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ORIGINAL ARTICLE

Multiplicative effect of stress and poor sleep quality on periodontitis: A university-based cross-sectional study

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Abstract

Background: The aim of this study was to evaluate the association of perceived stress and poor sleep quality with periodontitis in a university-based cohort of individuals.

Methods: A total of 235 individuals were included in this cross-sectional study. Perceived stress and sleep quality were evaluated through validated questionnaires, while periodontitis was identified with a full-mouth periodontal examination protocol using both European Federation of Periodontology/American Academy of Periodontology (EFP/AAP) and Centers for Disease Control and Prevention (CDC)/AAP case definitions. Simple and multiple linear and ordinal logistic regression analyses were performed to evaluate the association between perceived stress and sleep quality with periodontitis prevalence and severity.

Results: Stage III/IV periodontitis resulted associated with both moderate/high perceived stress (odds ratio [OR] = 5.4; 95% confidence interval [CI]: 2.2–13.5; $p < 0.001$) and poor sleep quality (OR = 3.0; 95% CI: 1.2–7.4; $p < 0.05$). The interaction between moderate/high perceived stress and poor sleep quality presented a multiplicative association with stage III/IV periodontitis (EFP/AAP; OR = 5.8; 95% CI: 1.6–21.3; $p < 0.001$). Multiple linear regression analyses indicated a similar trend of association also with linear periodontal parameters, that is, mean clinical attachment level (CAL) and mean probing pocket depth (PPD).

Conclusions: The findings from the present study suggest that stress and poor sleep quality may exert a multiplicative effect on periodontitis prevalence and severity.

KEYWORDS
epidemiology, periodontal diseases, risk factors, sleep hygiene, stress, psychological

1 | INTRODUCTION

Stress and lack of adequate rest are among the major issues of the modern lifestyle.[1] In particular, perceived stress refers to a condition described by the afflicted subject as threatening or uncontrollable[2]; in 2020, it affected around 20% of Americans.[3] Stress has a negative impact on general health, both as a consequence of direct biological mechanisms (e.g., immune system impairment) or indirect consequent behavioral changes (e.g., reduced physical activity, comfort eating, alcohol intake, smoking).[4] With regard to rest, epidemiological studies indicated how around 20% of the American population suffer from chronic sleep disorders.[5] Similarly to stress, poor sleep quality has a negative effect on systemic health, which has been explained through direct mechanisms involving systemic inflammation, oxidative stress, and immune system impairment, and indirect mechanisms related to the associated compensatory behaviors.[6]

Being that inflammation and oxidative stress are key components of periodontitis pathogenesis,[7,8] previous epidemiological studies have proposed high levels of perceived stress and poor sleep quality as modifiable risk indicators for periodontitis.[9,10] However, evidence from the medical field already highlighted that high stress and poor sleep quality exert a multiplicative effect on the mortality risk for cardiovascular disease (CVD) compared to subjects with low stress and adequate sleep quality.[11] The rationale behind such multiplicative systemic effects may reside on the reciprocal association found between stress and sleep quality[12]: the sleep-induced recovery process helps the human body attenuate stress-related acute load reactions,[13]resulting in a fine balance between the two factors. Indeed, whenever stress levels are chronically high and there is an incomplete recovery due to poor sleep quality, chronic allostatic load reactions and the disrupted immune/inflammatory responses are additionally triggered.[14] Therefore, it can be hypothesized that the combination of high stress and poor sleep quality may exert a negative effect on the periodontium that is likely to be of higher magnitude than the two factors alone. However, studies analyzing the possible multiplicative effect of high perceived stress and poor sleep quality on the periodontium are still lacking. This information would be clinically relevant, being that stress and sleep quality are modifiable in nature and, thus, potential targets of interventions in the context of the Step 1 of periodontal therapy.[15–17]

Therefore, the aim of the present cross-sectional study was to evaluate the multiplicative effect of stress and poor sleep quality on periodontitis prevalence and severity in a university-based cohort of individuals.

2 | MATERIALS AND METHODS

2.1 | Study design

The present study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for cross-sectional studies.[18] The research protocol was approved by the local ethics committee (protocol number: 18993/2021), and it was registered on Clinicaltrials.gov (NCT04771949).

2.2 | Setting and participants

All consecutive patients attending the Dentistry Department at the University Hospital of Siena were screened between January 2021 and August 2021. The following inclusion criteria were applied:

- Age between 18 and 70 years old;
- Presence of at least two remaining teeth;
- Ability and willingness to give informed consent.

