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SYSTEMATIC REVIEW

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Microbiota associated with peri-implantitis—A systematic review with meta-analyses

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Abstract

Aim: To answer the following PECO question: "In systemically healthy human subjects (P), which are the differences between peri-implantitis (E) and peri-implant health/mucositis (C) in terms of bacterial presence/count (O)?"

Materials and Methods: Cross-sectional studies fulfilling specific inclusion criteria established to answer the PECO question were included. Two review authors independently searched for studies, screened the titles and abstracts, did full-text analysis, extracted the data from the included reports, and performed the risk of bias assessment through an adaptation of the Newcastle/Ottawa tool for cross-sectional studies and of the JBI critical appraisal checklist. In case of disagreement, a third reviewer author took the final decision. Study results were summarized using random effects meta-analyses.

Results: A total of 12 studies were included, involving 1233 participants and 1513 implants. Peri-implantitis was associated with the presence of *S. epidermidis* (Odds ratio, OR = 10.28 [95% Confidence interval, CI: 1.26–83.98]), *F. nucleatum* (OR = 7.83 [95% CI: 2.24–27.36]), *T. denticola* (OR = 6.11 [95% CI: 2.72–13.76]), *T. forsythia* (OR = 4.25 [95% CI: 1.71–10.57]), *P. intermedia* (OR = 3.79 [95% CI: 1.07–13.35]), and *P. gingivalis* (OR = 2.46 [95% CI: 1.21–5.00]). Conversely, the presence of *A. actinomycetemcomitans* (OR = 3.82 [95% CI: 0.59–24.68]), *S. aureus* (OR = 1.05 [95% CI: 0.06–17.08]), and *C. rectus* (OR = 1.48 [95% CI: 0.69–3.17]) was not associated with peri-implantitis.

Conclusions: Peri-implantitis is associated with the presence of *S. epidermidis* and specific periodontopathogens (*P. gingivalis*, *T. forsythia*, *T. denticola*, *F. nucleatum*, and *P. intermedia*). (CRD42021254589)

KEYWORDS
bacteria, dental implants, epidemiology, microbiology, microbiota, peri-implant diseases, risk factors

1 | INTRODUCTION

In light of its high prevalence (Derks et al., 2016; Romandini et al., 2019; Romandini et al., 2021a), poor prognosis (Berglundh, Wennström, & Lindhe, 2018; Romandini et al., 2023), and limited efficacy of current treatment approaches (Baima et al., 2022; Derks et al., 2022; Regidor et al., 2023; Romandini et al., 2022), prevention and early diagnosis are of critical importance in the management of peri-implantitis. Due to the lack of specific symptoms associated with peri-implantitis, the two key elements for its early diagnosis are the availability of baseline documentation to assess early changes in radiographic bone levels and tight screening for disease occurrence during recalls (supportive peri-implant care) (Berglundh et al., 2021; Romandini et al., 2021b; Romandini et al., 2021c).

In prevention, the main strategies are as follows: (i) treating peri-implant mucositis as precursor of peri-implantitis (Costa et al., 2012; Verket et al., 2023) and (ii) interventions aimed at controlling modifiable risk factors (Carra et al., 2023). The presence of plaque has been consistently reported as the key risk indicator for peri-implant diseases (Berglundh, Wennström, & Lindhe, 2018; Romandini et al., 2021a; Schwarz et al., 2018). A "non-specific" accumulation of plaque seems sufficient to initiate peri-implant mucositis (Pontoriero et al., 1994; Salvi et al., 2012; Schwarz et al., 2014), but not all cases will progress to peri-implantitis, suggesting the possible relevance of specific bacterial signatures within the disbiotic biofilm to initiate the progressive bone loss. However, there is a lack of appropriate knowledge about the specific bacteria associated to peri-implantitis (Pérez-Chaparro et al., 2016). This information would be relevant not only to improve the knowledge on the ethiopathogenesis of peri-implantitis, but also in the seek of improved diagnostic procedures (microbiological testing) aimed for personalized treatment protocols and as surrogate short-term outcomes for disease control.

Therefore, the aim of this systematic review including meta-analyses was to summarize the available evidence on the bacterial composition of submarginal plaque in implants affected by peri-implantitis versus peri-implant health/mucositis.

2 | MATERIALS AND METHODS

This article is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021) and to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup, 2000). A detailed protocol has been designed before the start of this study and it has been registered on the International Prospective Register of Systematic Reviews–PROSPERO, identification number CRD42021254589.

2.1 | Focused question

This systematic review aimed to answer to the following focused question:

"In systemically healthy human subjects (P), which are the differences between peri-implantitis (E) and peri-implant health/mucositis (C) in terms of bacterial presence/count (O), in studies with cross-sectional design/comparisons (S)?"

2.2 | Inclusion and exclusion criteria

The inclusion criteria were organized according to the PECOS acronym:

(P) Population: Systemically healthy human subjects with at least one osseointegrated dental implant.
(E) Exposure: Presence of peri-implantitis. Peri-implantitis was defined as an inflammation in the peri-implant mucosa observed through bleeding and/or suppuration on probing associated with progressive bone loss assessed on radiographs (or bone levels ≥2 mm in the absence of baseline documentation) (Berglundh, Armitage, et al., 2018; Romandini et al., 2021c; Sanz et al., 2012).
(C) Comparison: Presence of peri-implant health and/or peri-implant mucositis. Peri-implant health was defined as the absence of signs of clinical inflammation in the tissues around dental implants. Peri-implant mucositis was defined as an inflammation in the mucosa around the implants assessed as the presence of bleeding on gentle probing, without continuous marginal peri-implant bone loss (or bone levels <2 mm in the absence of baseline documentation) (Berglundh, Armitage, et al., 2018).
(O) Type of outcome measures: The bacterial composition in biofilm samples obtained from peri-implant pockets or peri-implant sulcus (either in terms of presence of bacteria or their count assessed through number/proportion/presence exceeding a threshold).
(S) Types of studies: Cross-sectional studies and longitudinal studies with a cross-sectional evaluation (i.e., clinical trials or prospective cohort studies comparing the composition of peri-implant microbiota between peri-implantitis and peri-implant health/mucositis at baseline) and with a minimum of 30 patients both in the exposure and comparison groups. No study was excluded based on its risk of bias evaluation.

2.3 | Search methods for the identification of studies

The electronic literature search was carried out in duplicate by two independent review authors (EBSC and SS) in four databases: MEDLINE (via PubMed), Web of Science, Scopus, and Embase, from outset to October 06, 2022. No restrictions were applied in terms of language, status, or publication date. The complete search strategies are detailed in Appendix S1.

