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REVIEW PAPER

Impact of periodontal disease on cognitive disorders, dementia, and depression: a systematic review and meta-analysis

Vittorio Dibello · Carlo Custodero · Raffaele Cavalcanti · Domenico Lafornara · Antonio Dibello · Madia Lozupone · Antonio Daniele · Alberto Pilotto · Francesco Panza · Vincenzo Solfrizzi

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Abstract A growing body of research suggested that there was a link between poor periodontal health and systemic diseases, particularly with the early development of cognitive disorders, dementia, and depression. This is especially true in cases of changes in diet, malnutrition, loss of muscular endurance, and abnormal systemic inflammatory response. Our study aimed to determine the extent of these associations to better target the multi-level healthy aging challenge investigating the impact of periodontal disease on cognitive disorders (cognitive impairment and cognitive decline), dementia, and depression. We conducted a comprehensive literature search up to November 2023 using six different electronic databases. Two independent researchers assessed the eligibility of 7363 records against the inclusion criteria and found only 46 records that met the requirements. The study is registered on PROSPERO (CRD42023485688). We generated random effects pooled estimates and 95% confidence intervals (CI) to evaluate whether periodontal disease increased the risk of the investigated outcomes. The quality

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V. Dibello
Department of Orofacial Pain and Dysfunction, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

V. Dibello · C. Custodero · A. Pilotto · F. Panza (✉) · V. Solfrizzi
Cesare Frugoni" Internal and Geriatric Medicine and Memory Unit, University of Bari "Aldo Moro", Bari, Italy
e-mail: f_panza@hotmail.com

R. Cavalcanti
Department of General Surgery and Surgical-Medical Specialties, University of Catania, Catania, Italy

D. Lafornara
Division of Diagnostic Imaging, Department of Surgical and Biomedical Sciences, Santa Maria della Misericordia Hospital, University of Perugia, Perugia, Italy

A. Dibello
Stella Maris Nursing Home and Day Care Center, Monopoli, Bari, Italy

M. Lozupone
Department of Translational Biomedicine & Neuroscience 'DiBraiN', University of Bari Aldo Moro, Bari, Italy

A. Daniele
Department of Neuroscience, Catholic University of Sacred Heart, Rome, Italy

A. Daniele
Neurology Unit, IRCCS Fondazione Policlinico Universitario A. Gemelli, Rome, Italy

A. Pilotto
Geriatrics Unit, Department of Geriatric Care, Orthogeriatrics and Rehabilitation, Galliera Hospital, Genoa, Italy

assessment revealed moderate quality of evidence and risk of bias. Periodontal disease was found to be associated with both cognitive disorders (relative risk (RR) 1.25, 95% CI 1.11–1.40, in the analysis of cross-sectional studies); cognitive impairment (RR 3.01, 95% CI 1.52–5.95 for longitudinal studies, cognitive decline); and dementia (RR 1.22, 95% CI 1.10–1.36). However, no significant increased risk of depression among subjects with periodontal disease was found (RR 1.07, 95% CI 0.95–1.21). Despite the association with two of the three explored outcomes, the available evidence on periodontal diseases and dementia, cognitive disorders, and depression is controversial due to several limitations. Therefore, further investigations involving validated and standardized tools are required.

Keywords Periodontal disease · Alzheimer's disease · Cognitive impairment · Dementia · Depression · Cognitive decline

Introduction

Late-life mental health and neurological disorders, including cognitive impairment, dementia, and depression, have a high social and economic impact and cause substantial reduction in quality of life and life expectancy [1]. Cognitive impairment can be considered as an umbrella term to describe conditions characterized by deterioration of different cognitive domains. Increasing age is the most important factor associated with cognitive impairment. Globally, the number of people suffering from dementia increased by 117% between 1990 and 2016, with more than 55 million people currently affected and roughly 10 million new cases every year [2]. Mild cognitive impairment (MCI) is an intermediate condition with no impact on independence in activities of daily living which may predispose to future dementia. It has an estimated prevalence ranging between 15 and 20% in persons 60 years and older, and the annual conversion rate to dementia varies between 8 and 15% per year [3]. Depression is currently the number one cause of disability worldwide, with major repercussions on the psychophysical status of the population and which may represent itself a potentially modifiable risk factor for dementia [4, 5]. Given the growing population of older adults, these conditions may represent a global threat, and stronger effort should be taken on prevention strategies [6].

Chronic inflammation has been proposed as one of the most important underlying factors for accelerated aging and a common milieu of different mental health disorders [7]. The long-term peripheral overproduction of pro-inflammatory cytokines might determine central effects activating cerebral microglia, disrupting neurogenesis, and finally leading to negative outcomes such as cognitive impairment, dementia, and late-life depression. In this regard, the presence of inflammatory mediators in the pathogenesis of periodontal disease (PD) has drawn attention to the systemic impact of this disease on general health and its association with mental health disorders [8, 9]. PD is a chronic multifactorial inflammatory disease characterized by the progressive destruction of the supporting apparatus of the tooth caused by pathogenic bacteria or biofilm in dental plaque, and responsible for a substantial part of edentulism and masticatory dysfunction with consequent impact on dental care costs and general health [10]. PD may contribute to dementia, late-life cognitive disorders, and depression in several ways [11]. In fact, PD-causing bacteria are transmitted directly into the brain [12]; PD may also affect the brain via neural pathways [13]; moreover, inflammatory molecules induced by PD may affect the blood and brain [14], and, finally, tooth loss due to PD and reduced masticatory function may affect cognitive function [11].