The exclusion criteria were:

- Current pregnancy or lactation;
- Periodontal therapy performed in the previous 12 months;
- Administration of antibiotics within the previous 6 months;
- Inability to effectively communicate in Italian.

Individuals were enrolled in the study after they read and signed the written informed consent, in accordance with the Declaration of Helsinki.

2.3 | Assessment of study variables

2.3.1 | Clinical periodontal parameters

Details on the assessment of study variables are reported in a separate publication on the same study sample.[19] Briefly, all included participants received a full-mouth periodontal examination by two previously calibrated examiners (C.M., C.G.). Probing pocket depth (PPD), gingival recession (REC), plaque,[20] and bleeding on probing (BoP)[21] were recorded with a standardized periodontal probe* at six sites per tooth, third molars excluded. Whenever the cementum enamel junction was located subgingivally, negative values were recorded for REC. Clinical

* UNC 15 probe, Hu-Friedy Group, Chicago, IL.

attachment levels (CAL) were computed as the sum between PPD and REC values. Furthermore, mean PPD and mean CAL, as well as the proportion (%) of sites with PPD ≥4 mm and PPD ≥6 mm were calculated from PPD/CAL measurements.

Examiners' calibration was performed for both PPD and REC on two non-study subjects suffering from periodontitis, and it was considered satisfactory only when an agreement in at least 95% of measurements (with a maximum of 2 mm difference) was recorded between the two examiners. Intra-class correlation coefficients (ICCs) were computed using site-level measurements and not considering sites clustering at teeth/participant-level. Inter-examiner agreement resulted in ICC = 0.98 ($p < 0.001$) for PPD and in ICC = 0.96 ($p < 0.001$) for REC. For the first examiner, intra-examiner agreement resulted in ICC = 0.89 ($p = 0.002$) for PPD and in ICC = 0.92 ($p = 0.001$) for REC; for the second one, intra-examiner agreement resulted in ICC = 0.94 ($p < 0.001$) for PPD and in ICC = 0.98 ($p < 0.001$) for REC.

2.3.2 | Periodontitis case definitions

Periodontitis was diagnosed using both the European Federation of Periodontology/American Academy of Periodontology (EFP/AAP)[22] and the Centers for Disease Control and Prevention (CDC)/AAP criteria.[23] According to EFP/AAP criteria, periodontitis cases were identified whenever interdental CAL was detectable at ≥2 non-adjacent teeth, or whenever buccal or oral CAL ≥3 mm with pocketing (PPD >3 mm) was detectable at ≥2 teeth.[24] Cases were classified according to their stage and extent. Periodontitis stage was identified using severity (i.e., interdental CAL at site of greatest loss, number of missing teeth due to periodontitis) and complexity factors (i.e., sites with PPD ≥6 mm, furcation involvement, number of opposing pairs). The number of missing teeth due to periodontitis was drawn from clinical records whenever available, otherwise it was self-reported by the patient; the number of opposing pairs was clinically assessed. For each stage, extent was described as either localized (<30% of teeth involved) or generalized. According to the CDC/AAP criteria, periodontitis was categorized as being either mild, moderate, or severe. Severe periodontitis was defined as having ≥2 interproximal sites with CAL ≥6 mm and ≥1 interproximal site with PPD ≥5 mm. Moderate periodontitis was defined as having ≥2 interproximal sites with CAL ≥4 mm and ≥2 interproximal sites with PPD ≥5 mm, while mild periodontitis was defined as the presence of ≥2 interproximal sites with CAL ≥3 mm and ≥2 interproximal sites with PPD ≥4 mm.[23]

2.3.3 | Perceived stress

The Italian version of a validated 10-item questionnaire to measure patients' level of perceived stress (IPSS-10) was administered by the clinical examiners, who asked structured questions and gave the explanations provided by the questionnaire itself.[25] The instrument had 10 questions with response options ranging between 0 (never) and 4 (very often). All questions were negatively stated (from 4 to 0), except for four questions that were positively stated (from 0 to 4; items 4, 5, 7, and 8). The sum scores were calculated after reversing the positive items' scores and then summing up all scores. Total scores ranged between 0 and 40; the higher the score, the higher the level of perceived stress. Finally, the IPSS-10 score was categorized according to the guidelines in order to stratify participants into two subgroups: moderate/high (IPSS-10 >13) and low perceived stress (IPSS-10 ≤13).[26,27]

