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Association of Periodontitis and Subsequent Depression

A Nationwide Population-Based Study

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Abstract: Periodontitis is a systemic and chronic inflammatory disease associated with multiple physical conditions. Distress and depression are other problems affecting the progression of periodontitis. However, the causal relationship between depression and periodontitis has not been adequately investigated. This aim of this study was to determine the association between periodontitis and the subsequent development of depression.

We identified 12,708 patients with newly diagnosed periodontitis from 2000 to 2005 and 50,832 frequency-matched individuals without periodontitis. Both groups were followed until diagnosed with depression, withdrawal from the National Health Insurance program, or the end of 2011. The association between periodontitis and depressio was analyzed using Cox proportional hazard regression models.

The incidence density rate of depression was higher in the periodontitis group than in the nonperiodontitis group, with an adjusted hazard ratio of 1.73 (95% confidence interval 1.58–1.89) when adjusting for sex, age, and comorbidity. Cox models revealed that periodontitis was an independent risk factor for depression in patients, except for comorbidities of diabetes mellitus (DM), alcohol abuse, and cancer.

Periodontitis may increase the risk of subsequent depression and was suggested an independent risk factor regardless of sex, age, and most comorbidities. However, DM, alcohol abuse, and cancer may prevent the development of subsequent depression because of DM treatment, the paradoxical effect of alcohol, and emotional distress to cancer, respectively. Prospective studies on the relationship between periodontitis and depression are warranted.

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Abbreviations: CI = confidence interval, LHID = Longitudinal Health Insurance Database, NHIRD = National Health Insurance Research Database.

INTRODUCTION

Periodontitis, a periodontal disease, results from interaction between the immune system and oral bacteria that may promote oxidative stress and initiate an inflammatory cascade inducing the destruction of the oral structure.[1] The immunomicrobial pathogenesis of periodontitis involves chronic inflammation, which alters the balance among multiple systems, including the neural, immune, and endocrine systems.[2,3] Multiple systemic conditions, such as diabetes, cardiovascular diseases, and respiratory diseases, have been shown to have an inflammatory association with periodontitis,[4] and proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 are involved.[5] In addition, distress experienced by the patients with periodontitis showed correlation with the progression of periodontitis.[6,7] Also, as periodontitis became chronic, the occurrence of depression increased.[8] In addition, studies have demonstrated that chronic stress and depression fall into a spectrum and could induce dysregulation of the immune system, impairing the course of periodontitis.[9]

Depression, a disabling psychiatric disorder, manifests with depressed mood, vegetative symptoms, and cognitive impairment, and could impair the personal life quality and physical function.[10] Although some biomarkers were reported to be associated with depression, such as inflammatory cytokines, the serum level of neurotropic factors, and the hypothalamic–pituitary–adrenal (HPA) axis hormone, the clinical use was still unclear.[11] Moreover, serotonin is known as a neurotransmitter associated with depression, and selective

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C-CH, Y-CH, and C-HK contributed to the conception/design of the study; C-HK provided the study materials; all the authors contributed to the collection and/or assembly of data, data analysis and interpretation, article writing, and final approval of the article.

C-CH and Y-CH contributed equally to this work.

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serotonin reuptake inhibitors (SSRIs) have been used for the modulation of the serotonin pathway to treat depression.[12,13] Fluoxetine, an SSRI, has been shown to have a therapeutic effect on both depressive symptoms through modification of the serotonin pathway and the progression of periodontitis through anti-inflammatory response.[14,15] Although the association between depression and periodontitis has been noted, the causal relationship remains underinvestigated.

To test the association of periodontitis and subsequent depression, we conducted a nationwide population-based cohort study to investigate whether periodontitis increases the risk of depression.