Hand search were conducted in duplicate by the same reviewers from January 01, 2000 up to October 21, 2022 in six implant-related journals: *Clinical Oral Implants Research*, *Journal of Clinical*

Periodontology, *Journal of Dental Research*, *Clinical Implant Dentistry and Related Research*, *Journal of Periodontology*, *and International Journal of Oral and Maxillofacial Implants*. The bibliographies of all the included studies and of relevant systematic reviews (Lafaurie et al., 2017; Padial-Molina et al., 2016; Pérez-Chaparro et al., 2016) were cross-checked in duplicate by the same authors. All studies identified by at least one reviewer were included in the next phase (study selection).

2.4 | Study selection

The titles and abstracts were screened independently by two calibrated review authors (EBSC and SS) on Rayyan website (https://rayyan.ai). The full-text of any article meeting the inclusion criteria or with insufficient information in its title/abstract to make a clear decision was then analyzed by the same reviewers. The reasons for exclusion during the full-text analysis stage were recorded. Any disagreement was resolved by discussion with a third reviewer (MR). All studies meeting the inclusion criteria were included and underwent data extraction and assessment of risk of bias.

2.5 | Data extraction and management

Two reviewers (EBSC and SS) independently extracted in duplicate the needed information from the included studies, with the help of predefined data extraction tables. Disagreements were resolved through discussion; Where resolution was not possible, a third review author made the final decision (MR). In case of missing data, the authors of the included articles were contacted to provide additional information.

For each study, the following data was recorded:

- General information: Authors name, year of publication, country, or region of origin.
- Methods and population: Sample size, inclusion/exclusion criteria, gender (male, female), age (mean), smoking status (smokers, non-smokers), type of peri-implant health status (peri-implant health, peri-implant mucositis, or peri-implantitis), and implant systems used.
- Exposure and controls: Number of implants for each group.
- Outcomes: Microbiological evaluation methods and target microorganisms.
- Results: Estimates (Odds ratios—OR, or Differences in means—MD) with 95% Confidence intervals (CI) of association between peri-implant health status (peri-implantitis vs peri-implant mucositis/peri-implant health) and presence of bacteria/bacterial count (number, proportion, or exceeding a threshold). In case estimates were not available, group mean values (continuous outcomes) or numbers (binary outcomes) were extracted.
- Risk of bias assessment: Risk of bias was assessed through the use of both a modified version of the Newcastle–Ottawa Scale (NOS) (Wells et al., 2001) adapted for cross-sectional studies (reported in Appendix S1), and the Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross-sectional studies (Moola et al., 2020). Assessed items for NOS included: Study sample selection (two items, one star each), assessment of exposure/outcome variables (two items, two stars each), and confounding factors (two items, maximum three total stars) criteria. Therefore, each study could receive a maximum of nine stars. Overall NOS risk of bias was then evaluated as follows: low (≥7 stars), moderate (4–6 stars), or high (<4 stars). Assessed items for the JBI tool included: Inclusion criteria, description of study subjects/settings, assessment of the exposure/outcome, confounding factors, and statistical analyses. Based on the JBI assessment, an overall appraisal was made establishing whether the study was to be included or excluded.

2.6 | Data synthesis

Whenever needed (e.g., in presence of crude numbers), the corresponding estimate (OR/MD with 95% CI) was calculated. In presence of at least two studies for each association, meta-analyses were performed using Review Manager (RevMan) [Version 5.4.1, The Cochrane Collaboration, 2020] using a random effects models (DerSimonian & Kacker, 2007). The results were expressed as OR/MD with 95% CIs. Interstudy heterogeneity was initially assessed by carefully examining the characteristics of the included studies. Moreover, in each meta-analysis, the extent and impact of heterogeneity was assessed by visually inspecting the forest plots and by calculating Cochran's test, τ^2, and I^2 statistics. The I^2 statistic was used to quantify heterogeneity, with values of 25%, 50%, and 75% considered low, moderate, and high, respectively (Higgins, 2003). Subgroup analyses were also carried out considering separately the different comparison groups (peri-implant health, peri-implant mucositis, and mixed).

3 | RESULTS

3.1 | Study selection

The electronic search yielded 10,490 entries, of which 2243 were retrieved in Medline (via PubMed), 2340 in Web of Science, 2808 in Scopus, and 3099 in Embase. A total of three additional articles were identified through cross-reference checking and hand searching. After removing duplicates, a total number of 5570 publications were screened and from these, 5487 studies were discarded once the titles and abstracts were reviewed. Seventy-one additional articles were excluded after full-text review (reasons for exclusion after full-text analysis reported in Appendix S1) (agreement = 80.7%; $k = 0.62$; $p < .001$). Finally, 12 studies, involving 1233 participants with 1513 implants were included in this systematic review (Aleksandrowicz et al., 2020; Belibasakis et al., 2016; Canullo et al., 2015, 2018; de Waal et al., 2017; Leonhardt et al., 1999; Parthiban et al., 2017; Persson & Renvert, 2014; Polymeri et al., 2021; Sanz-Martin

et al., 2017; Sato et al., 2011; Wang et al., 2016). A flow chart that depicts this selection process is displayed in Figure 1.

3.2 | Characteristics of the included studies

The general characteristics of the included studies are reported in Table 1; detailed information on participants, exposures/comparisons, outcomes, and main results is described in Appendix S1 respectively.

Nine studies were performed in Europe (Aleksandrowicz et al., 2020; Belibasakis et al., 2016; Canullo et al., 2015, 2018; de Waal et al., 2017; Leonhardt et al., 1999; Persson & Renvert, 2014; Polymeri et al., 2021; Sanz-Martin et al., 2017), two in Asia (Parthiban et al., 2017; Sato et al., 2011), and the remaining one in North America (Wang et al., 2016). Eight studies used peri-implant health as comparison group (Aleksandrowicz et al., 2020; Belibasakis et al., 2016; Canullo et al., 2015, 2018; Leonhardt et al., 1999; Parthiban et al., 2017; Sanz-Martin et al., 2017; Wang et al., 2016); one study used peri-implant mucositis as comparison group (Sato et al., 2011); while the remaining studies used a mix of both as comparison group (de Waal et al., 2017; Persson & Renvert, 2014; Polymeri et al., 2021). The bacterial composition of the peri-implant microbiota was analyzed through different microbiological evaluation methods: Two studies used culture (de Waal et al., 2017; Leonhardt et al., 1999), one study used Checkerboard DNA–DNA hybridization (Persson & Renvert, 2014), six studies used qPCR (Canullo et al., 2015, 2018; Parthiban et al., 2017; Polymeri et al., 2021; Sato et al., 2011; Wang et al., 2016), one study used Fluorescence in situ hybridization (Belibasakis et al., 2016), and two studies used 16S rRNA gene-based PCR (Aleksandrowicz et al., 2020; Sanz-Martin et al., 2017).

The risk of bias assessment of the included studies is reported in Appendix S1. Seven studies were considered as moderate risk of bias and five as high risk of bias, according to the NOS. All studies were considered "to be included" according to the JBI critical appraisal checklist for analytical cross-sectional studies.