2.3.4 | Sleep quality

Sleep quality was assessed using the validated Italian version of Pittsburgh Sleep Quality Index (PSQI) questionnaire.[2] The PSQI was administered by the clinical examiners, who asked structured questions and gave the explanations provided by the questionnaire. The questionnaire included seven domains (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, daytime dysfunction), each one assessed with a 0 to 3 scoring system; the final scores ranged between 0 and 21, with higher values indicating worse sleep quality. Participants with a total score of 5 or higher were classified as having "poor sleep quality," vice versa for those with lower scores (classified as having "good sleep quality").[28]

2.3.5 | Covariates

Self-reported socio-demographic characteristics, including age, sex, weight, height, smoking and oral hygiene habits, occupation, and education level, were registered. Moreover, self-reported information regarding the presence of any comorbidity possibly affecting susceptibility to periodontitis was collected (i.e., diabetes, rheumatoid arthritis, osteoporosis, and cardiovascular and inflammatory bowel diseases); in case participants self-reported one of the mentioned comorbidities, the medical reports were checked for verification. The body mass index (BMI) was computed as weight (kg)/height (m^2). The detailed assessment methods of socio-demographic characteristics are reported

in the Supplementary Appendix in the online *Journal of Periodontology*.

2.4 | Sample size calculation

The sample size calculation was based on the null hypothesis that the prevalence of periodontitis in the present sample was the same as previously reported (37.3%).[29] For a 10% threshold in prevalence difference (with $\alpha = 0.05$), a sample of 185 participants would have resulted in 80% power to reject the null hypothesis. Due to the broader scope of the present work, this number was inflated of 20%; therefore, the inclusion of 235 participants was planned.

2.5 | Statistical analyses

Statistical analyses were performed through an ad hoc software[†], a priori setting the level of significance at 5%. Continuous variables were reported as mean and standard deviation (SD); categorical data were expressed as number of observations (percentage-%).

After verification of data distribution, the unpaired Student's t test and the Chi2 test were used to compare patients' characteristics according to the categories of perceived stress and sleep quality.

Simple and multiple ordinal logistic regression analyses were then performed to study the association between perceived stress/sleep quality (binary variables) and their interaction with periodontitis (EFP/AAP and CDC/AAP criteria). Simple and multiple logistic regression analyses were also performed using perceived stress/sleep quality (continuous variables) as exposure. Furthermore, after assumptions verification, multiple linear regression models were built to evaluate the association between perceived stress and sleep quality with additional periodontal variables, that is, mean CAL, and mean PPD. The multiple models were adjusted for age,[30,31] body mass index,[32] sex,[33] smoking,[34] education,[35,36] toothbrushing frequency,[37] and comorbidities (binary variable defined as the presence of at least one comorbidity among those mentioned above), a priori selected according previous evidence of their association with the exposure, the outcome, or both.[38] Results from regression analyses were expressed as odds ratios (ORs) or beta coefficient (β) with 95% CI. Sensitivity analyses by age (≤40 vs. >40 years) and number of teeth (≤20 vs. >20 teeth) were also performed.

[†] StataCorp. 2021, Stata Statistical Software: Release 17, StataCorp LLC, College Station, TX.

3 | RESULTS

3.1 | Participant characteristics

A total of 235 participants were included in the present study. Table 1 provides the descriptive statistics of the study population. The mean age was 53.9 years, and most of the included participants were females (57.9%) and never smokers (45.5%). The prevalence of periodontitis according to the EFP/AAP classification was 85.5%, while the prevalence according to the CDC/AAP classification was 64.7%. Approximately 52% of subjects were in the moderate/high-stress subgroup, and 48% were in the poor sleep quality subgroup.

3.2 | Perceived stress and periodontitis

Participants with moderate/high perceived stress presented a significantly higher periodontitis severity (staging) ($p = 0.00$). Other periodontal parameters (i.e., mean CAL and mean PPD, number of bleeding pockets, full-mouth bleeding score (FMBS), teeth lost for periodontal causes) were significantly worse in subjects with high compared to low perceived stress. Conversely, FMPS as well as domiciliary plaque control habits were comparable across subgroups of perceived stress ($p = 0.56$) (Table 1).

