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Systematic Review

Is There an Association Between Parkinson's Disease and Periodontitis? A Systematic Review and Meta-Analysis

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Abstract.
Background: Multiple observational studies have yielded controversial results regarding the association between Parkinson's disease (PD) and periodontitis.
Objective: This systematic review and meta-analysis was conducted to ascertain their bidirectional relationship.
Methods: A literature search for relevant studies was performed in PubMed, EMBASE, the Cochrane Library, and Web of Science databases from inception to December 19, 2022. Effect sizes (ES) with 95% confidence intervals were pooled under the random-effects model. Then, leave-one-out sensitivity analysis and contour-enhanced funnel plot were applied to assess the stability of the results.
Results: A total of 34 studies and 24 studies were included for systematic review and quantitative meta-analysis, respectively. Pooled ES indicated that periodontitis was not significantly associated with PD risk (HR = 1.13, 95% CI 0.88–1.45, $n = 3$; OR = 1.94, 95% CI 0.55–6.90, $n = 7$), while the Mendelian randomization study revealed no association between PD and periodontitis risk (coefficient [B] = –0.0001, standard error = 0.0001, $p = 0.19$). Furthermore, PD patients exhibited higher levels of periodontal pocket depth (SMD = 1.10, 95% CI 0.53–1.67), clinical attachment level (SMD = 1.40, 95% CI 0.55–2.26), plaque index (SMD = 0.81, 95% CI 0.22–1.39), and Oral Health Impact Profile-14 score (SMD = 0.91, 95% CI 0.33–1.49) compared to healthy controls.
Conclusions: Our meta-analysis identified no bidirectional association between PD risk and periodontitis risk, though the prevalence of periodontitis and poorer oral status was higher in PD patients.

Keywords: Parkinson's disease, periodontitis, systematic review, meta-analysis

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder manifested by bradykinesia, resting tremor, rigidity, and postural instability, affecting millions of elderly adults globally. Between 1990 and 2016, the age-standardized prevalence, disability-adjusted life-years rates and mortality of PD have skyrocketed in almost every region worldwide, increasing the heavy global financial burden [1, 2]. Despite the specific pathogenesis remaining elusive, inflammatory and immunological factors have been suggested to participate in its underlying mechanisms [3, 4].

Periodontitis is a chronic inflammatory disease of the oral cavity that is triggered by the formation of dental plaque biofilm [5]. Advanced periodontitis is a leading cause of loss of teeth and supporting structures, affecting approximately 10–15% of the global population [6]. According to the data from the 2009–2012 National Health and Nutrition Examination Survey, its overall prevalence among Americans over 30 years was estimated to be as high as 46% [7, 8]. It has been observed that the prevalence of total periodontitis rises from the 30–34 age group to the aged 65+ age group [7]. The progression of age, coupled with reduced dexterity, results in the accumulation of dental plaque, leading to more frequent and severe periodontal inflammation [9], which may elevate the longitudinal risk of periodontitis. Moreover, periodontitis has been reported to be correlated with several systemic diseases, such as diabetes mellitus, cardiovascular diseases [10], Alzheimer's disease (AD) [11], and cancer [12].

Various articles have reported the high prevalence of periodontitis and poor oral health in individuals with PD. For instance, a nested case-control study reported that the prevalence of periodontal diseases attained 48.73% in a cohort of 4765 PD patients [13]. In a cross-sectional case-control study, periodontitis was detected in 98 out of 104 PD patients [14]. Several factors could potentially explain the link between the prevalence or risk of periodontitis and PD. As is well documented, polypharmacy, cognitive impairment, motor dysfunction, and the subsequent deducing dental care elevate the risk of dental caries and periodontal disorders [15]. Sialorrhea, a commonly observed symptom of PD, is also hypothesized to promote periodontitis and other oral diseases, attributable to hypersalivation altering the composition of oral microbiota (like *K. oralis*) in PD cases and facilitating local inflammation in the oral cavity [16]. Additionally, the prevalence of sialorrhea has been reported to increase with age and disease duration in PD patients [17], insinuating that it may mediate the impact of age and PD duration on periodontitis risk. Similarly, gender is also considered a key factor in the development of sialorrhea, thereby influencing periodontitis risk, which can be supported by the finding that males with PD were twice more likely to develop sialorrhea compared to females [18]. Hyposmia, characterized by a reduced sense of smell in PD patients [19], which deteriorates significantly with age [20] and is often accompanied by taste dysfunction, contributes to prolonged mealtimes and inadequate chewing [15], thus the increasing risk of periodontal diseases. Moreover, since female gender might be a contributing factor for dysphagia [15, 21], another plausible explanation for the effect of gender on periodontitis risk is that dysphagia may result in acid reflux, which could trigger perimylolysis tooth erosion and potentially increase the periodontitis risk [22]. In addition, Fukayo et al. [23] reported that female PD patients brushed their teeth more frequently than male patients and tended to have a lower decayed, missing and filled teeth (DMFT) index than the male group, indicating that the alterations in dental care behavior may also be a reason for gender influencing periodontitis risk.

Despite numerous articles investigating the association between PD and periodontitis, their findings have been contradictory. While certain large-sample observational studies have noted that periodontal inflammatory disease is correlated with an elevated risk of developing PD [24, 25], other studies have yielded conflicting results. For example, a Mendelian randomization (MR) study revealed no convincing genetic association between the two diseases [26]. Meanwhile, the bidirectional relationship between PD and periodontitis has not been systematically assessed.

Therefore, we sought to systematically review studies focusing on PD and periodontitis and perform a meta-analysis to comprehensively investigate the bidirectional association between the two diseases and summarize the oral status of PD patients.

METHODS

Literature search

A systematic literature search of PubMed, EMBASE, the Cochrane Library, and Web of Science was performed for studies published until December

19, 2022 using the following keywords: Parkinson's disease, parkinsonism, periodontitis, and periodontal disease. The detailed search strategies for PubMed search are provided in the Supplementary Material.

Eligibility criteria

Studies were considered eligible for inclusion if they investigated the relationship between PD and periodontitis or the oral status of patients. Besides, we also reviewed the reference lists of the related articles and screened for potentially relevant conference abstracts. The exclusion criteria were as follows: 1) reviews, case reports, letters, comments, or other types of articles; 2) studies of animal or cell models; 3) studies without quantitative data. Regarding duplicate publications reporting the same cohort, the study with the largest sample size was included.

Data extraction

Two reviewers (Y.Q.C. and K.L) independently extracted the following data from included studies: 1) study characteristics (the first author, publication year, study design); 2) population parameters (sample size, country, age, gender); 3) assessment of PD and periodontitis or oral status (scale of diagnosis, disease duration, clinical parameter values); 4) hazard ratios (HR), odds ratios (OR), standardized mean differences (SMD), and their corresponding 95% confidence intervals (CI). If both unadjusted and adjusted effect sizes were available, data on the latter were collected.

Any discrepancies were resolved by arbitration with a third reviewer (D.H.Y.).

Quality assessment

The methodological quality of all eligible studies in the systematic review was independently assessed by Y.Q.C. and K.L. The Newcastle Ottawa Scale (NOS), consisting of three parameters of quality: selection, comparability and exposure or outcome assessment, was used to assess the quality of the cohort studies and case-control studies. Meanwhile, the quality of cross-sectional studies was assessed using the Joanna Briggs Institute (JBI) checklist. The quality assessment of the MR study was based on the STROBE-MR Checklist [27].

Outcomes

The co-primary outcomes of our study were the risk of PD in patients with periodontitis and the risk of periodontitis in PD patients. Secondary outcomes were periodontal clinical parameters values including periodontal pocket depth (PPD), clinical attachment level (CAL), plaque index (PI), and the percentage of bleeding on probing sites (BoP %), all of which examined the prevalence of periodontitis in PD cases. Besides, based on the enrolled studies, we also pooled other oral hygiene parameters to assess the oral status and oral health of PD patients.

Statistical analysis

We performed a quantitative meta-analysis of the studies included in the systematic review to merge results for the outcomes reported with the same metrics in more than two studies. All statistical analyses were conducted via R software (version 4.1.0). Effect sizes (ES) were calculated as hazard ratios (HR), odds ratios (OR), and standardized mean differences (SMD), along with their corresponding 95% confidence intervals (CIs). Heterogeneity was determined with the Cochran Q statistic and the I^2 statistic, with the significance level set at a 2-tailed value of $p < 0.05$ and I^2 >50% indicating significant heterogeneity. Given the presence of heterogeneity, the study estimates were combined under the random-effects model. Leave-one-out sensitivity analysis was carried out to assess the stability of the combined results. Contour-enhanced funnel plot [28] and the Duvall and Tweedle trim-and-fill approach [8] were used to evaluate potential publication bias.