3.3 | Presence of bacteria in peri-implantitis versus peri-implant health/mucositis

Eight studies reported results on the presence of bacteria in peri-implantitis versus non-peri-implantitis (Aleksandrowicz et al., 2020; Belibasakis et al., 2016; Canullo et al., 2015; de Waal et al., 2017; Leonhardt et al., 1999; Sanz-Martin et al., 2017; Sato et al., 2011; Wang et al., 2016). A total of three phylum, two groups, 44 species, and two subspecies were analyzed (Appendix S1). One of those studies was not included in the meta-analyses because was the only one reporting data on bacterial phylum and groups (Belibasakis et al., 2016). Figure 2 and Appendix S1 depict the results of the meta-analyses for

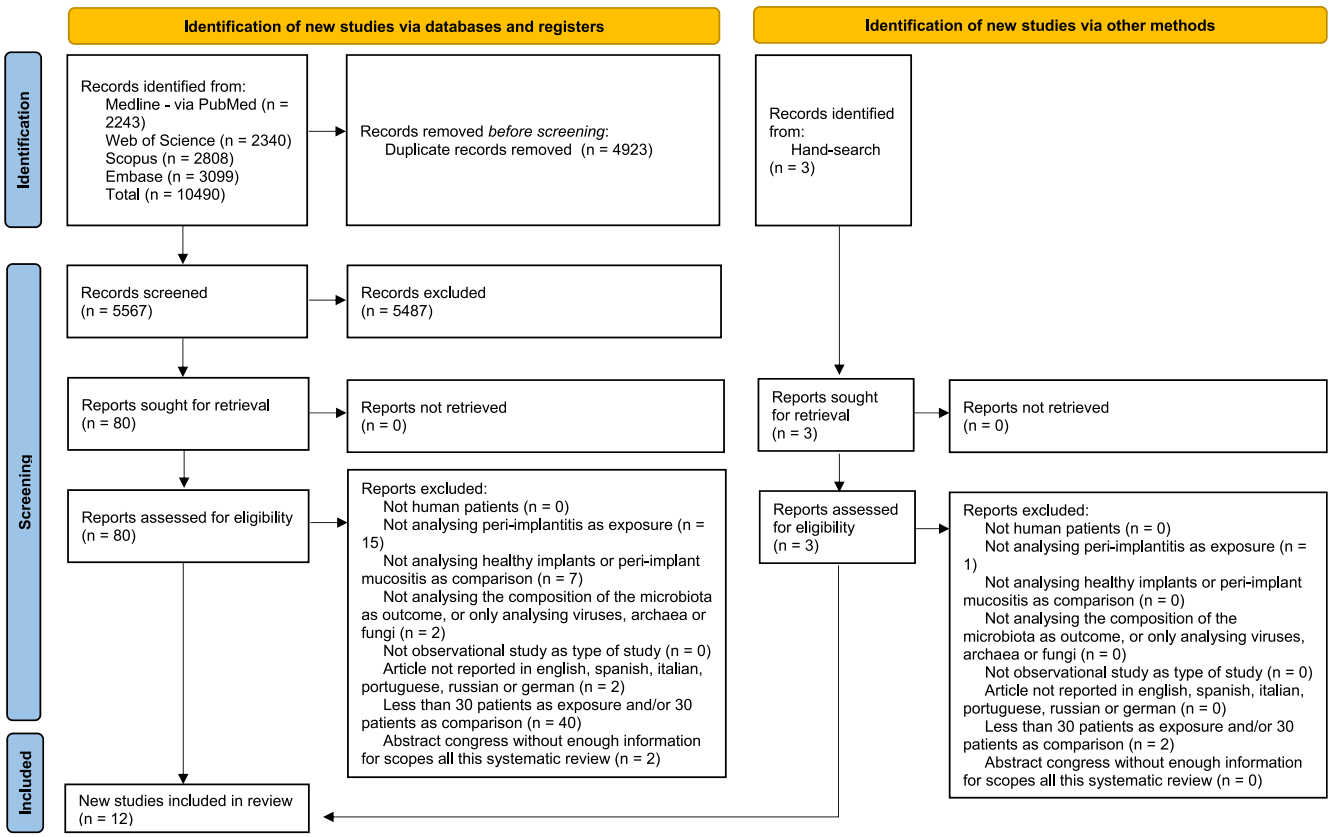

FIGURE 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources. From Page et al. (2021). For more information, visit: http://www.prisma-statement.org/.

TABLE 1 General overview of the included studies.

Reference	Country	Study design	Sample size—*N* implants (*N* participants)	Peri-implant health status (implant-level)—*N* (%) or "NA"		
				Peri-implant health	Peri-implant mucositis	Peri-implantitis
Aleksandrowicz et al. (2020)	Poland	Cross-sectional	78 (139)	37 (47.44%)	NA	41 (52.56%)
Belibasakis et al. (2016)	Switzerland	Cross-sectional	84 (84)	41 (48.81%)	NA	43 (51.19%)
Persson and Renvert (2014)	Sweden	Cross-sectional	213 (213)	47 (22.07%)	NA	166 (77.93%)
Sanz-Martin et al. (2017)	Switzerland	Cross-sectional	67 (67)	32 (47.76%)	NA	35 (52.24%)