Ordinal logistic regression analyses indicated how moderate/high perceived stress was significantly associated with stage I and III periodontitis with increasing estimates of association from stage I to stage III (Table 2; see Tables S1–S4 in online *Journal of Periodontology*), while the estimates were attenuated when considering the CDC/AAP criteria (see Tables S5–S7 in online *Journal of Periodontology*). Moreover, an increase in the PSS (continuous) was associated with significantly higher odds of severe periodontitis (CDC/AAP; OR = 2.4) (see Table S5 in online *Journal of Periodontology*). Furthermore, simple and multiple linear regression analyses demonstrated a significant association between moderate/high perceived stress and other measures of periodontitis, that is, mean CAL and mean PPD (Table 3).

3.3 | Sleep quality and periodontitis

Poor sleep quality presented a significantly higher periodontitis severity (staging) ($p = 0.03$). Other periodontal parameters (i.e., mean PPD, %PPD ≥4 mm, %PPD ≥6 mm, number of bleeding pockets, teeth lost for periodontal causes) were significantly worse in subjects with poor compared to good sleep quality. Conversely, domiciliary plaque control habits were comparable across subgroups

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TABLE 1 Patients' characteristics by perceived stress and sleep quality level

		Perceived stress			Sleep Quality		
	Overall	Moderate/high	Low		Poor	Good	
Variable	***n* = 235**	***n* = 122**	***n* = 113**	***p*-Value***	***n* = 113**	***n* = 122**	***p*-Value***
Age, years	53.9 ± 14.7	55.8 ± 12.9	51.8 ± 16.2	0.07	57.5 ± 12.6	50.5 ± 15.7	*<0.001*
BMI, kg/m^2	25.5 ± 4.8	25.3 ± 4.2	25.7 ± 5.4	0.93	25.9 ± 5.1	25.1 ± 4.5	0.22
Sex, females	136 (57.9)	73 (59.8)	63 (55.8)	0.31	72 (63.7)	64 (52.5)	0.08
Occupation							
Unemployed	42 (17.9)	25 (20.7)	17 (15.1)	0.41	18 (15.9)	24 (19.8)	0.24
Employed	133 (56.8)	64 (52.9)	69 (61.1)		61 (53.9)	72 (59.5)	
Retired	59 (25.2)	32 (26.5)	27 (23.9)		34 (30.1)	25 (20.7)	
Education							
Elementary/middle school	69 (29.5)	44 (36.1)	25 (22.3)	*0.02*	36 (31.9)	33 (27.3)	0.45
High school	107 (45.7)	55 (45.1)	52 (46.4)		53 (46.9)	54 (44.6)	
College or more	58 (24.8)	23 (18.8)	35 (31.3)		24 (21.3)	34 (28.1)	
Smoking							
Never	107 (45.5)	53 (43.4)	54 (47.8)	0.77	51 (45.1)	56 (45.9)	0.99
Former	67 (28.5)	37 (30.3)	30 (26.5)		32 (28.3)	35 (28.7)	
Smoker	61 (25.9)	32 (26.2)	29 (25.7)		30 (26.6)	31 (25.4)	
Familiarity for periodontitis, yes	87 (37.1)	53 (43.4)	34 (30.1)	*0.02*	43 (38.1)	44 (36.1)	0.79
Comorbidities[a], yes	43 (18.3)	21 (17.2)	22 (19.5)	0.69	27 (23.9)	16 (13.1)	0.09
Oral health status							
Periodontitis staging[b] (EFP/AAP)							
Healthy/gingivitis	34 (14.5)	7 (5.7)	27 (23.9)	*<0.001*	8 (7.1)	26 (21.3)	*0.03*
Stage 1	27 (11.5)	13 (10.7)	14 (12.4)		9 (7.9)	18 (14.8)	
Stage 2	56 (23.8)	27 (22.1)	29 (25.7)		25 (22.1)	31 (25.4)	
Stage 3	94 (40.0)	58 (47.5)	36 (31.9)		56 (49.6)	38 (31.2)	
Stage 4	24 (10.2)	17 (13.9)	7 (6.2)		15 (13.3)	9 (7.4)	
Periodontitis[c] (CDC/AAP)							
No periodontitis	83 (35.3)	21 (17.2)	62 (54.9)	*<0.001*	26 (23.0)	57 (46.7)	*<0.001*
Mild	29 (12.3)	20 (16.4)	10 (8.8)		16 (14.2)	13 (10.7)	
Moderate	70 (29.8)	57 (46.7)	13 (11.5)		41 (36.3)	29 (23.8)	
Severe	53 (22.6)	15 (12.3)	38 (33.6)		30 (26.6)	23 (18.9)	
No. of teeth	24.2 ± 5.4	23.7 ± 5.3	24.7 ± 5.6	0.06	23.7 ± 5.3	24.6 ± 5.5	0.08
Mean CAL, mm	2.8 ± 1.1	2.9 ± 1.1	2.4 ± 1.1	*<0.001*	2.9 ± 1.0	2.4 ± 1.1	*<0.001*
Mean PPD, mm	2.5 ± 0.7	2.6 ± 0.7	2.4 ± 0.6	*0.02*	2.6 ± 0.7	2.4 ± 0.6	*0.03*
% PPD≥4 mm	9.3 ± 11.6	11.0 ± 12.7	7.4 ± 9.9	*<0.001*	11.6 ± 12.8	7.2 ± 9.9	*<0.001*
% PPD≥6 mm	5.8 ± 9.4	6.4 ± 4.8	3.2 ± 3.9	*0.001*	7.5 ± 4.2	3.6 ± 3.0	*<0.001*
No. of bleeding pockets[d]	7.3 ± 10.4	8.9 ± 12.1	5.5 ± 7.8	*<0.001*	9.1 ± 10.9	5.7 ± 9.5	*<0.001*
FMPS	50.6 ± 24.3	51.3 ± 23.9	49.8 ± 24.6	0.69	50.6 ± 24.8	50.5 ± 23.8	0.98
FMBS	28.5 ± 17.8	30.1 ± 15.6	26.7 ± 19.8	*0.02*	29.7 ± 17.9	27.3 ± 17.7	0.25
Teeth lost for periodontitis, yes	76 (32.3)	51 (41.8)	25 (22.1)	*<0.001*	49 (43.4)	27 (22.1)	*<0.001*
Domiciliary plaque control							
Brushing frequency							
Not performed	4 (1.7)	2 (1.6)	2 (1.8)	0.37	1 (0.9)	3 (2.5)	0.22
Occasionally	46 (19.6)	28 (22.9)	18 (15.9)		27 (23.9)	19 (15.6)	
Every day	185 (78.7)	92 (75.4)	93 (82.3)		85 (75.2)	100 (81.9)	