METHODS

Data Source

This study used the Longitudinal Health Insurance Database (LHID), which is a subset of the National Health Insurance Research Database (NHIRD). The NHIRD contains all claims data from the Taiwan National Health Insurance program, a nationwide single-payer health insurance program. The NHIRD was developed and is maintained by the National Health Research Institutes. The LHID comprises data of 1 million insurants randomly selected from 1996 to 2000, and the age and sex distribution does not differ from that of the entire NHIRD. The reimbursement claims data in the LHID include beneficiary registry, disease records, and medical services, and the database is renewed every year. The original identification number in the LHID was removed, and a scrambled and anonymous serial number was provided before the release for the study to protect the privacy of patients. This study was approved to fulfill the condition for exemption by the institutional review board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

The disease history in the LHID was recorded on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The disease history data were collected from inpatient and outpatient files, and the cancer data were collected from the catastrophic illness registry.

Study Population

To investigate the association between periodontitis and depression, we conducted a retrospective population-based cohort study and constructed a periodontitis group and a non-periodontitis group. The selection of study subjects from the random sample of 1 million individuals was performed as follows (Fig. 1). The periodontitis group was selected on the basis of a patient age >20 years, a diagnosis of periodontitis (ICD-9-CM 523.4x and 523.5x), and an initial diagnosis date from 2000 to 2005. The index date of the periodontitis patients was set as the date of first diagnosis of periodontitis. The nonperiodontitis group was selected from patients without periodontitis (ICD-9-CM 523.xx) in the LHID and was frequency matched by sex and age (in 5-year bands) at a 1:4 ratio. The index date of the nonperiodontitis group was the same as that of the study patients, and a month and day were randomly assigned. Patients with a history of depression (ICD-9-CM 296.2x, 296.3x, 300.4x, and 311.xx) before the index date or within 1 month of the index date were excluded. Follow-up was terminated when a patient withdrew from the insurance program, depression diagnosis, or on December 31, 2011.

Sex and age differences had been reported in depression.[16,17] Hence, we considered sex and age as confounding factors for depression in our study. In addition, we considered depression-associated comorbidities as confounding factors. The comorbidities were defined by a diagnosis before the index date. The comorbidities included diabetes mellitus (DM, ICD-9-CM 250.xx), hyperlipidemia (ICD-9-CM 272.xx), hypertension (ICD-9-CM 401.xx–405.xx), alcohol abuse (ICD-9-CM 303.xx, 305.0x, and V113), stroke (ICD-9-CM 430.xx–438.xx), chronic obstructive pulmonary disease (ICD-9-CM 490.xx–496.xx), cancer (ICD-9-CM 140.xx–280.xx), ischemic heart

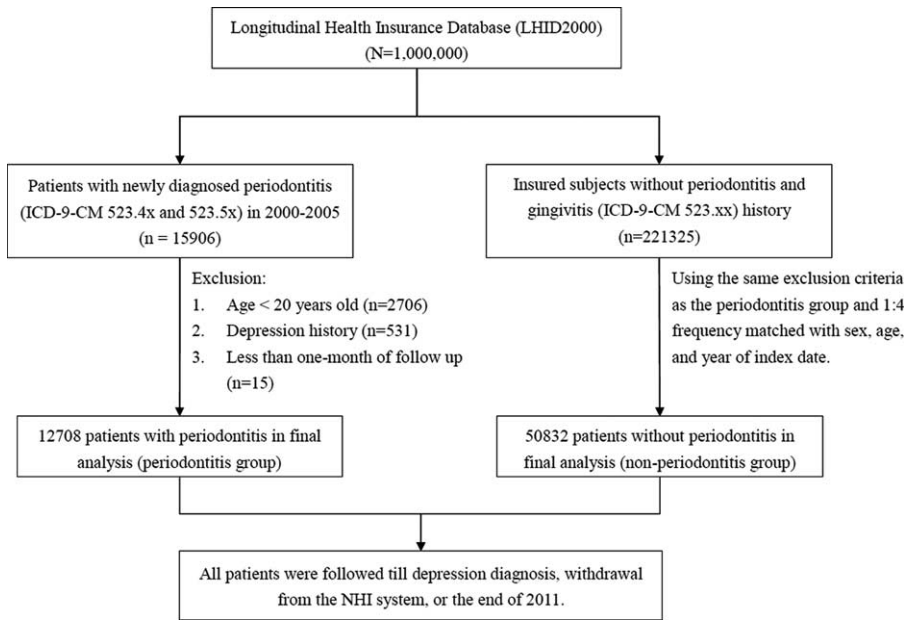

FIGURE 1. Flow chart showing selection of study subjects. ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID = Longitudinal Health Insurance Database.