Target microorganisms	Risk of bias
Fusobacterium nucleatum (*Fn*), *Porphyromonas gingivalis* (*Pg*), *Prevotella intermedia* (*Pi*), *Tannerella forsythia* (*Tf*), and *Treponema denticola* (*Td*)	High
Synergistetes cluster A, *Synergistetes* subcluster A1, *Synergistetes* subcluster A2, and *Treponema* cluster 1 (*Treponema* groups I–III: *Treponema denticola* [*Td*], *Treponema medium* [*Tm*], *Treponema parvum* [*Tp*], *Treponema vincentii* [*Tv*]), *Treponema* group IV (*Treponema lecithinolyticum* [*Tl*], and *Treponema maltophilum* [*Tm*])	Mod
Actinomyces odontolyticus (*Ao*), *Aggregatibacter actinomycetemcomitans* (*Aa*), *Campylobacter gracilis* (*Cg*), *Campylobacter rectus* (*Cr*), *Campylobacter showae* (*Cs*), *Fusobacterium nucleatum* (*Fn*) sp. *Naviforme*, *Fusobacterium nucleatum* (*Fn*) sp. *Nucleatum*, *Fusobacterium nucleatum* (*Fn*) sp. *Polymorphum*, *Fusobacterium periodonticum* (*Fp*), *Haemophilus influenzae* (*Hi*), *Helicobacter pylori* (*Hp*), *Parvimonas micra* (*Pm*), *Prevotella intermedia* (*Pi*), *Porphyromonas gingivalis* (*Pg*), *Pseudomonas aeruginosa* (*Pa*), *Staphylococcus anaerobius* (*San*), *Staphylococcus aureus* (*Sa*), *Staphylococcus haemolyticus* (*Sh*), *Streptococcus intermedius* (*Si*), *Streptococcus mitis* (*Sm*), *Tannerella forsythia* (*Tf*), *Treponema denticola* (*Td*), *Treponema socranskii* (*Ts*), *Veillonella parvula* (*Vp*)	High
Abiotrophia defectiva (*Ad*), *Acinetobacter Genus probe*, *Actinobaculum sp ot 183*, *Actinomyces cardiffensis* (*Ac*), *Actinomyces Genus probe 3*, *Actinomyces Genus probe 4*, *Actinomyces gerencseriae* (*Ag*), *Actinomyces israelii* (*Ai*), *Actinomyces massiliensis* (*Am*), *Actinomyces naeslundii* (*An*), *Actinomyces sp ot 448*, *Actinomyces sp ot 525*, *Aggregatibacter actinomycetemcomitans* (*Aa*), *Aggregatibacter aphrophilus;sp ot 458*, *Aggregatibacter paraphrophilus* (*Ap*), *Aggregatibacter segnis;sp ot 512*, *Aggregatibacter sp ot 458*, *Alloprevotella Genus probe*, *Alloprevotella rava* (*Ar*), *Alloprevotella sp ot 473*, *Alloprevotella sp ot 912*, *Alloprevotella tannerae* (*At*), *Anaeroglobus geminatus* (*Ag*), *Atopobium Genus probe*, *Atopobium parvulum* (*Ap*), *Atopobium rimae* (*Ar*), *Atopobium sp ot 199*, *Bacteroidaceae*[*G-1*] *sp ot 272*, *Bacteroidales*[*G-2*] *sp ot 274*, *Bacteroidales*[*G-3*] *sp ot 911*, *Bacteroides Genus probe*, *Bacteroides heparinolyticus* (*Bh*), *Bacteroides zoogleoformans* (*Bz*), *Bacteroidetes*[*G-3*] *sp ot 280*, *Bacteroidetes*[*G-3*] *sp ot 281*, *Bacteroidetes*[*G-3*] *sp ot 365*, *Bacteroidetes*[*G-3*] *sp ot 503*, *Bacteroidetes*[*G-5*] *Genus probe*, *Bacteroidetes*[*G-5*] *sp ot 505*, *Bacteroidetes*[*G-5*] *sp ot 511*, *Bacteroidetes*[*G-6*] *sp ot 516*, *Bergeyella sp ot 322*, *Bifidobacterium Genus probe 2*, *Bifidobacterium scardovii* (*Bs*), *Bulleidia extructa* (*Be*), *Campylobacter concisus* (*Cc*), *Campylobacter Genus probe 2*, *Campylobacter gracilis* (*Cg*), *Campylobacter sp ot 044*, *Capnocytophaga Genus probe 2*, *Capnocytophaga gingivalis* (*Cg*), *Capnocytophaga granulosa* (*Cgr*), *Capnocytophaga leadbetteri* (*Cl*), *Capnocytophaga ochracea* (*Co*), *Capnocytophaga sp ot 336*, *Capnocytophaga sp ot 864*, *Capnocytophaga sputigena* (*Cs*), *Cardiobacterium hominis* (*Ch*), *Cardiobacterium hominis;valvarum*, *Cardiobacterium valvarum* (*Cv*), *Catonella Genus probe*, *Catonella sp ot 451*, *Clostridiales*[*F-1*][*G-1*] *sp ot 093*, *Clostridiales*[*F-2*][*G-2*] *sp ot 085*, *Corynebacterium durum* (*Cd*), *Corynebacterium Genus probe*, *Corynebacterium matruchotii* (*Cm*), *Desulfobulbus Genus probe*, *Desulfobulbus sp ot 041*, *Dialister Genus probe 2 - Dialister invisus* (*Di*), *Dialister pneumosintes* (*Dp*), *Eggerthia catenaformis* (*Eca*), *Eikenella corrodens* (*Ec*), *Eikenella sp ot 011*, *Erysipelothrichaceae*[*G-1*] *sp ot 904*, *Erysipelothrichaceae*[*G-1*] *sp ot 905*, *Eubacterium*[*11*][*G-1*] *sulci*, *Eubacterium*[*11*][*G-5*] *saphenum*, *Eubacterium*[*11*][*G-6*] *minutum*, *Eubacterium*[*11*][*G-7*] *yurii*, *Filifactor alocis* (*Fa*), *Filifactor alocis;villosus*, *Finegoldia magna* (*Fm*), *Fretibacterium fastidiosum* (*Ff*), *Fretibacterium Genus probe 3*, *Fretibacterium sp ot 359;452*, *Fretibacterium sp ot 360*, *Fretibacterium sp ot 361*, *Fusobacterium Genus probe 2*, *Fusobacterium Genus probe 3*, *Fusobacterium Genus probe 4*, *Fusobacterium necrophorum* (*Fn*), *Fusobacterium nucleatum subsp nucleatum*, *Fusobacterium periodonticum* (*Fp*), *Gemella Genus probe*, *Gemella haemolysans* (*Gh*), *Gemella morbillorum* (*Gm*), *Gemella sanguinis* (*Gs*), *Granulicatella adiacens;paradiacens*, *Haemophilus Genus probe 3*, *Haemophilus parahaemolyticus* (*Hp*), *Haemophilus parainfluenzae*, *Haemophilus sp ot 035*, *Johnsonella ignava* (*Ji*), *Johnsonella ignava*; *sp ot 166*, *Johnsonella sp ot 166*, *Jonquetella anthropi* (*Ja*), *Kingella denitrificans;sp ot 012*, *Kingella oralis*, *Lachnoanaerobaculum orale* (*Lo*), *Lachnoanaerobaculum saburreum* (*Ls*), *Lachnospiraceae*[*G-3*] *sp ot 100*, *Lachnospiraceae*[*G-8*] *sp ot 500*, *Lactobacillus gasseri;johnsonii*, *Lactobacillus Genus probe 3*, *Lactobacillus iners*, *Lactobacillus jensenii*, *Lautropia mirabilis*, *Leptotrichia Genus probe 4*, *Leptotrichia goodfellowii*, *Leptotrichia hongkongensis*, *Leptotrichia sp ot 212*, *Leptotrichia sp ot 219*, *Leptotrichia sp ot 221*, *Leptotrichia sp ot 223*, *Leptotrichia sp ot 417*, *Leptotrichiaceae*[*G-1*] *sp ot 210*, *Leptotrichiaceae*[*G-1*] *sp ot 210;220*, *Megasphaera micronuciformis* (*Mm*), *Mogibacterium Genus probe*, *Mogibacterium timidum* (*Mt*), *Mollicutes*[*G-1*] *sp ot 504*, *Mycoplasma faucium* (*Mf*), *Neisseria bacilliformis* (*Nb*), *Neisseria elongata* (*Ne*), *Neisseria Genus probe 2*, *Neisseria oralis;sp ot 016*, *Olsenella sp ot 807*, *Oribacterium sp ot 078;372*, *Oribacterium sp ot 108*, *Parvimonas Genus probe*, *Parvimonas micra* (*Pm*), *Parvimonas sp ot 110*, *Peptococcus sp ot 167*, *Peptoniphilus sp ot 836*, *Peptostreptococcaceae*[*11*][*G-2*] *sp ot 091*, *Peptostreptococcaceae*[*11*][*G-4*] *sp ot 369*, *Peptostreptococcaceae*[*11*][*G-7*] *sp ot 081*, *Peptostreptococcaceae*[*13*][*G-1*] *sp ot 113*, *Peptostreptococcus stomatis* (*Ps*), *Porphyromonas endodontalis* (*Pe*), *Porphyromonas Genus probe 1*, *Porphyromonas Genus probe 2*, *Porphyromonas gingivalis* (*Pg*), *Porphyromonas sp ot 279*, *Porphyromonas sp ot 395*, *Porphyromonas uenonis* (*Pu*), *Prevotella baroniae* (*Pb*), *Prevotella dentalis*, *Prevotella denticola* (*Pd*), *Prevotella fusca* (*Pf*), *Prevotella Genus probe 2*, *Prevotella histicola* (*Ph*), *Prevotella intermedia* (*Pi*), *Prevotella maculosa* (*Pm*), *Prevotella marshii*, *Prevotella melaninogenica*, *Prevotella nanceiensis;sp ot 299*, *Prevotella nigrescens* (*Pn*), *Prevotella oralis* (*Po*), *Prevotella oris*, *Prevotella oulorum*, *Prevotella pallens* (*Pp*), *Prevotella pleuritidis* [*NV*], *Prevotella salivae* (*Ps*), *Prevotella sp ot 300*, *Prevotella sp ot 304*, *Prevotella sp ot 317*, *Prevotella sp ot 376*, *Prevotella sp ot 472*, *Prevotella sp ot 526*, *Prevotella veroralis* (*Pv*), *Pseudomonas Genus probe*, *Rothia aeria* (*Ra*), *Rothia dentocariosa* (*Rd*), *Rothia Genus probe*, *Rothia mucilaginosa* (*Rm*), *Scardovia wiggsiae* (*Sw*), *Selenomonas & Centipeda Genus probe*, *Selenomonas artemidis* (*Sa*), *Selenomonas sp ot 134*, *Selenomonas sp ot 136*, *Selenomonas sp ot 146*, *Selenomonas sp ot 149*, *Selenomonas sputigena* (*Ss*), *Sneathia amnionii* [*NV*], *SR1*[*G-1*] *sp ot 345*, *Staphylococcus Genus probe 3*, *Stomatobaculum sp ot 373*, *Streptococcus constellatus* (*Sc*), *Streptococcus Genus probe 4*, *Streptococcus gordonii;sanguinis*, *Streptococcus intermedius* (*Si*), *Streptococcus mutans* (*Sm*), *Streptococcus pneumoniae;pseudopneumoniae*, *Streptococcus sanguinis* (*Ss*), *Tannerella forsythia* (*Tf*), *Tannerella Genus probe*, *TM7 Genus probe*, *TM7*[*G-1*] *sp ot 348*, *TM7*[*G-1*] *sp ot 352*, *TM7*[*G-1*] *sp ot 353*, *TM7*[*G-5*] *sp ot 437*, *Treponema amylovorum* (*Ta*), *Treponema denticola* (*Td*), *Treponema Genus probe 2*, *Treponema Genus probe 3*, *Treponema Genus probe 4*, *Treponema Genus probe 5*, *Treponema Genus probe 6*, *Treponema lecithinolyticum* (*Tl*), *Treponema maltophilum* (*Tm*), *Treponema parvum* (*Tp*), *Treponema putidum*, *Treponema socranskii* (*Ts*), *Treponema sp ot 236*, *Treponema sp ot 238*, *Treponema sp ot 242*, *Treponema sp ot 247*, *Treponema sp ot 252*, *Treponema sp ot 254*, *Treponema sp ot 255*, *Treponema sp ot 256*, *Treponema sp ot 257*, *Treponema sp ot 258*, *Treponema sp ot 260*, *Treponema sp ot 262*, *Treponema sp ot 263*, *Treponema sp ot 268*, *Treponema sp ot 270*, *Treponema sp ot 508*, *Treponema vincentii* (*Tv*), *Veillonella atypica* (*Va*), *Veillonella dispar* (*Vd*), *Veillonella Genus probe 2*, *Veillonella parvula* (*Vp*), *Veillonella sp ot 780*, *Veillonella sp ot 917*, *Veillonellaceae Genus probe 3*, *Veillonellaceae*[*G-1*] *sp ot 145*, *Veillonellaceae*[*G-1*] *sp ot 155*	Mod