(Continues)

TABLE 1 (Continued)

		Perceived stress			Sleep Quality		
	Overall	Moderate/high	Low		Poor	Good	
Variable	***n* = 235**	***n* = 122**	***n* = 113**	***p*-Value***	***n* = 113**	***n* = 122**	***p*-Value***
Toothbrush type, powered	122 (51.9)	60 (49.2)	62 (54.9)	0.23	55 (48.7)	67 (54.9)	0.20
Interdental cleaning (IC)							
Not performed	75 (31.9)	41 (33.6)	35 (30.9)	0.78	37 (32.7)	38 (31.9)	0.98
Interdental floss	51 (21.7)	27 (22.1)	24 (21.2)		25 (22.1)	26 (21.3)	
Interproximal brushes	109 (45.9)	54 (44.3)	54 (47.8)		51 (45.1)	57 (46.7)	
Frequency of IC							
Not performed	75 (31.9)	42 (34.4)	33 (29.2)	0.56	37 (32.7)	38 (31.2)	0.99
Occasionally	48 (20.4)	26 (21.3)	22 (19.5)		23 (20.4)	25 (20.5)	
Every day	112 (47.7)	54 (44.3)	58 (51.3)		53 (46.9)	59 (48.4)	

Notes: Data are presented as mean ± standard deviation or numbers (percentages). Comparisons across subgroups of stress/sleep were performed using the unpaired Student's t test for continuous variables, and the Chi^2 test for categorical variables.

Abbreviations: AAP, American Academy of Periodontology; BMI, body mass index; CAL, clinical attachment level; CDC, Centers for Disease Control and Prevention; EFP, European Federation of Periodontology; FMBS, full-mouth bleeding score; FMPS, full-mouth plaque score; IC, interdental cleaning; PPD, probing pocket depth.

[a]Defined as the presence of at least one comorbidity among diabetes, rheumatoid arthritis, osteoporosis, cardiovascular, and inflammatory bowel diseases.

[b]According to the 2018 EFP/AAP classification.