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disease (ICD-9-CM 410.xx–414.xx), renal disease (ICD-9-CM 580.xx–589.xx), anxiety (ICD-9-CM 300.00), and sleep disorder (ICD-9-CM 307.4x and 780.5x).

Statistical Analyses

We described the structure of the periodontitis and nonperiodontitis groups by using mean and standard deviation for age and number and percentage for sex and comorbidities. To test the distribution difference between the groups, we applied the *t* test for age and the χ^2 test for sex and comorbidities. The incidence density rate of developing depression for the periodontitis and nonperiodontitis groups was calculated as the total number of depression events divided by the total observation time (per 1000 person-years). We used the Kaplan–Meier method to measure depression cumulative incidence curves for the 2 study groups and assessed the difference by using the log rank test. The risk of subsequent depression between the patients with and without periodontitis was presented as hazard ratios (HRs) and 95% confidence intervals (CIs), and was calculated using univariate and multivariate Cox proportional hazards models. We also estimated the risk of depression in patients with periodontitis stratified by sex, age group, and comorbidities, by using the Cox model.

Data management and statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC). The plot of cumulative curves was drawn using R software (R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at a 2-sided *P* value of <0.05.

RESULTS

We enrolled 12,708 patients with periodontitis and 50,832 subjects without periodontitis (Table 1). The 2 groups had a similar mean age (43 years) and the same sex ratio (51% men) because of the frequency matching for age and sex. The percentage of comorbidities in the periodontitis group was significantly greater than that of the nonperiodontitis group ($P < 0.001$), except for alcohol abuse, stroke, and cancer.

The incidence density rates of subsequent depression in the nonperiodontitis group was only 3.13 per 1000 person-years (Table 2), but the incidence density rates was 2-fold higher in the periodontitis group than in the nonperiodontitis group (6.18 per 1000 person-years). Figure 2 shows the cumulative curve of the depression incidence and reveals that the curve for the periodontitis patients was significantly higher than the curve for the nonperiodontitis patients (log rank test, $P < 0.001$). After adjustment of sex, age, and comorbidities, the periodontitis patients showed a 1.73-fold increased risk of depression compared with the nonperiodontitis patients (HR 1.73, 95% CI 1.58–1.89). The risk of depression was stratified by sex and age groups. Female periodontitis patients had a 1.76-fold increased risk of depression compared with female nonperiodontitis patients (HR 1.76, 95% CI 1.56–1.97). However, male periodontitis patients had only a 1.66-fold increased risk of depression compared with male nonperiodontitis patients (HR 1.66, 95% CI 1.43–1.92). In the youngest age group (20–34 years), periodontitis patients had a 1.86-fold increased risk of depression compared with nonperiodontitis patients (HR 1.86, 95% CI 1.52–2.28). Compared with nonperiodontitis patients, the risk of depression in periodontitis patients was greater by 1.73-, 1.64-, and 1.66-fold in patients aged 35 to 49 years, 50 to 64 years, and ≥65 years, respectively.

Table 3 shows the risk of depression in periodontitis patients stratified by comorbidity. We observed unanimous results that the periodontitis patients were more significantly associated with the risk of developing depression than nonperiodontitis patients when the study population was without comorbidities (all $P < 0.001$). However, in the study population with hyperlipidemia, hypertension, stroke, chronic obstructive pulmonary disease, ischemic heart disease, renal disease, anxiety, and sleep disorder, periodontitis patients still had a significantly higher risk of depression than nonperiodontitis patients.