(Continued)

TABLE 1 (Continued)

Reference	Country	Study design	Sample size—*N* implants (*N* participants)	Peri-implant health status (implant-level)—*N* (%) or "NA"		
				Peri-implant health	Peri-implant mucositis	Peri-implantitis
Parthiban et al. (2017)	India	Cross-sectional	190 (80)	113 (59.47%)	NA	77 (40.53%)
de Waal et al. (2017)	Netherlands	Cross-sectional	154 (154)	69 (44.81%)	NA	85 (55.19%)
Leonhardt et al. (1999)	Sweden	Cross-sectional	88 (88)	51 (57.95%)	NA	37 (42.05%)
Canullo et al. (2015)	Spain	Cross-sectional	235 (110)	122 (51.91%)	NA	113 (48.09%)
Wang et al. (2016)	USA	Cross-sectional	68 (68)	34 (50%)	NA	34 (50%)
Polymeri et al. (2021)	Netherlands	Cross-sectional	41 (41)	11 (27%)	24 (58%)	6 (15%)
Sato et al. (2011)	Japan	Cross-sectional	105 (105)	NA	59 (56.19%)	46 (43.81%)
Canullo et al. (2018)	Italy	Cross-sectional	190 (84)	113 (59.47%)	NA	77 (40.53%)

Abbreviations: Mod, Moderate; *N*, Number; NA, Not Applicable.