RESULTS

Literature search

The literature search yielded 2,708 studies, and three additional publications were identified by reviewing reference lists. After excluding duplicates, a total of 1,985 unique titles and abstracts were screened. Subsequently, the full text of 52 potentially eligible articles was reviewed. Following a thorough assessment, 18 studies were excluded: four studies using the same data from another publication, four studies reporting dementia or cognitive impairment as the outcome, and ten conference abstracts did not report quantitative data. Therefore, 34 studies were included in the systematic review. Concerning studies

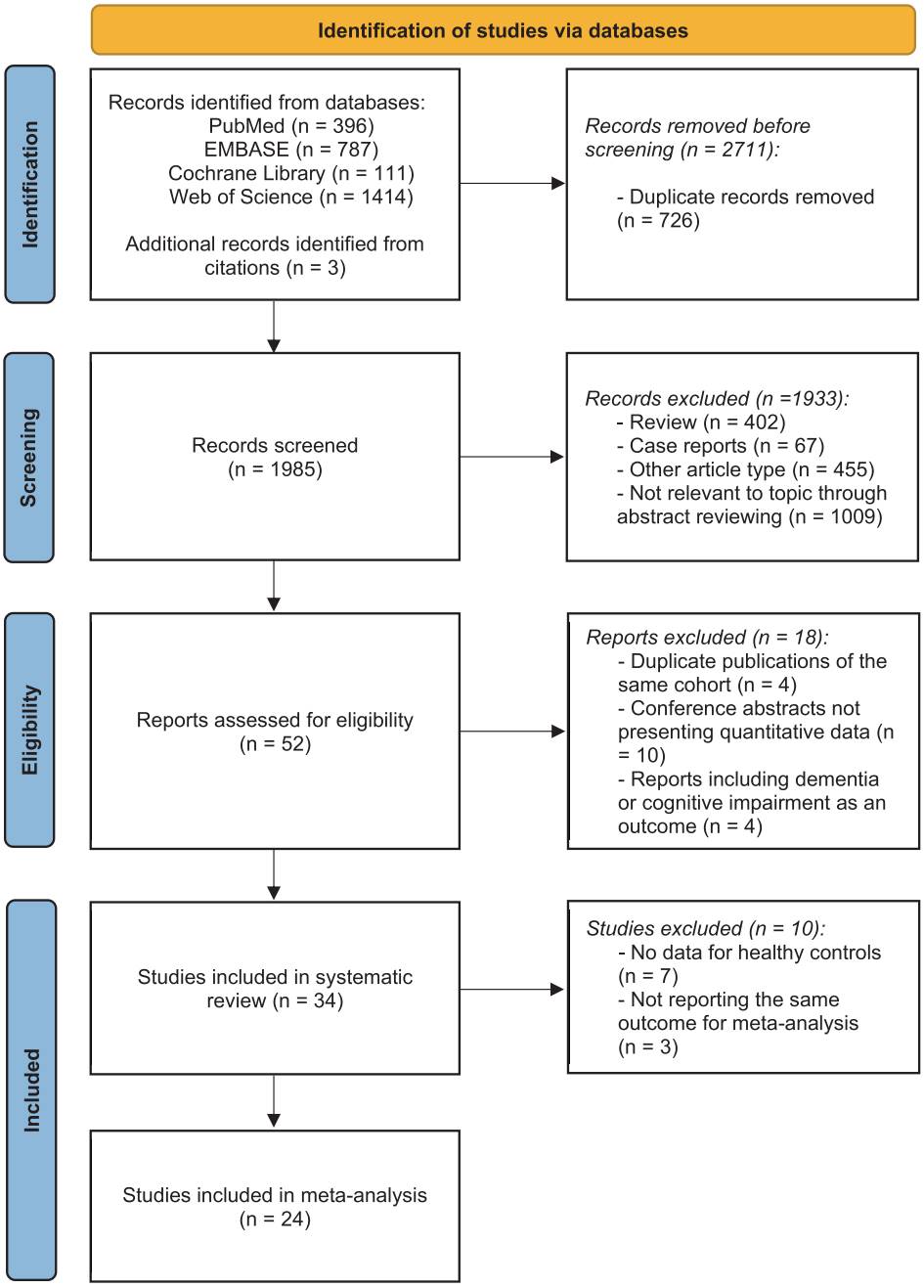


Fig. 1. PRISMA flow diagram delineating study identification.

with data on control groups, a quantitative meta-analysis was performed on 24 studies (involving 7,720,793 participants) reporting the same outcomes. The process of study identification is illustrated in the PRISMA flow chart [29] in Fig. 1.

Study characteristics and quality assessment

The characteristics of 34 studies included in the systematic review are summarized in Table 1. The included studies comprised six cohort studies, sixteen

Table 1
Characteristics of included studies in the systematic review

Study	Year	Country	Study Design	Groups	Sample Size	Age (Mean ± SD)	Sex (M/F)	Assessment of Parkinson's Disease	Assessment of Periodontitis or Oral Status
Botelho et al. [34]	2020	Portugal	Cohort	PD with Periodontitis PD without Periodontitis	20 17	61.6 ± 13.8 53.1 ± 14.6	10/10 5/12	PD diagnosis: cases reporting the use of Benztropine, Carbidopa, Levodopa and other antiparkinsonian medication	1. Periodontitis diagnosis: 2 or more sites with CAL ≥3 mm and a PPD ≥4 mm or one site with PPD ≥5 mm; 2. Number of missing teeth
Jeong et al. [25]	2021	Korea	Cohort	Periodontitis Healthy Control	903,063 5,922,621	55.47 ± 9.97 54.21 ± 10.54	485,941/ 417,122 2,941,386/ 2,981,235	PD diagnosis: ICD-10 code for PD (G20)	Periodontitis diagnosis: ICD-10 code for Periodontitis
Ledwon et al. [48]	2020	Austria	Cohort	PD with periodontal care PD Control	61 32	70.8 ± 8.4 69.8 ± 8.0	34/27 21/11	1. PD diagnosis: patients receiving antiparkinsonian drug 2. UPDRS-III	1. Number of teeth 2. PI 3. BoP% 4. PDD 5. Tooth mobility
Liu et al. [49]	2013	Taiwan of China	Cohort	Periodontitis Healthy Control	53,351 266,755	NA	NA	1. PD diagnosis: ICD-9-CM code 332 2. HR of risk of PD	Periodontitis diagnosis: ICD-9-CM code 523.4
Liu et al. [31]	2017	Sweden	Cohort	PD Non-PD	307 19,868	55.5 ± 13.9 43.4 ± 18.1	175/132 9,781/ 10,087	PD diagnosis: (ICD-7 code: 350; ICD-8 code: 342.00; ICD-9 code: 332.0; ICD-10 code: G20)	1. Number of existing teeth 2. Dental plaque 3.The presence of oral mucosal lesions
Woo et al. [50]	2020	Korea	Cohort	Periodontitis Healthy Control	30,580 122,585	67.8 ± 9.3 69.1 ± 9.3	98,434/ 54,731	1. PD diagnosis: (ICD-10 G20; G21-26) 2. HR of risk of PD	1. Periodontitis diagnosis: (ICD-10 K052-056) 2. Number of tooth loss
Botelho et al. [26]	2021	Portugal	Mendelian Randomization	Periodontitis Healthy Control PD Healthy Control	1,817 2,215 20,184 397,324	NA	NA	OR of risk of PD	OR of risk of periodontitis
Auerbacher et al. [51]	2022	Germany	Case control	PD Healthy Control	24 30	73 ± 9 62.5 ± 12	14/10 11/19	NA	1. DMFT 2. Number of missed teeth 3. Number of decayed teeth 4. Presence of edentulism
Bakke et al. [52]	2011	Denmark	Case control	PD Healthy Control	15 15	68.47 ± 6.26 NA	6/9 6/9	1. Hoehn & Yahr Stage 2. UPDRS-III 3. PD duration	1. OHIP 2. OHI 3.Nordic Orofacial Test-Screening

(*Continued*)

Table 1
(*Continued*)

Study	Year	Country	Study Design	Groups	Sample Size	Age (Mean ± SD)	Sex (M/F)	Assessment of Parkinson's Disease	Assessment of Periodontitis or Oral Status
Balash et al. [53]	2014	Israel	Case control	PD Healthy Control	96 93	68.1 ± 7.1 66.6 ± 8.4	NA	NA	OR of risk of periodontitis
Barbe et al. [54]	2017	Germany	Case control	PD Healthy Control	30 30	69.3 ± 8.0 69.3 ± 7.9	17/13 17/13	1. MDS-UPDRS-II 2. PD duration	1. Periodontitis diagnosis: Community Periodontal Index of Treatment Needs 2. OHIP-14 3. PI 4.Xerostomia
Cicciù et al. [55]	2012	Italy	Case control	PD Healthy Control	45 45	NA	17/28 10/35	Hoehn & Yahr Stage	1. PDD 2. Number of missed teeth 3. Number of decayed teeth
Einarsdóttir et al. [56]	2009	Iceland	Case control	PD Healthy Control	67 55	(<60) $n = 40$ (60- 0) $n = 42$ (>70) $n = 40$	39/28 21/34	NA	1. Periodontitis diagnosis: PPD ≥4 mm 2. OR of risk of periodontitis 3. Presence of gingivitis 4. DMFT 5. Number of missed teeth
Fleury et al. [16]	2021	Switzerland	Case control	PD Healthy Control	20 20	63.34 ± 5.51 63.90 ± 7.26	9/11 9/11	1. Hoehn & Yahr Stage 2. PD duration	1. PPD 2. PI 3. BoP%
Fukayo et al. [23]	2003	Japan	Case control	PD Healthy Control	31 104	(60–69) $n = 12$ (≥70) $n = 19$ (60–69) $n = 76$ (≥70) $n = 28$	17/14 61/43	Hoehn & Yahr Stage	DMFT
Garcia-de-la-Fuente et al. [14]	2022	Spain	Case control	PD Healthy Control	104 106	66.2 ± 9.3 59.2 ± 14.1	66/38 37/69	NA	1. Presence of periodontitis 2. PI 3.CAL 4. DMFT 5. Community Periodontal Index of Treatment Needs 6. Number of decayed teeth 7. Number of missed teeth 8. Presence of xerostomia