[c]According to the CDC/AAP classification.

[d]Defined as the number of sites with probing depth≥5 mm and positive to bleeding on probing.

*$p < 0.05$ is considered statistically significant. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

TABLE 2 Effect estimates from ordinal logistic regression models for the association between perceived stress, sleep quality, and their interaction with periodontitis (EFP/AAP classification)

	Stage I[a]		Stage II[a]		Stage III/IV[a]	
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Exposure variables	**Crude**	**Adjusted[b]**	**Crude**	**Adjusted[b]**	**Crude**	**Adjusted[b]**
PSQI (continuous)	3.2 (0.9, 7.2)	2.5 (0.7, 5.1)	2.9 (0.9, 6.2)	2.3 (0.8, 5.3)	5.5 (0.9, 9.7)	2.5 (0.2, 5.2)
PSS (continuous)	3.6 (0.9, 7.9)	2.2 (0.4, 5.0)	2.3 (0.4, 5.9)	2.1 (0.7, 6.2)	3.2 (0.9, 6.1)	2.9 (0.6, 4.9)
Poor sleep quality (vs. good sleep quality)	1.4 (0.5, 4.0)	1.2 (0.4, 3.8)	2.0 (0.8, 4.9)	1.7 (0.7, 4.4)	*4.0 (1.8, 8.7)**	*3.0 (1.2, 7.4)**
Moderate/high perceived stress (vs. low perceived stress)	2.3 (0.8, 6.4)	*2.2 (1.0, 8.8)**	2.3 (0.9, 5.7)	*2.6 (1.1, 6.6)**	*4.6 (2.1, 10.1)**	*5.4 (2.2, 13.5)**
Interaction between sleep quality and perceived stress						
Poor sleep quality (vs. good sleep quality)	2.4 (0.7, 9.0)	3.2 (0.7, 15.0)	1.3 (0.4, 3.3)	1.2 (0.3, 4.9)	*3.4 (1.3, 9.0)**	*2.5 (1.1, 8.2)**
Moderate/high perceived stress (vs. low perceived stress)	3.5 (0.7, 12.0)	*5.5 (1.1, 26.3)**	1.4 (0.4, 4.5)	2.0 (0.9, 7.7)	*3.9 (1.4, 10.9)**	*4.0 (1.0, 15.6)**
Moderate/high stress # poor sleep quality[c]	3.7 (0.5, 12.9)	1.0 (0.1, 7.1)	*2.7 (1.1, 17.9)**	2.7 (0.7, 9.9)	*6.4 (2.1, 19.1)**	*5.8 (1.6, 21.3)**

Abbreviations: CI, confidence interval; OR, odds ratio; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale.

[a]vs. healthy or gingivitis.

[b]Adjusted for age, sex, smoking, body mass index, education, brushing frequency, and comorbidities (defined as the presence of at least one comorbidity among diabetes, rheumatoid arthritis, osteoporosis, cardiovascular and inflammatory bowel diseases).

[c]The interaction term equaled 1 whenever the participant had moderate/high stress and poor sleep quality, otherwise it equaled 0 (i.e., reference category).

*$p < 0.05$ is considered statistically significant. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

of sleep quality ($p = 0.99$) (Table 1). Ordinal logistic regression analyses indicated how poor sleep quality was significantly associated with stage III/IV periodontitis (EFP/AAP; OR = 3.0), as well as with severe periodontitis (CDC/AAP; OR = 2.5) (Table 2; see Table S5 in online *Journal of Periodontology*). When considering PSQI (continuous) as exposure, only a non-statistically significant tendency in the same direction was noted (Tables 2 and 3; see Tables S1–S7 in online *Journal of Periodontology*). Moreover, multiple linear regression analyses indicated a significant association between poor sleep quality and mean CAL, but not mean PPD (Table 3).