species analyzed in at least two studies. Peri-implantitis was associated with the presence of *Staphylococcus epidermidis* (*Se*) (OR = 10.28 [95% CI = 1.26–83.98]; $p = .03$; $I^2 = 0\%$), *Fusobacterium nucleatum* (*Fn*) (OR = 7.83 [95% CI = 2.24–27.36]; $p = .001$; $I^2 = 32\%$), *Treponema denticola* (*Td*) (OR = 6.11 [95% CI = 2.72–13.76]; $p < .0001$; $I^2 = 67\%$), *Tannerella forsythia* (*Tf*) (OR = 4.25 [95% CI = 1.71–10.57]; $p = .002$; $I^2 = 82\%$), *Prevotella intermedia* (*Pi*) (OR = 3.79 [95% CI = 1.07–13.35]; $p = .04$; $I^2 = 83\%$), and *Porphyromonas gingivalis* (*Pg*) (OR = 2.46 [95% CI = 1.21–5.00]; $p = .01$; $I^2 = 70\%$) when compared to non-peri-implantitis. Conversely, the presence of *Aggregatibacter actinomycetemcomitans* (*Aa*) (OR = 3.82 [95% CI = 0.59–24.68]; $p = .16$; $I^2 = 53\%$), *Staphylococcus aureus* (*Sa*) (OR = 1.05 [95% CI = 0.06–17.08]; $p = .97$; $I^2 = 0\%$), and *Campylobacter rectus* (*Cr*) (OR = 1.48 [95% CI = 0.69–3.17]; $p = .31$; $I^2 = 0\%$) was not associated with peri-implantitis. A single study reported a negative association between presence of *Veillonella dispar* (*Vd*) (OR = 0.24 [95% CI = 0.08–0.72]; $p = .01$), *Rothia dentocariosa* (*Rd*) (OR = 0.20 [95% CI = 0.07–0.57]; $p = .003$), and *Streptococcus sanguinis* (*Ss*) (OR = 0.23 [95% CI = 0.08–0.66]; $p = .006$) with peri-implantitis (Sanz-Martin et al., 2017).

Subgroup analyses for peri-implantitis versus peri-implant health indicated an association of peri-implantitis with the presence of *T. denticola* (OR = 7.15 [95% CI = 2.34–21.83]; $p = .0006$; $I^2 = 75\%$). Conversely, the presence of *F. nucleatum* (OR = 8.23 [95% CI = 0.54–124.89]; $p = .13$; $I^2 = 65\%$), *Pg* (OR = 1.74 [95% CI = 0.81–3.75]; $p = .16$; $I^2 = 62\%$), *Pi* (OR = 2.41 [95% CI = 0.70–8.32]; $p = .17$; $I^2 = 78\%$), *Tf* (OR = 2.81 [95% CI = 0.90–8.78]; $p = .08$; $I^2 = 81\%$), and *Aa* (OR = 2.23 [95% CI = 0.03–186.68]; $p = .72$; $I^2 = 82\%$) showed no statistically significant differences. Results for peri-implantitis versus peri-implant mucositis were only analyzed in a single study (Sato et al., 2011), $n = 105$ implants, which reported an association of peri-implantitis with a high level of *Pg* (OR = 6.03 [95% CI = 2.55–14.26]; $p < .0001$), *Tf* (OR = 6.68 [95% CI = 2.79–15.99]; $p < .0001$), and *Td* (OR = 4.18 [95% CI = 1.83–9.55]; $p = .0007$). Results for peri-implantitis versus mixed groups were only analyzed in a single study (de Waal et al., 2017), $n = 154$ implants, which reported an association of peri-implantitis with a high level of *Fn* (OR = 6.91 [95% CI = 2.20–21.70]; $p = .0009$), *Pg* (OR = 4.54 [95% CI = 1.37–15.04]; $p = .01$), *Pi* (OR = 15.14 [95% CI = 5.06–45.30]; $p < .00001$), and *Tf* (OR = 13.29 [95% CI = 5.44–32.46]; $p < .00001$).

3.4 | Bacterial count in peri-implantitis versus peri-implant health/mucositis

Nine studies reported results on bacterial count in peri-implantitis versus non-peri-implantitis: Five of them expressed the results in terms of number of bacteria (Belibasakis et al., 2016; Canullo et al., 2015, 2018; Parthiban et al., 2017; Sato et al., 2011), two in terms of proportions (Sanz-Martin et al., 2017; Wang et al., 2016), one in terms of both proportions and presence of bacteria exceeding a count thresholds (de Waal et al., 2017), and one in terms of both number of bacteria and presence of bacteria exceeding a count thresholds (Persson & Renvert, 2014) (Appendix S1). Six of those studies did not report estimates or sufficient information from crude numbers to allow data synthesis through meta-analyses (Belibasakis et al., 2016; Canullo et al., 2018; Parthiban et al., 2017; Sanz-Martin et al., 2017; Sato et al., 2011; Wang et al., 2016), while de Waal et al. (2017) was not included in the meta-analyses because was the

Target microorganisms	Risk of bias
Aggregatibacter actinomycetemcomitans (*Aa*), *Campylobacter rectus* (*Cr*), *Candida albicans* (*Ca*), *Eikenella corrodens* (*Ec*), *Fusobacterium nucleatum* (*Fn*), *Parvimonas micra* (*Pm*), *Porphyromonas gingivalis* (*Pg*), *Prevotella intermedia* (*Pi*), *Tannerella forsythia* (*Tf*), *Treponema denticola* (*Td*)	Mod
Aggregatibacter actinomycetemcomitans (*Aa*), *Campylobacter rectus* (*Cr*), *Fusobacterium nucleatum* (*Fn*), Gram-negative rod-shaped bactéria, *Parvimonas micra* (*Pm*), *Porphyromonas gingivalis* (*Pg*), *Prevotella intermedia* (*Pi*), *Staphylococcus aureus* (*Sa*), *Staphylococcus epidermidis* (*Se*), *Staphylococcus warneri* (*Sw*), *Tannerella forsythia* (*Tf*)	Mod
Aggregatibacter actinomycetemcomitans (*Aa*), *Candida albicans* (*Ca*), *Enterobacter aerogenes* (*Ea*), *Enterobacter cloace* (*Ecl*), *Enterococcus faecalis* (*Ef*), *Escherichia coli* (*Ec*), *Klebsiella pneumonie* (*Kp*), *Klebsiella* spp. (*Ks*), *Porphyromonas gingivalis* (*Pg*), *Prevotella intermedia/nigrescens* (*Pi*), *Proteus morgani* (*Pm*), *Staphylococcus aureus* (*Sa*), *Staphylococcus epidermidis* (*Se*)	High
Aggregatibacter actinomycetemcomitans (*Aa*), *Campylobacter rectus* (*Cr*), *Candida albicans* (*Ca*), *Eikenella corrodens* (*Ec*), *Fusobacterium nucleatum* (*Fn*), *Peptostreptococcus micros* (*Pm*), *Porphyromonas gingivalis* (*Pg*), *Prevotela intermedia* (*Pi*), *Tanerella forsythia* (*Tf*), *Treponema denticola* (*Td*)	Mod
Aggregatibacter actinomycetemcomitans (*Aa*), *Porphyromonas gingivalis* (*Pg*), *Prevotella intermedia* (*Pi*), *Tannerella forsythia* (*Tf*), *Treponema denticola* (*Td*)	High
Actinobacteria, *Bacteria*, *Bacteroidetes*, *Chloroflexi*, *Firmicutes*, *Fusobacteria*, *Gracilibacteria GN02*, *Proteobacteria*, *Saccharibacteria TM7*, *Spirochaetes*, *Synergistetes*, *Anaeroglobus geminatus* (*Ag*), *Fusobacterium nucleatum* (*Fn*), *Haemophilus parainfluenzae* (*Hp*), *Neisseria oralis* (*No*), *Prevotella nigrescens* (*Pn*), *Prevotella oris* (*Po*), *Rothia aeria* (*Ra*), *Rothia mucilaginosa* (*Rm*), *Streptococcus mutans* (*Sm*), *Streptococcus oralis* (*So*), *Streptococcus salivarius* (*Ss*), *Treponema denticola* (*Td*), *Veillonella parvula* (*Vp*)	Mod
Aggregatibacter actinomycetemcomitans (*Aa*), *Porphyromonas gingivalis* (*Pg*), *Tannerella forsythensis* (*Tf*), *Treponema denticola* (*Td*)	High
Aggregatibacter actinomycetemcomitans (*Aa*), *Campylobacter rectus* (*Cr*), *Candida albicans* (*Ca*), *Eikenella corrodens* (*Ec*), *Fusobacterium nucleatum* (*Fn*), *Parvimonas micra* (*Pm*), *Porphyromonas gingivalis* (*Pg*), *Prevotela intermedia* (*Pi*), *Tannerella forsythia* (*Tf*), *Treponema denticola* (*Td*)	Mod