Hanaoka et al. [57]	2009	Japan	Case control	PD Controls with mild neurological disorders	89 68	72.1 ± 5.0 69.0 ± 5.8	38/51 26/42	Hoehn & Yahr Stage	Periodontitis diagnosis: PPD $\geq$4 mm
Kennedy et al. [43]	1994	USA	Case control	PD craving sweets PD not craving sweets Healthy Control	14 14 14	65.7 ± 6.2 67.6 ± 9.2 64.1 ± 6.8	9/5 7/7 6/8	1. Hoehn & Yahr Stage 2. PD duration	1. Presence of mucositis 2. Presence of gingivitis 3. DMFT
Müller et al. [42]	2011	Germany	Case control	PD Healthy Control	101 75	66.2 ± 10.5 71.0 ± 11.5	55/46 35/40	1. Hoehn & Yahr Stage 2. UPDRS-I 3. UPDRS-II 4. UPDRS-III 5. UPDRS-IV	1. CAL 2. PDD 3. PI 4. OHI 5. Number of missed teeth
Nakayama et al. [58]	2004	Japan	Case control	PD Healthy Control	104 191	(60–69) $n = 38$ ($\geq$70) $n = 66$ (60–69) $n = 121$ ($\geq$70) $n = 70$	44/60 78/113	Hoehn & Yahr Stage	1. Tooth movement 2. Presence of edentulism
Persson et al. [59]	1992	Sweden	Case control	PD Historical Control in 1911-1913	30 585	73.0 ± 7.3 NA	17/13 279/302	PD duration	1. BoP% 2. Mean number of teeth
Schwarz et al. [60]	2006	Germany	Case control	PD Healthy Control	70 85	64.5 ± 6.8 62.0 ± 6.3	39/31 41/44	NA	CPITN (Community Periodontal Index for Treatment Needs)
van Stiphout et al. [61]	2018	Netherlands	Case control	PD Healthy Control	74 74	70.2 ± 8.8 67.9 ± 10.1	48/26 39/35	1. Hoehn & Yahr Stage 2. PD duration	1. Tooth movement 2. Presence of edentulism 3. Much dental plaque
Barbe et al. [62]	2017	Germany	Cross-sectional	PD	100	71.0 ± 8.7	72/28	1. MDS-UPDRS-II 2. PD duration	OHIP-14
Gardner et al. [63]	2013	USA	Cross-sectional	PD Healthy Control	620 393	72.2 ± 9.2 NA	373/247 NA	UPDRS-II	1. Prevalence of xerostomia 2. Rating of dental health
Gopalakrishnan et al. [64]	2021	India	Cross-sectional	PD	50	(30–49) $n = 12$ (50–59) $n = 13$ ($\geq$60) $n = 25$	41/9	NA	1. Prevalence of periodontitis and gingivitis 2. Prevalence of xerostomia

(*Continued*)

Table 1
(*Continued*)

Study	Year	Country	Study Design	Groups	Sample Size	Age (Mean ± SD)	Sex (M/F)	Assessment of Parkinson's Disease	Assessment of Periodontitis or Oral Status
John et al. [30]	2021	India	Cross-sectional	PD Healthy Control	32 42	58.41 ± 10.62 54.36 ± 9.72	18/14 22/20	1. Hoehn & Yahr Stage 2. PD duration	1. Periodontitis diagnosis: CAL score ≥3 mm 2. PDD 3. OHI 4. DMFT
Lyra et al. [65]	2020	Portugal	Cross-sectional	PD	28	72.3 ± 8.1	23/5	1. Hoehn & Yahr Stage 2. MDS-UPDRS	1. Periodontitis diagnosis: interdental CAL ≥2 non-adjacent teeth, or Buccal or Oral CAL ≥3 mm with PDD >3 mm is detectable at ≥2 teeth 2. OHIP-14 3. PI
Lyra et al. [35]	2022	Portugal	Cross-sectional	PD with Periodontitis PD without Periodontitis	23 28	60.04 ± 14.39 65.36 ± 14.79	13/10 14/14	PD diagnosis: cases reporting the use of specific PD medications	1. Periodontitis diagnosis: positive self-report on one of several oral health-related questions 2. Number of missed teeth
Pradeep et al. [66]	2015	India	Cross-sectional	PD Healthy Control	45 46	64.5 ± 9.1 63.9 ± 13.1	30/15 28/18	Hoehn & Yahr Stage	1. BoP% 2. CAL 3. PDD
Purisinsith et al. [67]	2021	Thailand	Cross-sectional	PD	274	NA	144/133	NA	OHIP-14
Ribeiro et al. [68]	2016	Brazil	Cross-sectional	PD Healthy Control	17 20	69.41 ± 4.65 72.00 ± 5.69	9/8 10/10	1. PD diagnosis: patients receiving levodopa treatment 2. PD duration	1. DMFT 2. Visual plaque index 3. Number of decayed teeth
Silva et al. [69]	2015	Brazil	Cross-sectional	PD	59	65.4 ± 8.7	30/29	1. Hoehn & Yahr Stage 2. PD duration	OHIP-14
Verhoeff et al. [70]	2022	Netherlands	Cross-sectional	PD Healthy Control	341 411	65.5 ± 8.4 62.6 ± 5.3	60/63 (There were missing data) 209/202	1. MDS-UPDRS-II 2. PD duration	OHIP-14

PD, Parkinson's disease; ES, effect size; HR, hazard ratio; OR, odds ratio; PDD, periodontal pocket depth; CAL, clinical attachment level; PI, plaque index; BoP%, the percentage of bleeding on probing sites; OHI, oral hygiene index; OHIP-14, Oral Health Impact Profile-14; DMFT, decayed, missing, and filled teeth index; UPDRS, United Parkinson's Disease Rating Scale; MDS-UPDRS, Movement Disorder Society-sponsored United Parkinson's Disease Rating Scale.

case-control studies, eleven cross-sectional studies, and an MR study. The majority of the studies assessed the severity of PD using Hoehn and Yahr (H&Y) stage, United Parkinson's Disease Rating Scale (UPDRS), or Movement Disorder Society-sponsored United Parkinson's Disease Rating Scale (MDS-UPDRS). However, the diagnostic criteria and clinical periodontal examination protocols for periodontitis and oral status varied and were inconsistent among the studies. Due to a lack of data on healthy controls and the heterogeneity of outcomes, three cohort studies, fifteen case-control studies, five cross-sectional studies, and the MR study were eventually included in the meta-analysis.

Table 2 presents the detailed quality score of each included study. All six cohort studies and the majority of the case-control studies (13 out of 16 studies) were deemed to be of high methodological quality (low risk of bias), with a NOS score of $\geq$7 (Table 2A, B). Likewise, the ten cross-sectional studies were also of high quality, according to the JBI checklists (Table 2C). Additionally, the detailed checklist items of the Mendelian randomization study according to the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) Checklist are listed in Table 2D.

Association between periodontitis and risk of PD

The overall HR for the 3 cohort studies (involving 7,298,955 participants) was 1.13 (95% CI 0.88–1.45, $p = 0.3436$, $I^2 = 96\%$; Fig. 2A), demonstrating substantial evidence that periodontitis is not associated with the incidence of PD. In line the results of cohort studies, the combined OR, including 4,844 participants from six retrospective studies and one Mendelian randomization study [26] also showed an overall null effect (OR 1.94, 95%

Table 2
Methodological quality assessment of included studies

A. Quality assessment of cohort studies based on the Newcastle–Ottawa Scale (NOS).

Study	Year	Overall score	Selection (4★)				Comparability (2★)	Outcome (3★)		
			Representativeness of the exposed cohort	Selection of the control cohort	Ascertainment of exposure	Outcome of interest not present at start	Comparability of cohorts	Assessment of outcome	Sufficient follow-up	Adequacy of follow up cohorts
Botelho et al. [34]	2020	7	★	★	★	★	★	★	★	
Jeong et al. [25]	2021	9	★	★	★	★	★★	★	★	★
Ledwon et al. [48]	2020	7		★	★	★	★★	★	★	
Liu et al. [49]	2013	9	★	★	★	★	★★	★	★	★
Liu et al. [31]	2017	8		★	★	★	★★	★	★	★
Woo et al. [50]	2020	9	★	★	★	★	★★	★	★	★

B. Quality assessment of case-control studies based on the Newcastle–Ottawa Scale (NOS).

Study	Year	Overall score	Selection (4★)				Comparability (2★)	Exposure (3★)		
			Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate
Auerbacher et al. [51]	2022	7		★	★	★	★★	★	★	
Bakke et al. [52]	2011	7	★	★	★	★	★★		★	
Balash et al. [53]	2014	7		★	★	★	★★	★	★	
Barbe et al. [54]	2017	9	★	★	★	★	★★	★	★	★
Cicciù et al. [55]	2012	7	★	★	★	★	★★		★	
Einarsdóttir et al. [56]	2009	7		★	★	★	★★	★	★	
Fleury et al. [16]	2021	8	★	★	★	★	★★	★	★	
Fukayo et al. [23]	2003	6	★	★	★	★	★		★	
Garcia-de-la-Fuente et al. [14]	2022	7		★	★	★	★★	★	★	
Hanaoka et al. [57]	2009	7	★	★		★	★★	★	★	
Kennedy et al. [43]	1994	8	★	★	★	★	★★	★	★	
Müller et al. [42]	2011	8	★	★	★	★	★★	★	★	
Nakayama et al. [58]	2004	7	★	★	★	★	★★		★	
Persson et al. [59]	1992	6	★	★		★	★		★	★
Schwarz et al. [60]	2006	6		★	★	★	★★		★	
van Stiphout et al. [61]	2018	8	★	★	★	★	★★	★	★	