TABLE 1. Baseline Demographic Factors and Comorbidity of Study Participants Based on Periodontitis Status

	Nonperiodontitis N = 50832		Periodontitis N = 12708		
Characteristics	**n**	**%**	**n**	**%**	***P***
Sex					0.99
Women	24672	48.54	6168	48.54	
Men	26160	51.46	6540	51.46	
Age, y					0.99
20–34	14032	27.60	3508	27.60	
35–49	20804	40.93	5201	40.93	
50–64	12004	23.62	3001	23.62	
≥65	3992	7.85	998	7.85	
Mean (SD)	43.84	(13.89)	43.91	(13.65)	0.60
Comorbidity					
DM	2664	5.24	793	6.24	<0.001
Hyperlipidemia	3458	6.80	1649	12.98	<0.001
Hypertension	7558	14.87	2212	17.41	<0.001
Alcohol abuse	53	0.10	10	0.08	0.51
Stroke	3420	6.73	904	7.11	0.13
COPD	6654	13.09	2499	19.66	<0.001
Cancer	562	1.11	147	1.16	0.66
IHD	2794	5.50	969	7.63	<0.001
Renal disease	1585	3.12	531	4.18	<0.001
Anxiety	604	1.19	304	2.39	<0.001
Sleep disorder	2107	4.15	1019	8.02	<0.001

COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, IHD = ischemic heart disease, SD = standard deviation.

DISCUSSION

Our study is the first population-based cohort study to investigate periodontitis as a risk factor for depression by using a matched cohort and long-term (10 years) follow-up period. Results from our analyses showed a higher incidence of subsequent depression among patients with periodontitis. Our data suggested that periodontitis may be an independent risk factor for subsequent depression regardless of age, sex, and the comorbidities listed in this paper, except for DM, alcohol abuse, and cancer.

We hypothesized that the possible mechanism of the increased risk of depression in periodontitis patients may be associated with neuroinflammation and disturbed serotonin synthesis. Distress was noted in patients with periodontitis, and psychological stress is associated with the outcome and progression of periodontitis.[6,18] Periodontitis is a disease showing low-grade systemic inflammation and releasing proinflammatory cytokines, including IL-1β, IL-6, and TNF-α, into

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TABLE 2. Incidence Density Rates and HRs of Depression Based on Periodontitis Status Stratified by Sex and Age

	Periodontitis						Compared to Nonperiodontitis group	
	No			Yes			HR (95% CI)	
Characteristics	Event no.	Person-years	IR	Event no.	Person-years	IR	Crude	Adjusted†
Overall	1326	423299.17	3.13	752	121744.35	6.18	1.99 (1.82–2.17)***	1.73 (1.58–1.89)***
Sex								
Women	811	207996.53	3.90	455	58831.68	7.73	2.00 (1.78–2.24)***	1.76 (1.56–1.97)***
Men	515	215302.64	2.39	297	62912.67	4.72	1.99 (1.73–2.30)***	1.66 (1.43–1.92)***
Age, y								
20–34	243	109526.10	2.22	157	34474.89	4.55	2.05 (1.68–2.51)***	1.86 (1.52–2.28)***
35–49	533	182787.00	2.92	293	50089.62	5.85	2.02 (1.75–2.32)***	1.73 (1.49–2.00)***
50–64	399	102247.24	3.9	213	27996.10	7.61	1.97 (1.67–2.32)***	1.64 (1.38–1.94)***
≥65	151	28738.83	5.25	89	9183.73	9.69	1.91 (1.47–2.49)***	1.66 (1.27–2.17)***

CI = confidence interval, HR = hazard ratio, IR = incidence density rates, per 1000 person-years.
† Mutually adjusted for sex, age, and comorbidity in Cox proportional hazards regression.
*** $P < 0.001$.

systemic circulation.[19] Furthermore, psychological stress in patients with periodontitis exhibited a disturbed HPA axis and related hypercortisolism, which affects immune dysfunction and neuroinflammation and may result in subsequent development of depression.[20,21] By contrast, proinflammatory cytokines could induce indoleamine 2,3-dioxygenase secretion reducing the availability of tryptophan and disturbing serotonin synthesis.[22] Moreover, increased tryptophan catabolites are anxiogenic and depressogenic, which is ascribed to clinical manifestations of depression.[23] To summarize, the aforementioned condition could be considered as neuroprogression[24] leading to subsequent depression. Thus, periodontitis is a risk factor for developing depression.