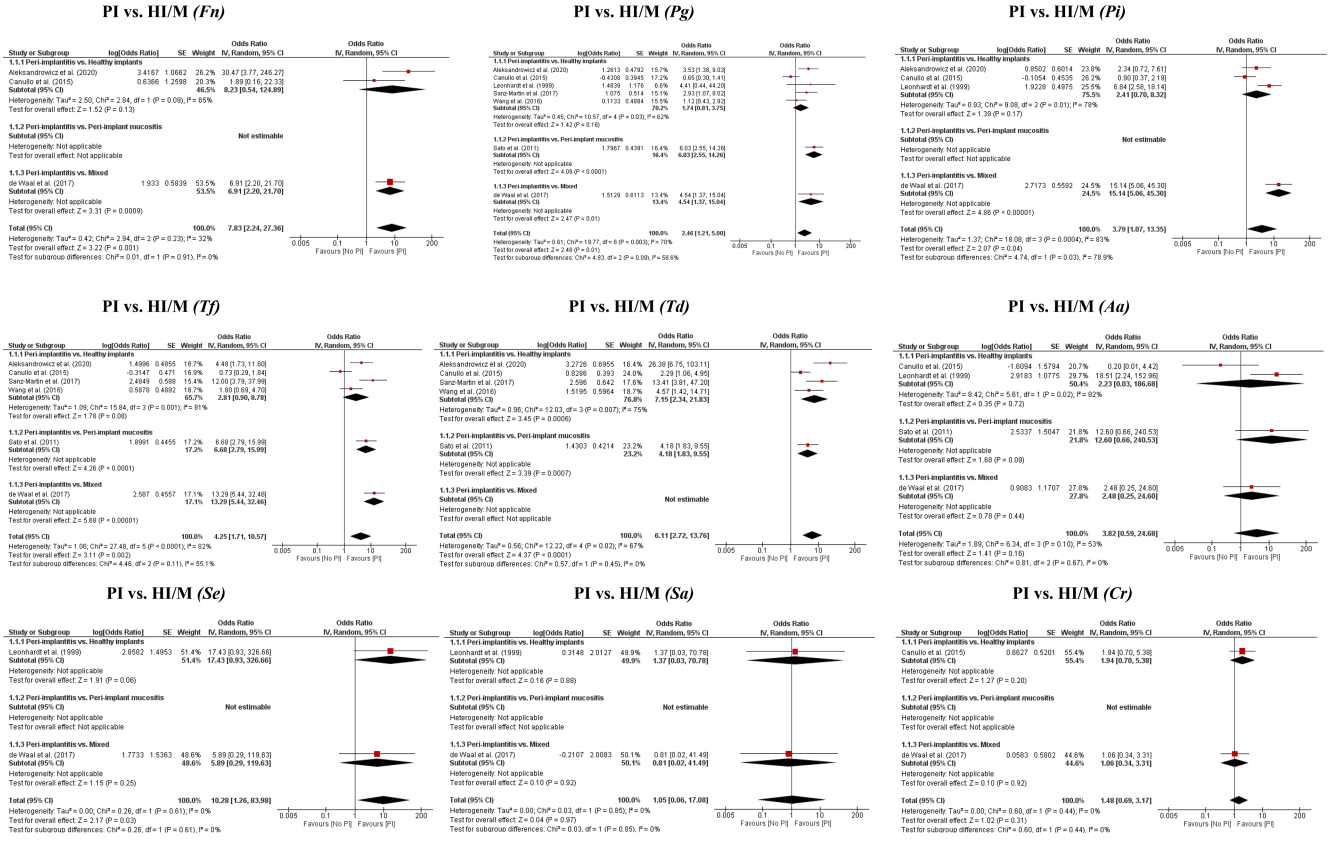

FIGURE 2 Meta-analyses: Peri-implantitis as exposure (outcome: Presence of bacteria).

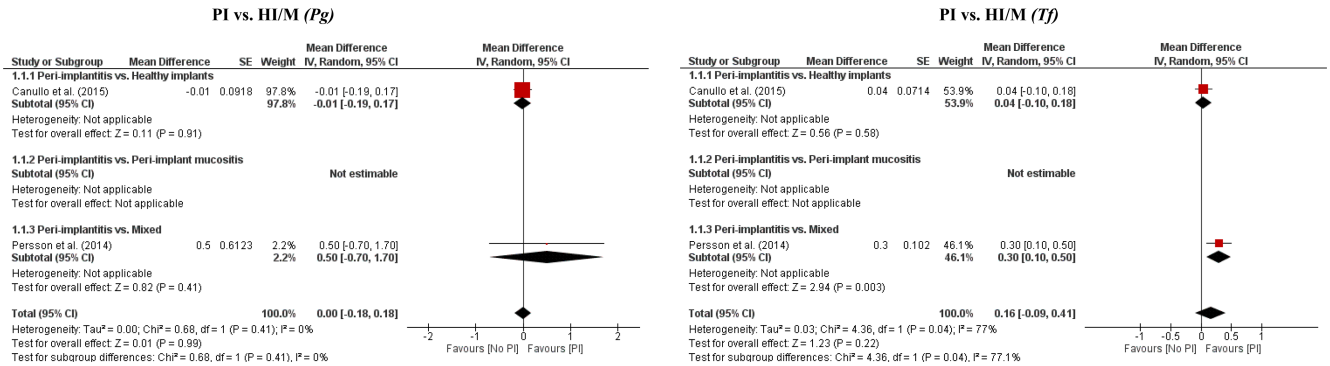

FIGURE 3 Meta-analyses: Peri-implantitis as exposure (outcome: Bacterial count).