C. Quality assessment of cross-sectional studies based on Joanna Briggs Institute (JBI) checklists.

Study	Year	Overall score	Q1*	Q2*	Q3*	Q4*	Q5*	Q6*	Q7*	Q8*	Q9*
Barbe et al. [62]	2017	8	Y	Y	Y	Y	Y	Y	Y	Y	U
Gardner et al. [63]	2013	6	Y	U	Y	N	Y	Y	Y	Y	U
Gopalakrishnan et al. [64]	2021	5	Y	U	Y	Y	Y	U	Y	N	U
John et al. [30]	2021	8	Y	Y	Y	Y	Y	Y	Y	Y	U
Lyra et al. [65]	2020	8	Y	Y	N	Y	Y	Y	Y	Y	Y
Lyra et al. [35]	2022	7	Y	Y	N	Y	Y	Y	N	Y	Y
Pradeep et al. [66]	2015	9	Y	Y	Y	Y	Y	Y	Y	Y	Y
Purisinsith et al. [67]	2021	6	Y	Y	Y	N	Y	U	Y	Y	U
Ribeiro et al. [68]	2016	7	Y	Y	N	Y	Y	Y	Y	Y	U
Silva et al. [69]	2015	8	Y	Y	Y	Y	Y	Y	Y	N	Y
Verhoeff et al. [70]	2022	9	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y, Yes; N, No; U, Unclear. *Q1: Was the sample frame appropriate to address the target population? *Q2: Were study participants sampled in an appropriate way? *Q3: Was the sample size adequate? *Q4: Were the study subjects and the setting described in detail? *Q5: Was the data analysis conducted with sufficient coverage of the identified sample? *Q6: Were valid methods used for the identification of the condition? *Q7: Was the condition measured in a standard, reliable way for all participants? *Q8: Was there appropriate statistical analysis? *Q9: Was the response rate adequate, and if not, was the low response rate managed appropriately?

D. Quality assessment of the mendelian randomization study based on the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) Checklist.

Study	Year	Tool for quality assessment	Checklist item	Result of quality assessment
Botelho et al. [26]	2021	STROBE-MR Checklist	Title and Abstract	1. Have indicated MR as the design.
			1. Title and Abstract	2. Explain plausible potential causal relationship between exposure (PD and periodontitis) and outcome (risk of periodontitis and risk of PD).
			Introduction	3. Have stated prespecified causal hypotheses.
			2. Background	4. Describe eligibility criteria and the sources of participants, selection of genetic variants.
			3. Objectives	5. Have stated 3 main IV assumptions for main analysis.
			Methods	6. Utilize inverse-variance weighted method, weighted median and MR-Egger as MR effect estimation methods.
			4. Study design and data sources	7. Compute F-statistic and use MR-Egger method to assess the assumption.
			5. Assumptions	8. Use the leave-one-out analysis.
			6. Statistical methods	9. Use R (v 3.6.1) through MRPRESSO and TwoSampleMR packages.
			7. Assessment of assumptions	10. Calculate Pseudo R^2 and F-statistic to justify of the similarity of the genetic variant–exposure associations.
			8. Sensitivity analyses and additional analyses	11. Report MR estimates of the relationship between PD and periodontitis by odds ratio and visualize the results through forest plot.
			9. Software and preregistration	12. Calculate I^2 and Q statistic to assess the heterogeneity across genetic variants.
			Results	13. Present a bidirectional MR and perform leave-one-out analyses.
			10. Descriptive data	14. Have summarized key results.
			11. Main results	15. Have discussed limitations of the study and imprecision of assumption.
			12. Assessment of assumptions	16. Have provided a cautious overall interpretation of results.
			13. Sensitivity analyses and additional analyses	17. None.
			Discussion	
			14. Key results	
			15. Limitations	
			16. Interpretation	
			17. Generalizability	

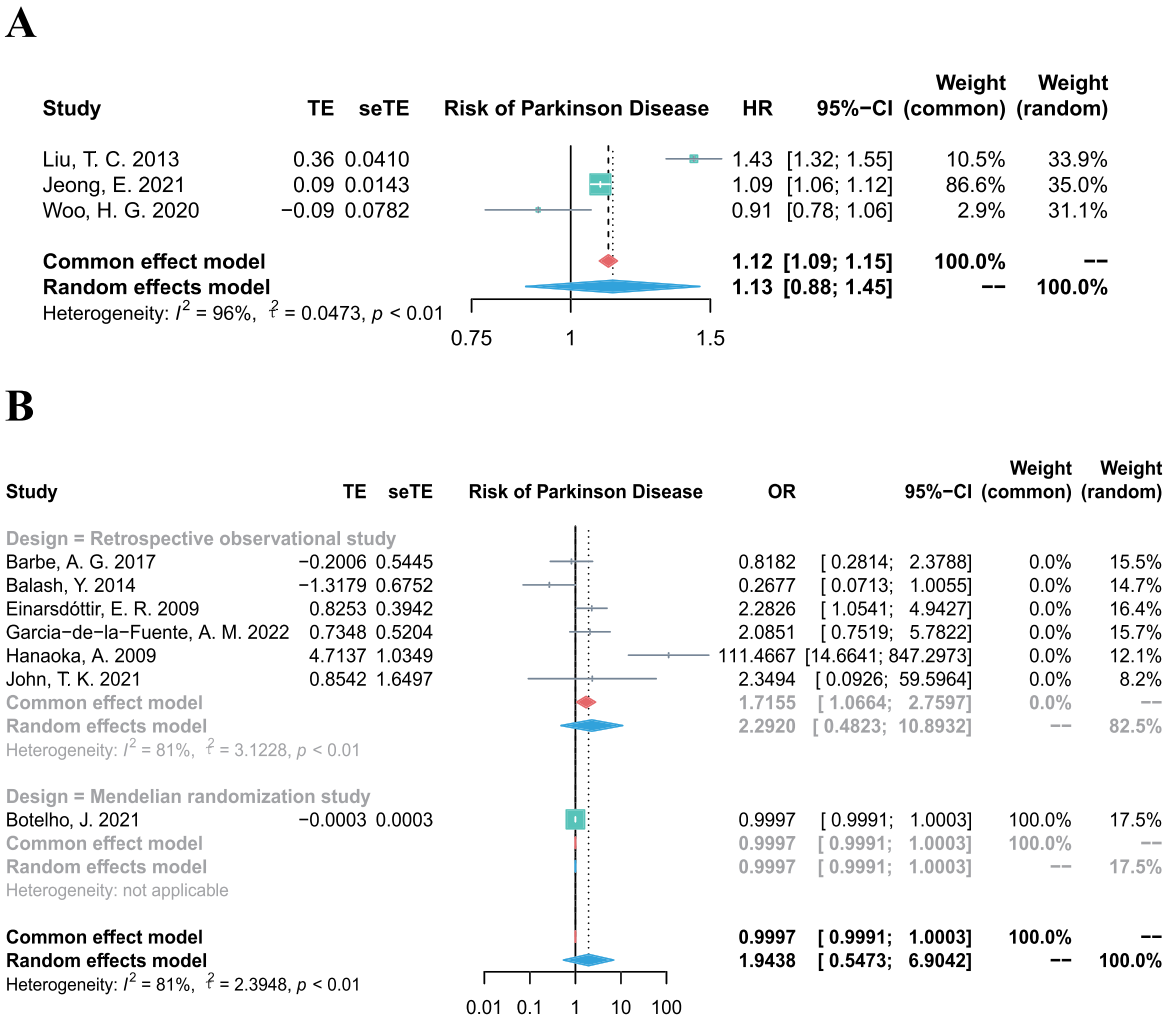


Fig. 2. Forest plots of meta-analysis for the association between periodontitis and risk of Parkinson's disease, combining the HR of three cohort studies (A), and combining the OR of six retrospective studies (B).

CI 0.55–6.90, $p = 0.3040$, $I^2 = 81\%$; Fig. 2B) for the association between periodontitis and the risk of PD.

Association between PD and risk of periodontitis

The bidirectional Mendelian randomization study was the only study that investigated the relationship between PD and the risk of periodontitis, and found no significant genetic association between them when analyzing the data from genome-wide association studies involving 417,508 participants (coefficient [B] = –0.0001, standard error [SE] = 0.0001, $p = 0.19$) [26].

Association between PD and prevalence of periodontitis

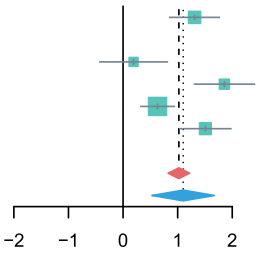
Owing to the diverse and heterogeneous outcomes in the included studies, periodontal clinical parameter values were integrated to evaluate the prevalence of periodontitis and the periodontal status of PD patients. The pooled PPD in PD patients was significantly higher than that in control groups (SMD = 1.10, 95% CI 0.53–1.67, $p = 0.0002$, $I^2 = 85\%$; Fig. 3A). Similarly, the CAL of PD patients was significantly higher (SMD = 1.40, 95% CI 0.55–2.26, $p = 0.0013$, $I^2 = 92\%$; Fig. 3B) compared to control groups, and the PI of PD patients was also significantly higher (SMD = 0.81, 95% CI

A

Study	PD Total	PD Mean	PD SD	Control Total	Control Mean	Control SD	SMD	95%−CI	Weight (common)	Weight (random)
Cicciù, M. 2012	45	5.56	0.72	45	4.18	1.29	1.31	[0.85; 1.77]	18.5%	20.3%
Einarsdóttir, E. R. 2009	67	4.15	.	55	3.81	.			0.0%	0.0%
Fleury, V. 2021	20	3.00	0.16	20	2.96	0.24	0.19	[−0.43; 0.81]	10.0%	18.3%
John, T. K. 2021	32	2.59	0.68	42	1.61	0.36	1.86	[1.30; 2.41]	12.6%	19.2%
Müller, T. 2011	101	19.70	36.32	75	2.23	1.12	0.63	[0.33; 0.94]	41.2%	21.9%
Pradeep, A. R. 2015	45	4.53	1.38	46	2.75	0.92	1.51	[1.04; 1.98]	17.6%	20.2%
Common effect model	**310**			**283**			**1.02**	**[0.83; 1.22]**	**100.0%**	**--**
Random effects model							**1.10**	**[0.53; 1.67]**	**--**	**100.0%**