TABLE 3 Effect estimates from linear regression models for the association between perceived stress, sleep quality, and their interaction with mean CAL and mean PPD

	Mean CAL (mm)		Mean PPD (mm)	
	β (95% CI)		β (95% CI)	
Exposure variables	**Crude**	**Adjusted[a]**	**Crude**	**Adjusted[a]**
PSQI (continuous)	*0.7 (0.3, 1.1)**	*0.4 (0.1, 0.8)**	*0.9 (0.3, 1.6)**	*0.2 (0.02, 1.0)**
PSS (continuous)	*0.7 (0.4, 1.2)**	*0.5 (0.2, 1.9)**	*0.4 (0.04, 1.2)**	0.2 (−0.1, 1.3)
Poor sleep quality (vs. good sleep quality)	*0.1 (0.04, 0.2)**	*0.3 (0.05, 0.6)**	*0.1 (0.02, 0.2)**	0.1 (−0.03, 0.3)
Moderate/high perceived stress (vs. low perceived stress)	*0.1 (0.06, 0.2)**	*0.4 (0.1, 0.6)**	*0.1 (0.03, 0.2)**	*0.2 (0.004, 0.3)**
Interaction between sleep quality and perceived stress				
Poor sleep quality (vs. good sleep quality)	*0.1 (0.01, 0.3)**	*0.2 (0.001, 0.5)**	0.2 (0.06, 0.4)	0.1 (−0.1, 0.4)
Moderate/high perceived stress (vs. low perceived stress)	0.1 (−0.003, 0.2)	*0.3 (0.01, 0.6)**	*0.2 (0.03, 0.4)**	*0.2 (0.001, 0.4)**
Moderate/high stress # poor sleep quality[b]	*0.7 (0.4, 0.9)**	*0.5 (0.2, 0.7)**	*0.2 (0.04, 0.4)**	0.2 (−0.02, 0.3)

Abbreviations: CAL, clinical attachment level; CI, confidence interval; PPD, probing pocket depth; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale.

[a]Adjusted for age, sex, smoking, body mass index, education, brushing frequency, and comorbidities (defined as the presence of at least one comorbidity among diabetes, rheumatoid arthritis, osteoporosis, and cardiovascular and inflammatory bowel diseases).

[b]The interaction term equaled 1 whenever the participant had moderate/high stress and poor sleep quality, otherwise it equaled 0 (i.e., reference category).

* $p < 0.05$ is considered statistically significant. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

3.4 | Interaction between perceived stress and sleep quality

When considering the interaction between perceived stress and sleep quality, ordinal logistic regressions indicated how the subgroup with combined "moderate/high stress, poor sleep quality" (OR = 5.8) resulted associated with stage III/IV periodontitis (EFP/AAP) with around a double magnitude than either poor sleep quality or moderate/high perceived stress alone (Table 2); these results remained consistent also for severe periodontitis (CDC/AAP) (see Table S5 in online *Journal of Periodontology*). Multiple linear regression analyses indicated a similar trend of association also with other additional periodontal parameters, that is, mean CAL and mean PPD (Table 3).

4 | DISCUSSION

The present cross-sectional study indicated that moderate/high perceived stress and poor sleep quality are associated with severe forms of periodontitis (defined with both the EFP/AAP and the CDC/AAP criteria). The estimates of association were found to be multiplicative for subjects reporting moderate/high perceived stress and poor sleep quality, irrespective of the disease classification employed, subgroups of age, and participant's total number of teeth. Furthermore, moderate/high perceived stress and poor sleep quality also showed a linear relationship with additional periodontal parameters, such as mean CAL and mean PPD. Plaque control was comparable across stressed/non-stressed subjects and among those reporting poor/good sleep quality, suggesting that these associations are not due to this factor.

Results of the current investigation on the association between perceived stress and periodontitis are consistent with those obtained by a previous report conducted on 621 Brazilian individuals,[9] where a significant association was also found. Nonetheless, the magnitude of association was weaker than the one found in the present study, possibly due to the different periodontitis case definitions employed.[22,23] Indeed, the present study underlined similar, but more attenuated results for the CDC/AAP compared to the EFP/AAP criteria, consistent with those findings reporting discrepancies in the identification of periodontitis cases between the two case definitions.[40] The association between stress and periodontitis may be boiled down to mainly two pathways: a direct biological negative impact on the immune and endocrine system, and behavioral adaptive changes (including smoking).[1] As for the direct biological impact, stress triggers an increase in neuroendocrine hormones, such as glucocorticoids and catecholamines which, in turn, exert suppressive effects on the immune system, by reducing lymphocyte proliferation, antibody production, and natural killer cell activity.[41] Consequently, subjects with chronic stress tend to be more prone to infections.