only one with available estimates for bacterial proportions. Meta-analyses were therefore only possible for two studies reporting on count expressed in terms of number of bacteria (Canullo et al., 2015; Persson & Renvert, 2014) (Figure 3 and Appendix S1). Data synthesis indicated no differences between peri-implantitis and peri-implant health/mucositis with respect to *Pg* (MD = 0.00 [95% CI = −0.18–0.18]; $p = .99$; $I^2 = 0\%$) and *Tf* (MD = 0.16 [95% CI = −0.09–0.41]; $p = .22$; $I^2 = 77\%$) for this outcome. No subgroup meta-analyses were possible.

4 | DISCUSSION

In this systematic review with meta-analyses including a total of 1233 participants with 1513 implants, peri-implantitis was associated with the presence of *S. epidermidis*, *P. gingivalis*, *T. forsythia*, *T. denticola*, *F. nucleatum*, and *P. intermedia*. A tendency for association with the presence of *A. actinomycetemcomitans* was also found, but it did not reach the statistical significance level. Conversely, the presence of *S. aureus* and *C. rectus* was not associated with peri-implantitis. Evidence from single studies also indicated a possible positive association of specific phylum (*Synergistetes* cluster A, subclusters A1/A2), groups (*Treponema denticola/Treponema medium/Treponema parvum/Treponema vincentii*) and species (e.g., *Filifactor alocis*, *Fretibacterium fastidiosum*, and *Peptostreptococcaceae*[*11*] [*G-2*] *spot 0912 and* [*G-4*] *spot 369*) with peri-implantitis. Conversely, single studies indicated a possible protective role (i.e., negative association) of *Veillonella dispar*, *Rothia dentocariosa*, and *Streptococcus sanguinis*. Results for bacterial count as outcome and for subgroup analyses were mostly inconclusive.

The association of *P. Gingivalis*, *T. forsythia*, *T. denticola*, *F. nucleatum*, and *P. intermedia* with peri-implantitis is not new (Eick et al., 2016; Hultin et al., 2002; Lafaurie et al., 2017; Pérez-Chaparro et al., 2016; Tenenbaum et al., 2017). A study by Ghensi et al. (2020) identified these five bacterial species among the "peri-implantitis-related complex," using shotgun metagenomic sequencing of the plaque microbiome. These results suggest a similar microbial etiology between periodontitis and some forms of peri-implantitis, since *P. gingivalis*, *T. forsythia*, and *T. denticola* formed the so-called "red complex" of microbial species associated with severe periodontitis, while *F. nucleatum* and *P. intermedia* are part of the "orange complex" (Socransky et al., 1998). Moreover, since these bacteria are considered as late colonizers, a possible relevance of biofilms may be also hypothesized in the etiopathogenesis of peri-implantitis. However, in light of the well-documented epidemiological association between moderate/severe forms of periodontitis and peri-implantitis (Derks et al., 2016; Romandini et al., 2021a), a confounding effect from periodontitis (i.e., secondary contamination) cannot be ruled out.

The association between *S. epidermidis* and peri-implantitis had not been previously reported, since the studies that were included in the meta-analyses reported a tendency for association, but they were under-powered to show a statistically significant association (de Waal et al., 2017; Leonhardt et al., 1999). In this study, *S. epidermidis* was the bacterial specie with the strongest estimate of association with peri-implantitis (OR = 10.28). A preclinical study already underlined how peri-implant tissues may represent an important niche for *S. epidermidis* in experimental biomaterial-associated infections (Broekhuizen et al., 2007). Notably, *S. epidermidis* only colonized the peri-implant tissues and not the implant surface. This finding may be suggestive of some forms of peri-implantitis associated with planktonic infections. This possibility is consistent with clinical observations from the authors of some biofilm-free peri-implantitis, usually associated with suppuration on probing. Since *S. epidermidis* has been already related to suppurative planktonic infections of biomaterials (Denegri et al., 2014; Okano et al., 2022), it can be hypothesized that this bacterial etiology may be responsible for a different phenotypic manifestation of peri-implantitis, distinct from the classical "periodontitis-like" etiology associated with red/orange complex bacteria. However, this speculation needs verification in future studies.

Some limitations should be considered when interpreting the findings from this systematic review. The search strategy resulted in the identification of only 12 studies, all of them considered as moderate/high risk of bias, mainly for issues related to study sample selection and confounding factors. Accordingly, the external validity of the present findings is limited by the use of nonrepresentative and heterogenous samples in the analyzed populations.

Similarly, a risk of confounding bias (e.g., from periodontitis, smoking status, and implant surface) may also exist, since most of the included studies did not report adjusted estimates of association. While known periodontopathogens were considered in most of the included articles, many other bacteria were sparsely analyzed, preventing any solid conclusion about their association with peri-implantitis. Furthermore, in lack of cohort studies, only cross-sectional designs were considered, which further prevented any evaluation of causality and direction of association. Finally, most meta-analyses were characterized by a moderate-high heterogeneity, possibly to be attributed to the inherent differences between studies in analyzed populations and in microbiological analytical methods.

5 | CONCLUSIONS

Peri-implantitis was associated with the presence of *S. epidermidis*, and specific periodontopathogens (*P. gingivalis*, *T. forsythia*, *T. denticola*, *F. nucleatum*, and *P. intermedia*). Prospective cohort studies are needed to confirm the present findings and to expand knowledge on the other bacteria. When designing those studies, researchers are encouraged to employ adequately powered representative samples and to report analyses adjusted for possible confounders (e.g., periodontitis, smoking, and implant surface). Moreover, modern microbiological assessment techniques (e.g., pyrosequencing) should be preferred over conventional (e.g., culture) and molecular (e.g., PCR) techniques, to give a broader view on the peri-implantitis-associated microbiota. These studies should not only focus on the presence of bacteria or on their count, but also on their phenotypic expression and on the complex relationships with the host.

AUTHOR CONTRIBUTIONS

EBSC contributed to study design, data acquisition and interpretation, data analysis, and article drafting. MR contributed to study conception and design, data acquisition and interpretation, data analysis, and article drafting. SS contributed to study design, data acquisition, and critically revised the article. ACPS and MS contributed to study design and critically revised the article. All authors have given their approval of the final article to be published and agree to be held accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest and no specific funding related to this systematic review.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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