Heterogeneity: I^2 = 85%, $\hat{\tau}^2$ = 0.3632, p < 0.01

Periodontal Pocket Depth

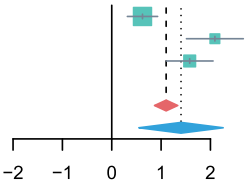


B

Study	PD Total	PD Mean	PD SD	Control Total	Control Mean	Control SD	SMD	95%−CI	Weight (common)	Weight (random)
Müller, T. 2011	101	20.01	36.21	75	2.82	1.54	0.62	[0.32; 0.93]	58.8%	35.2%
John, T. K. 2021	32	3.92	1.11	42	2.18	0.51	2.09	[1.51; 2.67]	16.6%	31.6%
Pradeep, A. R. 2015	45	5.03	1.38	46	3.14	0.96	1.58	[1.11; 2.05]	24.6%	33.2%
Common effect model	**178**			**163**			**1.10**	**[0.87; 1.34]**	**100.0%**	**--**
Random effects model							**1.40**	**[0.55; 2.26]**	**--**	**100.0%**

Heterogeneity: I^2 = 92%, $\hat{\tau}^2$ = 0.5132, p < 0.01

Clinical Attachment Level

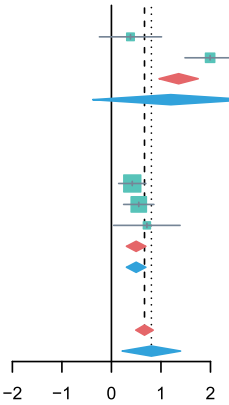


C

Study	PD Total	PD Mean	PD SD	Control Total	Control Mean	Control SD	SMD	95%−CI	Weight (common)	Weight (random)
Methods = Plaque Index										
Fleury, V. 2021	20	1.15	0.48	20	0.99	0.32	0.38	[−0.24; 1.01]	7.8%	18.4%
Pradeep, A. R. 2015	45	2.88	0.89	46	1.35	0.61	1.99	[1.49; 2.50]	11.9%	19.8%
Common effect model	65			66			1.36	[0.96; 1.75]	19.6%	--
Random effects model							1.20	[−0.38; 2.78]	--	38.2%
Heterogeneity: I^2 = 93%, $\hat{\tau}^2$ = 1.2085, p < 0.01										
Methods = Visual Plaque Index										
Garcia−de−la−Fuente, A. M. 2022	104	72.19	22.19	106	62.00	25.92	0.42	[0.15; 0.69]	40.7%	22.1%
Müller, T. 2011	101	20.38	30.58	75	7.25	7.41	0.55	[0.25; 0.86]	32.9%	21.9%
Ribeiro, G. R. 2016	17	91.76	16.86	20	64.10	48.91	0.72	[0.05; 1.39]	6.8%	17.8%
Common effect model	222			201			0.50	[0.30; 0.69]	80.4%	--
Random effects model							0.50	[0.30; 0.69]	--	61.8%
Heterogeneity: I^2 = 0%, $\hat{\tau}^2$ = 0, p = 0.66										
Common effect model	**287**			**267**			**0.67**	**[0.49; 0.84]**	**100.0%**	**--**
Random effects model							**0.81**	**[0.22; 1.39]**	**--**	**100.0%**

Heterogeneity: I^2 = 87%, $\hat{\tau}^2$ = 0.3875, p < 0.01

Plaque Index



D

Study	PD Total	PD Mean	PD SD	Control Total	Control Mean	Control SD	SMD	95%−CI	Weight (common)	Weight (random)
Fleury, V. 2021	20	53.66	28.56	20	48.38	20.03	0.21	[−0.41; 0.83]	22.9%	32.8%
Persson, M. 1992	21	53.30	32.73	379	54.90	19.87	−0.08	[−0.52; 0.36]	45.8%	33.8%
Pradeep, A. R. 2015	45	50.51	17.61	46	20.37	6.40	2.27	[1.73; 2.80]	31.4%	33.4%
Common effect model	**86**			**445**			**0.72**	**[0.43; 1.02]**	**100.0%**	**--**
Random effects model							**0.80**	**[−0.65; 2.25]**	**--**	**100.0%**

Heterogeneity: I^2 = 96%, $\hat{\tau}^2$ = 1.5659, p < 0.01

Bleeding on Probing Sites%

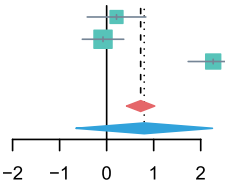


Fig. 3. Forest plots of meta-analysis for PPD (A), CAL (B), PI (C), and BoP% (D) in patients with Parkinson's disease.

Table 3
Overview of the oral status and dental manifestation of patients with Parkinson's disease

Outcomes	No. of studies	No. of participants	ES (95% CI)	p	Heterogeneity (I^2, p for Cochran Q)
OHIP-14	3	842	SMD: 0.91 (0.33, 1.49)	0.0022	$I^2 = 80\%$, $p < 0.01$
Xerostomia	4	1431	OR: 3.60 (2.79, 4.65)	<0.0001	$I^2 = 26\%$, $p = 0.26$
Salivary flow rate	6	570	SMD: –0.43 (–0.80, –0.05)	0.0260	$I^2 = 76\%$, $p < 0.01$
Tooth mobility	3	433	OR: 6.67 (1.73, 25.68)	0.0058	$I^2 = 69\%$, $p = 0.04$
Oral hygiene index	3	280	SMD: 1.35 (–0.06, 2.75)	0.0598	$I^2 = 95\%$, $p < 0.01$
Edentulism	7	1336	OR: 1.44 (0.65, 3.20)	0.3644	$I^2 = 73\%$, $p < 0.01$
DMFT	7	674	SMD: 0.10 (–0.50, 0.70)	0.7397	$I^2 = 91\%$, $p < 0.01$
Tooth loss	6	689	SMD: 0.34 (–0.26, 0.94)	0.2644	$I^2 = 89\%$, $p < 0.01$
Decayed teeth	7	1124	SMD: 0.28 (–0.09, 0.65)	0.1417	$I^2 = 81\%$, $p < 0.01$

ES, effect size; SMD, standard mean difference; OR, odds ratio; CI, confidence interval; OHIP-14, Oral Health Impact Profile-14; DMFT, decayed, missing, and filled teeth index.

0.22–1.39, $p = 0.0072$, $I^2 = 87\%$; Fig. 3C). Besides, although the BoP % was higher in PD groups than that in control groups, there was high heterogeneity and no statistically significant difference (SMD = 0.80, 95% CI –0.65–2.25, $p = 0.2803$, $I^2 = 96\%$; Fig. 3D). Above all, PD patients exhibited higher values of periodontal clinical parameters, indicating a higher prevalence of periodontitis among PD cases.

Oral status in PD

Nevertheless, considering PD patients are likely to present poor oral hygiene in clinical practice, we also conducted meta-analysis on additional clinical parameters of oral hygiene status and summarized the oral manifestation of PD patients in Table 3. PD patients experienced an unfavorable oral health-related quality of life, as evidenced by significantly higher scores on the Oral Health Impact Profile (OHIP-14) in the PD group (SMD = 0.91, 95% CI 0.33–1.49, $p = 0.0022$, $I^2 = 80\%$). Compared to controls, PD patients had a higher prevalence of xerostomia (OR = 3.60, 95% CI 2.79–4.65, $p < 0.0001$, $I^2 = 26\%$), in accordance with their declining salivary flow rate (SMD = –0.43, 95% CI –0.80– –0.05, $p = 0.0260$, $I^2 = 76\%$). While PD patients suffered from significantly higher tooth mobility (OR = 6.67, 95% CI 1.73–25.68, $p = 0.0058$, $I^2 = 69\%$), they also had a tendency to experience edentulism (OR = 1.44, 95% CI 0.65–3.20, $p = 0.3644$, $I^2 = 73\%$) and exhibit a higher number of loss teeth (SMD = 0.34, 95% CI –0.26–0.94, $p = 0.2644$, $I^2 = 89\%$), decayed teeth (SMD = 0.28, 95% CI –0.09–0.65, $p = 0.1417$, $I^2 = 81\%$), and a higher DMFT index (SMD = 0.10, 95% CI –0.50–0.70, $p = 0.7397$, $I^2 = 91\%$), although these differences were not statistically significant. Overall, the prevalence of poorer oral health tended to be higher in PD patients. The relevant forest plots are displayed in the Supplementary Material.

Sensitivity analysis

The leave-one-out sensitivity analysis revealed that no single study altered the pooled effect of HR and OR (Fig. 4A, B), proving the robustness of our results, which demonstrated no significant association between periodontitis and the risk of PD. Additional results of the sensitivity analyses on other outcomes (PPD, CAL, PI, and BoP%) are provided in the Supplementary Material.

