodology used in conducting qualitative and quantitative analyses and pre-specified sensitivity analyses confirmed the main findings of this review and the overall assessment of the high overall certainty of evidence.

5 | CONCLUSIONS

There is robust evidence to suggest that treatment of periodontitis by non-surgical means reduces systemic inflammation as assessed by serum CRP levels. This in turn could result in systemic health benefits, especially in individuals at risk of or suffering from chronic disorders such as CVD, renal and metabolic disease. Future research should ascertain whether (a) the systemic effect following the treatment of periodontitis is sustained over time and (b) it would eventually result in a reduction of clinical events and complications.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

ETHICAL STATEMENT

This material is the authors' own original work, which has not been previously published elsewhere. The paper is not currently being considered for publication elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner. The paper properly credits the meaningful contributions of co-authors and co-researchers. The results are appropriately placed in the context of prior and existing research. All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference. All authors have been personally and actively involved in substantial work leading to the paper and will take public responsibility for its content. The violation of the Ethical Statement rules may result in severe consequences

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