Although periodontitis was an independent risk factor for subsequent depression in our study, we observed that patients

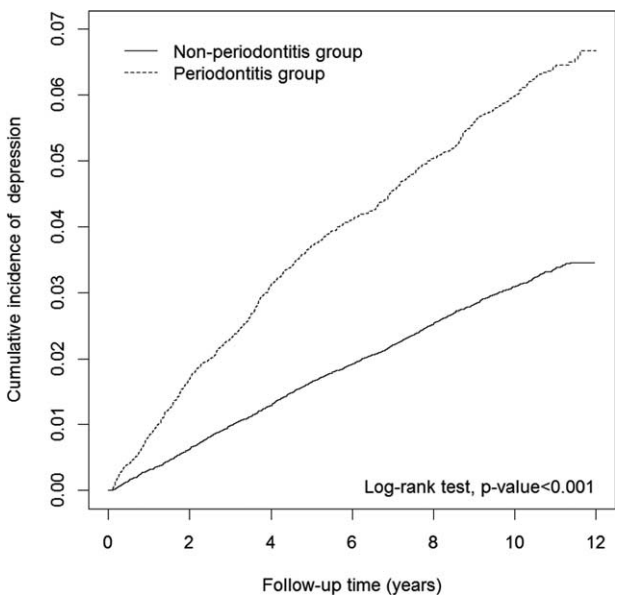

FIGURE 2. Cumulative incidence curves of depression for groups with and without periodontitis.

with periodontitis and DM, alcohol abuse, or cancer did not have a higher risk of subsequent depression higher than those without these comorbidities. Studies have shown that DM and periodontitis have a bidirectional relationship based on the interaction between the inflammation of periodontitis and impaired glycemic control.[25] The impaired glycemic control could induce insulin resistance, which was considered as a chronic and low-grade inflammatory condition.[26] At the same time, the inflammatory process induced by hyperglycemia had mutual progression in periodontitis.[27] Although mutual progression has been observed in DM and periodontitis, direct correlation was noted between better periodontal health and improved glycemic control.[28] Hence, well-controlled DM could improve periodontitis. As a result, progression to depression was delayed. In addition, studies have shown that the prevalence of periodontitis was higher in those having alcohol consumption and showed dose-dependent characteristics.[29] However, some studies have shown that moderate alcohol use could reduce the incidence of depression.[30] Thus, we hypothesized that the amount of alcohol consumption may influence pathogenesis of subsequent depression. Because of the limited sample size, we did not identify a significant association of periodontitis and depression in patients with alcohol abuse. Finally, studies had shown that cancer and periodontitis share common pathogenesis of chronic inflammation.[31] Also, periodontitis was considered as a risk factor for cancer.[32] However, in patients with cancer, depression and emotional distress were pervasive and prevalent.[33,34] Hence, it was difficult to determine whether the depression was subsequent to periodontitis or related to cancer.

To our understanding, this is the first populatoin-based study to investigate the association between periodontitis and depression. We adopted a frequency-matched cohort study design by using the patients with periodontitis and adequate adjusted for sex, age, and index year. However, some limitations should be noted before the interpretation of data. The diagnosis of periodontitis in the NHIRD was based on ICD-9-CM codes. Hence, the severity of periodontitis as a risk factor for the developing depression was not explored. However, the causal relationship was evaluated mainly on the basis of chronological order when these 2 conditions were diagnosed. Nevertheless, the possibility that depression causes

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TABLE 3. Incidence Density Rates and HRs of Depression Based on Periodontitis Status Stratified by Comorbidity