Publication bias assessment

Due to the limited number of included studies for each outcome in the meta-analysis, a contour-enhanced funnel plot was only performed for the seven retrospective studies regarding periodontitis and the risk of PD. Asymmetry of the funnel plot was observed. In the contour-enhanced funnel plot (Fig. 5), the hollow dots filled by trim-and-fill approach depicted that one filled study was situated in sky-blue areas indicating high statistical significance ($p < 0.01$), whereas another filled study was located in white areas of no statistical significance. This discrepancy demonstrates that the potential publication bias may stem from the study conducted by John et al. [30]. However, even after excluding this study in the leave-one-out sensitivity analysis, the combined OR remained statistically insignificant (OR = 1.94, 95% CI 0.47–8.10, $p = 0.3614$; Fig. 4B), which further supports the stability of our results.

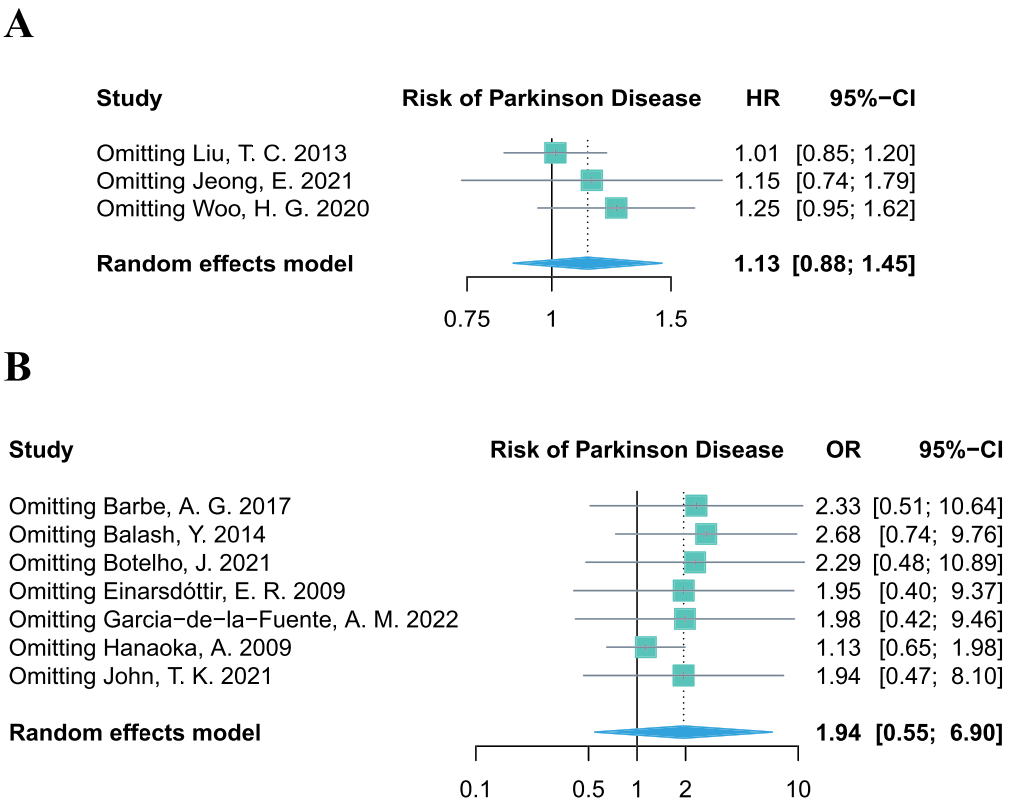


Fig. 4. Leave-one-out sensitivity analysis of studies focusing on periodontitis and the risk of Parkinson's disease.

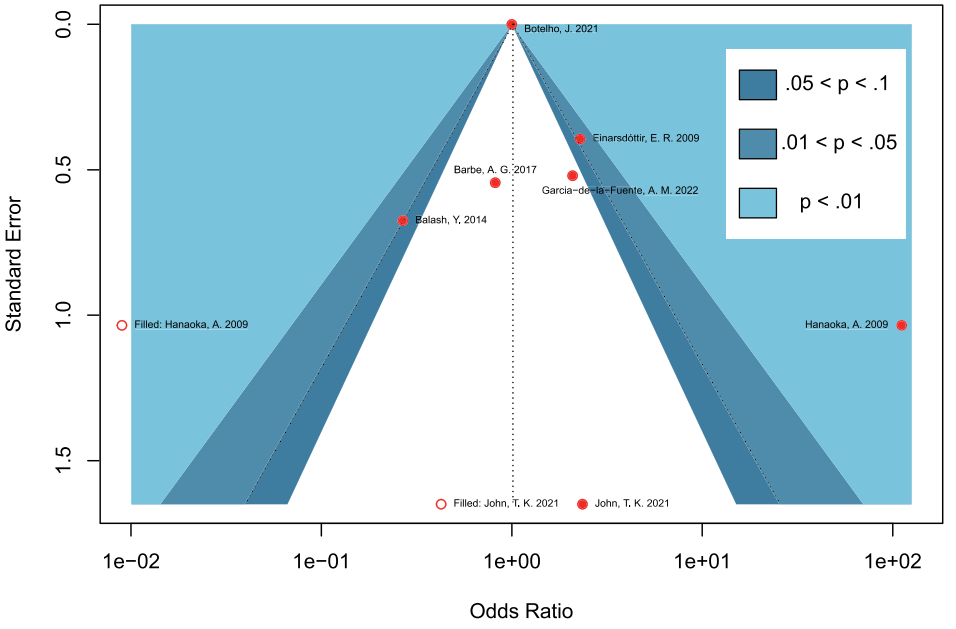


Fig. 5. Contour-enhanced funnel plots assessing the potential publication bias on studies concerning periodontitis and the risk of Parkinson's disease.

DISCUSSION

The principal findings of our meta-analysis imply that patients with periodontitis do not tend to have a higher risk of developing PD, and that PD patients might not confer a higher risk of periodontitis. Nonetheless, it was observed that PD patients presented a higher prevalence of periodontitis and other periodontal diseases, as well as poorer oral hygiene.

Our findings, which demonstrate no association between periodontitis and PD risk, are in agreement with a prospective cohort study recruiting 15,528 patients [31]. This study illustrated that the risk of PD was not significantly associated with dental plaque whether in males (pooled HR = 1.23, 95% CI 0.81–1.86, $p = 0.3309$, $I^2 = 0\%$) or in females (pooled HR = 0.86, 95% CI 0.56–1.31, $p = 0.4788$, $I^2 = 0\%$). However, due to the heterogeneity of the outcomes (the presence of dental plaque but not confirmed periodontitis), this study was only included for the systematic review but not in the quantitative meta-analysis.

Previous studies have stressed the significant role of periodontitis in the pathogenesis of PD, demonstrating that periodontitis triggers the systemic translocation of bacteremia and inflammatory mediators, resulting in the breakdown of the blood-brain barrier and activation of microglia, eventually driving in necrosis and apoptosis of dopaminergic neurons and contributing to the mechanism of PD [32, 33].

In contrast to these viewpoints, we posit that the subsequent inflammatory processes may play a dominant role in the progression of PD, rather than periodontitis itself, with periodontitis serving as one of the numerous initiating factors of inflammation. Our hypotheses are supported by the following evidence.

As was reported in one of the included studies [16], although there were no differences in dental or periodontal parameters between 20 PD patients and 20 healthy controls, the elevated pro-inflammatory cytokine levels, such as interleukine-1β and tumor necrosis factor-α, were still observed in the gingival crevicular fluid of PD cases compared with controls. This reflected the presence of active peripheral inflammatory responses in the oral cavity of PD patients, irrespective of the presence of periodontitis, thus partially corroborating our assumptions.

Furthermore, a study [34] enrolling 37 PD patients reported an increase in the number of various inflammatory cells, including leukocytes, basophils, and segmented neutrophils, in PD cases complicated by periodontitis. Intriguingly, another study involving 51 PD participants described the levels of circulating high-sensitive C-reactive protein were increased in the periodontitis group, whereas the lymphocyte levels were elevated in the group without periodontitis [35]. However, these studies did not include a periodontitis control group without PD, which prevented the investigation of whether the rising levels of inflammatory cells and parameters were primarily attributed to PD or periodontitis itself. Thus, further studies are required to clarify the mediating role played by inflammatory factors in these two diseases.

Apart from that, previous research has emphasized the essential role of inflammation in the development of PD. It has been suggested that systemic inflammation events could induce neuronal death and contribute to the progression of neurodegenerative diseases [36]. Specifically, activated glial and peripheral immune cells could mediate neuroinflammatory processes which are deleterious to neurodegeneration and stimulates the death of dopaminergic cells [3]. Besides, inflammation appears to be the bridges connecting several chronic diseases with PD. For example, there are shared inflammation dysregulated pathways linking diabetes with PD [37]. Additionally, chronic kidney disease promotes PD development by exacerbating inflammation and oxidative stress via excessive activation of immune response caused by metabolic toxins [38]. Hence, further studies should be undertaken to investigate the extent to which inflammation plays a role in the progression of PD.