With regard to sleep quality, results from the present research are consistent with those from a previous study, which reported a significant association between staging and grading of periodontitis and PSQI.[10] A proper comparison of the magnitude of association with the present study could not be performed, due to the differences in the outcome assessment methods and in the employed

thresholds for the categorization of variables. Substantial evidence supports the biological plausibility of the association between poor sleep quality and periodontitis, and this relationship seems to be bi-directional.[42] Indeed, poor sleep quality was found to be associated with higher markers of systemic inflammation which may influence the development of periodontitis[43]; in turn, the presence of a state of systemic inflammation, which can be triggered by periodontitis,[44] may negatively impact sleep quality.[7]

The combination of moderate/high perceived stress and poor sleep quality was associated with a higher prevalence of both periodontitis and severe periodontitis, and with worse periodontal parameters, irrespective of socio-demographic characteristics and plaque control. Therefore, the results from the current study suggest the presence of a multiplicative effect of poor sleep quality and perceived stress on periodontitis occurrence and severity, similar to what was observed for CVD.[11] To the best of the authors' knowledge, no previous study evaluated the combined effect of perceived stress and sleep quality on periodontal health. On the grounds of these considerations, it can be hypothesized that the pro-inflammatory systemic action of stress and poor sleep quality and the suppressive action on the immune functions of moderate/high perceived stress may exert a multiplicative effect on the periodontium,[45,17] which may be conducive to an increased susceptibility to periodontitis onset and severity, as well as a worse response to periodontal therapy.[17] In particular, chronic psychological stress was shown to hyperactivate the hypothalamic-pituitary axis (leading to increased cortisol production and release) and the sympathetic nervous system which, similarly to the systemic effects of poor sleep quality, eventually leads to an increase in the markers of systemic inflammation, such as C-reactive proteins and interleukin-6; in turn, systemic inflammation was demonstrated to have a detrimental impact on the periodontium.[12,14,43] This information may be relevant for clinicians since stress and sleep quality may be potential targets of interventions in the context of the Step 1 of periodontal therapy,[15] and for researchers since they may represent potential confounders to be taken into account in well-established associations between periodontitis and systemic diseases.[46–48]

Some limitations are worth mentioning when interpreting these findings, including the cross-sectional study design (which hampers the investigation of the temporality of association and does not rule out the reverse causality hypothesis), the risk of information bias for periodontitis (e.g., due to the lack of radiographic information in some non-periodontitis or incipient periodontitis cases) and stress/sleep quality (i.e., self-reported) assessments. Furthermore, the risk of residual confounding cannot be ruled out, also due to the lack of a detailed consideration of the medical conditions and medications that may have affected the periodontal status of the participants as well as the estimates of association between the exposure and the outcome. In addition, all the included participants came from urban or suburban areas in the south-east part of a region in Central Italy (Tuscany), where most adults are Caucasian; hence, any possible variability in the results related to ethnicity could not be investigated. Moreover, given that the study population was selected among patients coming to a public university hospital, the risk of selection bias could not be excluded. Overall, these two factors may also reduce the generalizability of the study findings. In addition, the reduced sample size resulted in wide confidence intervals for the multiplicative association of stress and sleep quality with periodontitis, which lead to insecurity towards the central estimates and—consequently—on the reported concept of a multiplicative effect. Finally, no saliva or blood samples were collected, so assessments of inflammatory markers could not be performed. Nonetheless, to the best of the authors knowledge, this represents the first study investigating the multiplicative effect of perceived stress and sleep quality on periodontal health. Assessments of perceived stress and sleep quality were performed using reliable and validated tools for the selected sample, whose validity and reproducibility for the Italian population were previously demonstrated.[2,49]

5 | CONCLUSION

The present study indicated a multiplicative association of perceived stress and sleep quality with periodontitis. Specifically, individuals whose lifestyle is characterized by both moderate/high perceived stress and poor sleep quality have a from 5- to 6-times increased odds of suffering from severe forms of periodontitis.

AUTHOR CONTRIBUTIONS

Crystal Marruganti contributed to study conception, study design, data analysis, and manuscript drafting. Carlo Gaeta contributed to data interpretation and manuscript drafting. Mario Romandini contributed to data analysis, data interpretation, and manuscript drafting. Edoardo Ferrari Cagidiaco and Stefano Parrini contributed to data interpretation, and critically revised the manuscript. Nicola Discepoli contributed to study design. Simone Grandini contributed to study conception, study design, and manuscript drafting.

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CONFLICT OF INTEREST STATEMENT

The authors deny any conflict of interest related to this study.

DATA AVAILABILITY STATEMENT

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

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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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