	Periodontitis						Compared to Nonperiodontitis Group	
	No			Yes			HR (95% CI)	
Comorbidity	Event no.	Person-years	IR	Event no.	Person-years	IR	Crude	Adjusted[†]
DM								
No	1201	404062.65	2.97	693	114445.45	6.06	2.05 (1.87–2.25)***	1.78 (1.62–1.96)***
Yes	125	19236.52	6.50	59	7298.91	8.08	1.30 (0.95–1.77)	1.22 (0.89–1.67)
Hyperlipidemia								
No	1131	394843.56	2.86	596	106673.37	5.59	1.96 (1.78–2.17)***	1.77 (1.60–1.95)***
Yes	195	28455.61	6.85	156	15070.98	10.35	1.55 (1.25–1.91)***	1.49 (1.21–1.85)***
Hypertension								
No	967	363411.40	2.66	559	101379.64	5.51	2.08 (1.88–2.31)***	1.79 (1.61–1.99)***
Yes	359	59887.77	5.99	193	20364.71	9.48	1.62 (1.36–1.93)***	1.50 (1.26–1.79)***
Alcohol abuse								
No	1316	422909.80	3.11	750	121666.41	6.16	2.00 (1.83–2.19)***	1.74 (1.59–1.90)***
Yes	10	389.37	25.68	2	77.94	25.66	1.07 (0.23–4.93)	0.89 (0.14–5.62)
Stroke								
No	1143	397992.94	2.87	643	113671.01	5.66	1.98 (1.80–2.18)***	1.75 (1.58–1.93)***
Yes	183	25306.23	7.23	109	8073.34	13.50	1.93 (1.52–2.44)***	1.61 (1.27–2.06)***
COPD								
No	1023	368812.41	2.77	524	98322.92	5.33	1.93 (1.74–2.15)***	1.73 (1.56–1.93)***
Yes	303	54486.76	5.56	228	23421.43	9.73	1.78 (1.50–2.12)***	1.66 (1.39–1.97)***
Cancer								
No	1309	420258.98	3.11	741	120443.19	6.15	1.99 (1.82–2.18)***	1.74 (1.59–1.91)***
Yes	17	3040.19	5.59	11	1301.16	8.45	1.61 (0.75–3.46)	1.26 (0.57–2.78)
IHD								
No	1165	401790.64	2.90	635	113007.85	5.62	1.95 (1.77–2.15)***	1.72 (1.56–1.90)***
Yes	161	21508.52	7.49	117	8736.50	13.39	1.83 (1.44–2.32)***	1.70 (1.33–2.16)***
Renal disease								
No	1238	411874.73	3.01	692	116902.08	5.92	1.98 (1.81–2.18)***	1.74 (1.58–1.91)***
Yes	88	11424.44	7.70	60	4842.28	12.39	1.67 (1.20–2.32)**	1.58 (1.13–2.22)**
Anxiety								
No	1236	418885.62	2.95	681	119430.05	5.70	1.94 (1.77–2.13)***	1.75 (1.59–1.92)***
Yes	90	4413.55	20.39	71	2314.30	30.68	1.53 (1.21–2.09)**	1.41 (1.03–1.94)*
Sleep disorder								
No	1086	407480.18	2.67	577	113460.70	5.09	1.91 (1.73–2.12)***	1.82 (1.64–2.02)***
Yes	240	15818.98	15.17	175	8283.66	21.13	1.42 (1.17–1.73)***	1.36 (1.12–1.65)**

CI = confidence interval, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HR = hazard ratio, IHD = ischemic heart disease, IR = incidence density rates, per 1000 person-years.

[†] Mutually adjusted for sex, age, and comorbidity in Cox proportional hazards regression.

** $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

periodontitis cannot be discounted. Numerous demongraphic variables, such as socioeconomic status and family history, were available and provided useful data regarding factors associated with periodontitis and depression. Finally, the result we noted was in this studied population, we could not make sure the result was suitable for other populations. However, our study was composed of adequate amounts in periodontitis and control group, as well as in comorbidities. We thought this study design could have some strength in the application of our finding.

The findings suggest that periodontitis increases the risk of subsequent depression. Even though periodontitis patients with DM, alcohol abuse, and cancer did not have higher risk for subsequent depression, proper interventions toward glycemic control, alcohol amount control, and psychological approach toward cancer may be beneficial for the prevention of further progression. Additional prospective clinical studies on the relationship between periodontitis and depression are warranted.

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