Intriguingly, it is worthwhile noting that our results regarding causal inference between PD and the periodontitis risk were primarily inferred from the MR study, since it was the sole study in the literature examining their association. However, MR study could only assist in confirming their weak association with genetic liability. As documented in the MR study, MR may be powerless in the presence of a strong environmental interaction and may not be able to elucidate the influence of a disease on the occurrence of another disease during a specific period of lifetime, thereby resulting in potentially inaccurate conclusions [26]. In line with this perspective, the result of the lack of association between PD and the risk of periodontitis should be interpreted with caution. Considering the higher prevalence of periodontitis and worse oral cavity health among PD patients, we speculate that it is the several environmental factors that mediate the spurious weak association between PD and periodontitis risk, and

that these factors cannot be evaluated at the genetic level using an MR study. For instance, motor deficits in PD patients might be an influencing environmental factor. Indeed, the manifestation of motor impairment, hypokinesia, and involuntary movements in PD patients hinder their capability to maintain their daily oral hygiene, ultimately giving rise to poor oral health prognosis and deterioration in their quality of life [39]. Meanwhile, insufficient dental management induced by cognitive impairment may also be an environmental factor placing PD patients at risk for dental caries and periodontal diseases [15], as neglect of oral cavity disorders by PD cases, their caregivers and their professional physician has been reported [40]. Furthermore, other common symptoms of PD patients, like hyposmia, taste dysfunction [19], dysphagia [21], and masticatory disturbance [41], would contribute to longer meal times and more inadequate mastication, inducing a reduction in food intake quantity and quality, thereby causing nutritional imbalance and deterioration of oral health disorders in PD [15]. Last but not least, fluctuations in eating habits, such as preference for soft sticky foods [42] or sweets [43], would also conduce to the formation of cariogenic environments and subsequently lead to the occurrence of periodontal diseases [15]. In a nutshell, the aforementioned non-negligible environmental factors may potentially account for the high prevalence of periodontal diseases and poor oral health of PD patients, and more studies are necessitated to explore their effect.

The association between the risk of periodontitis and another degenerative disease, AD, has yielded inconsistent conclusions as well. In addition to a longitudinal study determining no statistical differences in several periodontal parameters between AD patients and healthy controls during 3 years of follow-up [44], no significant association between AD and periodontitis risk (RR = 1.4, 95% CI 0.9–2.1) was also reported by another study including 174 AD patients [45]. However, a population-based cohort study recruiting 8,640 individuals demonstrated an inverse association between AD and periodontitis risk (HR = 1.667, 95% CI 1.244–2.232, $p = 0.0004$) [46]. Hence, the relationship between AD and the risk of periodontitis also remains paradoxical and requires further investigation. Likewise, since our result on the weak association between PD and periodontitis risk may be biased and unreliable in our study, their casual association remains to be further investigated and clarified by additional well-designed and large-scale observational studies.

Our study possesses several strengths. To the best of our knowledge, this is the first systematic review and meta-analysis to comprehensively evaluate the bidirectional association between periodontitis and PD. Moreover, integrating the evidence from a Mendelian randomization study enhances the robustness and persuasiveness of our findings, since MR is widely recognized as providing higher-quality evidence compared to conventional observational studies by utilizing genetic variation as an instrumental variable to detect causality. Furthermore, contrary to previous theories, our intriguing findings provide no compelling evidence to support a bidirectional correlation between the incidence of the two diseases, neither in clinical manifestation nor in genetic liability [26], which may challenge traditional hypotheses concerning their potential relationship. Lastly, our study demonstrated that PD patients indeed suffer from poor oral hygiene, which has implications for guiding the management of dental diseases and improving oral care among PD patients.

Some potential limitations of our study should also be acknowledged. First of all, high heterogeneity was detected in our results, which can be chiefly attributed to variations in diagnostic criteria for periodontitis and measurements of outcomes. The lack of consensus on the definitions of periodontitis, discrepancies in periodontal examination methods, and the heterogeneity in dental conditions pose challenges in estimating the actual prevalence of periodontitis [47] while these factors were also an important source of high heterogeneity in our results and the asymmetry of the funnel plot. Thus, caution should be exercised in interpreting our results due to the existing heterogeneity. However, sensitivity analysis and contour-enhanced funnel plots supported the stability of our findings, reinforcing the credibility of our results. Secondly, as previously mentioned, the weak association between PD and the risk of periodontitis may be unreliable and should be interpreted with caution. This is primarily due to only one MR study addressing this topic while large-scale cohort studies focusing on the risk of periodontitis in PD patients with long-term follow-up are scarce, which also prevented an accurate reviewing and assessment of the incidence of periodontitis in PD cases. Finally, despite the limited number of included studies, grey literature databases comprising unpublished articles were not searched, given the uncertainty in their level of evidence quality. Despite these limitations, our study comprehensively evaluated the association between PD and periodontitis and provide profiles of

the oral status of PD patients, which could aid dentists and specialist physicians in formulating considerate dental care strategies for PD patients to optimize their overall quality of life.

Conclusion

Our meta-analysis demonstrated that there might be no bidirectional association between periodontitis risk and PD risk, while PD patients tend to suffer from poor oral health.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available upon reasonable request from the corresponding author.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JPD-230059.

REFERENCES

[1] GBD 2016 Parkinson's Disease Collaborators (2018) Global, regional, and national burden of Parkinson's disease, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* **17**, 939-953.

[2] GBD 2016 Neurology Collaborators (2019) Global, regional, and national burden of neurological disorders, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* **18**, 459-480.

[3] Hirsch EC, Hunot S (2009) Neuroinflammation in Parkinson's disease: A target for neuroprotection? *Lancet Neurol* **8**, 382-397.

[4] Tansey MG, Romero-Ramos M (2019) Immune system responses in Parkinson's disease: Early and dynamic. *Eur J Neurosci* **49**, 364-383.

[5] Darveau RP (2010) Periodontitis: A polymicrobial disruption of host homeostasis. *Nat Rev Microbiol* **8**, 481-490.

[6] Kinane DF, Stathopoulou PG, Papapanou PN (2017) Periodontal diseases. *Nat Rev Dis Primers* **3**, 17038.

[7] Papapanou PN, Susin C (2017) Periodontitis epidemiology: Is periodontitis under-recognized, over-diagnosed, or both? *Periodontol 2000* **75**, 45-51.

[8] Duval S, Tweedie R (2000) Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**, 455-463.

[9] Persson GR (2018) Periodontal complications with age. *Periodontol 2000* **78**, 185-194.

[10] Liccardo D, Cannavo A, Spagnuolo G, Ferrara N, Cittadini A, Rengo C, Rengo G (2019) Periodontal disease: A risk factor for diabetes and cardiovascular disease. *Int J Mol Sci* **20**, 1414.

[11] Leira Y, Dominguez C, Seoane J, Seoane-Romero J, Pias-Peleteiro JM, Takkouche B, Blanco J, Aldrey JM (2017) Is periodontal disease associated with Alzheimer's disease? A systematic review with meta-analysis. *Neuroepidemiology* **48**, 21-31.

[12] Nwizu N, Wactawski-Wende J, Genco RJ (2020) Periodontal disease and cancer: Epidemiologic studies and possible mechanisms. *Periodontol 2000* **83**, 213-233.

[13] Chen CK, Huang JY, Wu YT, Chang YC (2018) Dental scaling decreases the risk of Parkinson's disease: A nationwide population-based nested case-control study. *Int J Environ Res Public Health* **15**, 1587.

[14] Garcia-de-la-Fuente AM, Lafuente-Ibanez-de-Mendoza I, Lartitegui-Sebastian MJ, Marichalar-Mendia X, Echebarria-Goikouria MA, Aguirre-Urizar JM (2022) Facts and controversies regarding oral health in Parkinson's disease: A case-control study in Spanish patients. *Medicina Oral Patologia Oral Cirugia Bucal* **27**, E419-E425.

[15] Auffret M, Meuric V, Boyer E, Bonnaure-Mallet M, Verin M (2021) Oral health disorders in Parkinson's disease: More than meets the eye. *J Parkinsons Dis* **11**, 1507-1535.

[16] Fleury V, Zekeridou A, Lazarevic V, Gaïa N, Giannopoulou C, Genton L, Cancela J, Girard M, Goldstein R, Bally JF, Mombelli A, Schrenzel J, Burkhard PR (2021) Oral dysbiosis and inflammation in Parkinson's disease. *J Parkinsons Dis* **11**, 619-631.

[17] van Wamelen DJ, Leta V, Johnson J, Ocampo CL, Podlewska AM, Rukavina K, Rizos A, Martinez-Martin P, Chaudhuri KR (2020) Drooling in Parkinson's disease: Prevalence and progression from the non-motor international longitudinal study. *Dysphagia* **35**, 955-961.

[18] Rana AQ, Yousuf MS, Awan N, Fattah A (2012) Impact of progression of Parkinson's disease on drooling in various ethnic groups. *Eur Neurol* **67**, 312-314.

[19] Shah M, Deeb J, Fernando M, Noyce A, Visentin E, Findley LJ, Hawkes CH (2009) Abnormality of taste and smell in Parkinson's disease. *Parkinsonism Relat Disord* **15**, 232-237.

[20] Doty RL (2012) Olfactory dysfunction in Parkinson disease. *Nat Rev Neurol* **8**, 329-339.

[21] Argolo N, Nobrega AC (2013) Dysphagia complaint and gender in Parkinson's disease. *Eur J Neurol* **20**, e42.

[22] DeBowes SL, Tolle SL, Bruhn AM (2013) Parkinson's disease: Considerations for dental hygienists. *Int J Dent Hyg* **11**, 15-21.

[23] Fukayo S, Nonaka K, Shimizu T, Yano E (2003) Oral health of patients with Parkinson's disease: Factors related to their better dental status. *Tohoku J Exp Med* **201**, 171-179.

[24] Chen CK, Wu YT, Chang YC (2017) Periodontal inflammatory disease is associated with the risk of Parkinson's disease: A population-based retrospective matched-cohort study. *PeerJ* **5**, e3647.

[25] Jeong E, Park JB, Park YG (2021) Evaluation of the association between periodontitis and risk of Parkinson's disease: A nationwide retrospective cohort study. *Sci Rep* **11**, 16594.

[26] Botelho J, Machado V, Mendes JJ, Mascarenhas P (2021) Causal association between periodontitis and Parkinson's disease: A bidirectional mendelian randomization study. *Genes (Basel)* **12**, 772.

[27] Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, VanderWeele TJ, Higgins JPT, Timpson NJ, Dimou N, Langenberg C, Golub RM, Loder EW, Gallo V, Tybjaerg-Hansen A, Davey Smith G, Egger M, Richards JB (2021) Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. *JAMA* **326**, 1614-1621.

[28] Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L (2008) Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* **61**, 991-996.

[29] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hrobjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **372**, n71.

[30] John TK, Vasanthy B, Madhavanpillai BR, Gomez MS, Kuriakose R (2021) Does parkinsonism affect periodontal health? A cross-sectional study in a tertiary hospital. *J Indian Soc Periodontol* **25**, 538-543.

[31] Liu Z, Roosaar A, Axéll T, Ye W (2017) Tobacco use, oral health, and risk of Parkinson's disease. *Am J Epidemiol* **185**, 538-545.

[32] Alvarenga MOP, Frazao DR, de Matos IG, Bittencourt LO, Fagundes NCF, Rosing CK, Maia LC, Lima RR (2021) Is there any association between neurodegenerative diseases and periodontitis? A systematic review. *Front Aging Neurosci* **13**, 651437.

[33] Kaur T, Uppoor A, Naik D (2016) Parkinson's disease and periodontitis - the missing link? A review. *Gerodontology* **33**, 434-438.

[34] Botelho J, Lyra P, Proença L, Godinho C, Mendes JJ, Machado V (2020) Relationship between blood and standard biochemistry levels with periodontitis in Parkinson's disease patients: Data from the NHANES 2011-2012. *J Pers Med* **10**, 69.

[35] Lyra P, Botelho J, Machado V, Rota S, Walker R, Staunton J, Proenca L, Chaudhuri KR, Mendes JJ (2022) Self-reported periodontitis and C-reactive protein in Parkinson's disease: A cross-sectional study of two American cohorts. *NPJ Parkinsons Dis* **8**, 40.

[36] Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH (2005) Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *J Neurosci* **25**, 9275-9284.

[37] Santiago JA, Potashkin JA (2013) Shared dysregulated pathways lead to Parkinson's disease and diabetes. *Trends Mol Med* **19**, 176-186.

[38] Melendez-Flores JD, Estrada-Bellmann I (2021) Linking chronic kidney disease and Parkinson's disease: A literature review. *Metab Brain Dis* **36**, 1-12.

[39] Newadkar U, Khairnar S, Dodamani A, Newadkar R (2017) Oral health issues and challenges in Parkinson's disease. *Int J Nutr Pharmacol Neurol Dis* **7**, 54-59.

[40] Zlotnik Y, Balash Y, Korczyn AD, Giladi N, Gurevich T (2015) Disorders of the oral cavity in Parkinson's disease and parkinsonian syndromes. *Parkinsons Dis* **2015**, 379482.

[41] Ribeiro GR, Campos CH, Rodrigues Garcia RCM (2017) Parkinson's disease impairs masticatory function. *Clin Oral Investig* **21**, 1149-1156.

[42] Müller T, Palluch R, Jackowski J (2011) Caries and periodontal disease in patients with Parkinson's disease. *Spec Care Dentist* **31**, 178-181.

[43] Kennedy MA, Rosen S, Paulson GW, Jolly DE, Beck FM (1994) Relationship of oral microflora with oral health status in Parkinson's disease. *Spec Care Dentist* **14**, 164-168.

[44] Ship JA, Puckett SA (1994) Longitudinal study on oral health in subjects with Alzheimer's disease. *J Am Geriatr Soc* **42**, 57-63.

[45] Syrjala AM, Ylostalo P, Ruoppi P, Komulainen K, Hartikainen S, Sulkava R, Knuuttila M (2012) Dementia and oral health among subjects aged 75 years or older. *Gerodontology* **29**, 36-42.

[46] Ma KS, Hasturk H, Carreras I, Dedeoglu A, Veeravalli JJ, Huang JY, Kantarci A, Wei JC (2022) Dementia and the risk of periodontitis: A population-based cohort study. *J Dent Res* **101**, 270-277.

[47] Holtfreter B, Albandar JM, Dietrich T, Dye BA, Eaton KA, Eke PI, Papapanou PN, Kocher T, Joint EU/USA Periodontal Epidemiology Working Group (2015) Standards for reporting chronic periodontitis prevalence and severity in epidemiologic studies: Proposed standards from the Joint EU/USA Periodontal Epidemiology Working Group. *J Clin Periodontol* **42**, 407-412.

[48] Ledwon B, Miskiewicz A, Grabowska E, Kowalski J, Gorska R (2020) The relationship between periodontal disease and motor impairment in the course of Parkinson's disease. *Postepy Higieny I Medycyny Doswiadczalnej* **74**, 340-347.

[49] Liu TC, Sheu JJ, Lin HC, Jensen DA (2013) Increased risk of parkinsonism following chronic periodontitis: A retrospective cohort study. *Mov Disord* **28**, 1307-1308.

[50] Woo HG, Chang Y, Lee JS, Song TJ (2020) Association of tooth loss with new-onset Parkinson's disease: A nationwide population-based cohort study. *Parkinsons Dis* **2020**, 4760512.

[51] Auerbacher M, Gebetsberger L, Kaisarly D, Schmidmaier R, Hickel R, Drey M (2023) Oral health in patients with neurodegenerative and cerebrovascular disease: A retrospective study. *Disabil Rehabil* **45**, 2316-2324.

[52] Bakke M, Larsen SL, Lautrup C, Karlsborg M (2011) Orofacial function and oral health in patients with Parkinson's disease. *Eur J Oral Sci* **119**, 27-32.

[53] Balash Y, Peretz C, Rozenberg A, Zlotnik Y, Ezra A, Rabinovich A, Giladi N, Gurevich T (2014) Chronic inflammatory gingival disease in patients with Parkinson's disease. *Mov Disord* **29**, S336-S337.

[54] Barbe AG, Heinzler A, Derman S, Hellmich M, Timmermann L, Noack MJ (2017) Hyposalivation and xerostomia among Parkinson's disease patients and its impact on quality of life. *Oral Dis* **23**, 464-470.
[55] Cicciù M, Risitano G, Lo Giudice G, Bramanti E (2012) Periodontal health and caries prevalence evaluation in patients affected by Parkinson's disease. *Parkinsons Dis* **2012**, 541908.
[56] Einarsdóttir ER, Gunnsteinsdóttir H, Hallsdóttir MH, Sveinsson S, Jónsdóttir SR, Olafsson VG, Bragason TH, Saemundsson SR, Holbrook WP (2009) Dental health of patients with Parkinson's disease in Iceland. *Spec Care Dentist* **29**, 123-127.
[57] Hanaoka A, Kashihara K (2009) Increased frequencies of caries, periodontal disease and tooth loss in patients with Parkinson's disease. *J Clin Neurosci* **16**, 1279-1282.
[58] Nakayama Y, Washio M, Mori M (2004) Oral health conditions in patients with Parkinson's disease. *J Epidemiol* **14**, 143-150.
[59] Persson M, Osterberg T, Granérus AK, Karlsson S (1992) Influence of Parkinson's disease on oral health. *Acta Odontol Scand* **50**, 37-42.
[60] Schwarz J, Heimhilger E, Storch A (2006) Increased periodontal pathology in Parkinson's disease. *J Neurol* **253**, 608-611.
[61] van Stiphout MAE, Marinus J, van Hilten JJ, Lobbezoo F, de Baat C (2018) Oral health of Parkinson's disease patients: A case-control study. *Parkinsons Dis* **2018**, 9315285.
[62] Barbe AG, Bock N, Derman SH, Felsch M, Timmermann L, Noack MJ (2017) Self-assessment of oral health, dental health care and oral health-related quality of life among Parkinson's disease patients. *Gerodontology* **34**, 135-143.
[63] Gardner J, Kuyper D, Madden M, Wielinski C (2013) Dental health of patients and carepartners in Parkinson's disease. *J Parkinsons Dis* **3**, 90.
[64] Gopalakrishnan T, Mastan KMK, Mouli PEC, Guntuku NL, Priyadharshini A, Sangeetha GF (2021) Evaluation of oral manifestations of patients with parkinson's disease–an observational study. *Indian J Forensic Med Toxicol* **15**, 1424-1429.
[65] Lyra P, Machado V, Proença L, Domingos J, Godinho C, Mendes JJ, Botelho J (2020) Parkinson's disease, periodontitis and patient-related outcomes: A cross-sectional study. *Medicina (Kaunas)* **56**, 383.
[66] Pradeep AR, Singh SP, Martande SS, Raju AP, Rustagi T, Suke DK, Naik SB (2015) Clinical evaluation of the periodontal health condition and oral health awareness in Parkinson's disease patients. *Gerodontology* **32**, 100-106.
[67] Purisinsith S, Kanjanabuch P, Puapatanakul P, Phannajit J, Johnson DW, Robinson B, Kanjanabuch T (2021) Oral health-related quality of life (OHRQoL) in PD: A preliminary result from Thailand PDOPPS. *Nephrology* **26**, 24-27.
[68] Ribeiro GR, Campos CH, Garcia RC (2016) Oral health in elders with Parkinson's disease. *Braz Dent J* **27**, 340-344.
[69] Silva PF, Biasotto-Gonzalez DA, Motta LJ, Silva SM, Ferrari RA, Fernandes KP, Bussadori SK (2015) Impact in oral health and the prevalence of temporomandibular disorder in individuals with Parkinson's disease. *J Phys Ther Sci* **27**, 887-891.
[70] Verhoeff MC, Lobbezoo F, van Leeuwen AM, Schuller AA, Koutris M (2022) Oral health-related quality of life in patients with Parkinson's disease. *J Oral Rehabil* **49**, 398-406.