The available evidence on relationship between PD and dementia, late-life cognitive disorders, and depression is still controversial due to several limitations, such as the different methods and classifications used for the assessment of both PD and cognitive outcomes, the consideration of tooth loss as an index of PD even when this was not directly or solely attributable to it, and often the evaluation of mental health disorders as risk factors for PD, but not the contrary [8, 9]. The present systematic review and meta-analysis aimed to investigate in a comprehensive way the impact of PD on dementia, cognitive disorders (cognitive impairment and cognitive decline), and depression.

Methods

Search strategy and data extraction

The present systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, adhering to the PRISMA 27-item checklist [15]. An a priori protocol was established and registered on PROSPERO, a prospective international register of systematic reviews (CRD42023485688). Two scholars performed separate searches in the US National Library of Medicine (PubMed), Medical Literature Analysis and Retrieval System Online (MEDLINE), EMBASE, Scopus, Ovid, and Google Scholar databases to find original articles investigating any association between the studied exposure, i.e., PD and the three adverse health-related analyzed outcomes. The exposure factors were selected to include any indicator(s) of PD, regardless of the measurement method (clinical examination or self-reported), while the outcome(s) as to include adverse health-related outcomes, namely cognitive disorders, dementia, and depression. Search strings included a wide range of subject headings and synonyms for inflammatory PD (such as periodontitis, pericoronitis, periodontal pocket, and gingivitis) and adverse health-related outcomes (such as dementia, mild cognitive impairment, cognitive decline, and depressive disorder). Full details of the search strategy used in PubMed and MEDLINE and adapted to the other four electronic sources is shown in Supplementary Table S1. The literature search covers the timeframe from the database inception to November 22, 2023. No language limitation was introduced. Two investigators (VD, CC) searched for papers, screened titles, and abstracts of the retrieved articles separately and in duplicate, checked the complete texts, and selected records for inclusion.

The following information was extracted by the two investigators (VD, CC, or FP) separately and in duplicate in a piloted form: (1) general information of single studies (author, year of publication, country, settings, design, sample size, age); (2) PD tools and classifications; (3) arbitrarily selected cognitive and mental adverse outcomes (dementia, cognitive impairment/decline, and depression); and (4) tools used by examiners for the assessment and diagnosis of cognitive outcomes. For further information (missing or incomplete data) or to request unavailable articles, the primary authors were contacted. Data were cross-checked, any discrepancies were discussed, and disagreements were resolved by a third investigator (VS). Lastly, data extracted from selected studies were structured in tables of evidence.

Selection criteria

PECO (Population, Exposure, Control, and Outcome) statement was used for defining the inclusion criteria (for cross-sectional studies, there is no difference between exposure and outcome): (a) population, adults (over 18 years old); (b) exposure, every indicator of clinical PD parameters (clinical attachment level, probing depth, and bleeding on probing) measured at least once in the study, regardless of the form of measurement (clinical or radiographic exam, self-reported); (c) control, control group subjects who do not meet the diagnostic criteria of PD (including studies evaluating tooth loss or edentulism as indicators of periodontitis, unless specifically documented otherwise); (d) outcome, no skimming was applied to assessment methods used to evaluate the three outcomes, i.e., dementia(s), cognitive impairment, and depression; (e) study design, studies (including case-control, cohort, and cross-sectional studies) providing quantitative measures of the association between PD and adverse health-related outcomes, without regards to the country where they were conducted. Exclusion criteria are the following: (a) exposure, no diagnosis of PD or inadequate or not directly related criteria for its assessment; (b) control, absence of healthy control patients; (c) outcome, no diagnosis of any of the three outcomes; (d) study design, studies on non-human subjects, individuals under 18 years of age, intervention studies; (e) article type, technical reports, letters to the editor, case reports, case series, meta-analysis, systematic, and narrative review articles were excluded.

Quality assessment within and across studies and overall quality assessment

The methodological quality of included studies was independently appraised by paired investigators (VD and CC or FP), using the National Institutes of Health Quality Assessment Toolkits for Observational Cohort and Cross-Sectional Studies [16]. The ratings high (good), moderate (fair), or poor were

assigned to studies according to the criteria stated in the toolkit. This tool contains 14 questions that assess several aspects associated with the risk of bias, type I and type II errors, transparency, and confounding factors, i.e., study question, population, participation rate, inclusion criteria, sample size justification, time of measurement of exposure/outcomes, time frame, levels of the exposure, defined exposure, blinded assessors, repeated exposure, defined outcomes, loss to follow-up, and confounding factors. Items 6, 7, and 13 do not refer to cross-sectional studies, and the maximum possible scores for cross-sectional and prospective studies were 8 and 14, respectively. Disagreements regarding the methodological quality of the included studies were resolved through discussion until a consensus was reached, or resolved by a fourth investigator (VS). A modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) rating system was used to assess the overall quality of evidence of the studies included in the present systematic review [17]. The following factors were considered: the strength of association for PD and adverse health-related outcomes, methodological quality/design of the studies, consistency, directedness, precision, size, and (where possible) dose-response gradient of the estimates of effects across the evidence base. Evidence was graded as very low, low, moderate, and high, similar to a GRADE rating system.

Statistical methods and data synthesis

We extracted the number of events and total number of participants among subjects with and without PD. When not available, we converted odds ratios (ORs) or hazard ratios (HRs) to relative risks (RRs) using established approaches [18]. In particular, VanderWeele demonstrated that the optimal approximate conversion of OR to RR is its square-root transformation, assuming that the prevalence of the outcome among the unexposed lays in a normally distributed interval between 0.2 and 0.8. Dividing and multiplying, by 1.25, the square-root transformation of the OR lower and upper limits, we can obtain RR confidence interval [18]. For the conversion of HR to RR, we applied a respective formula proposed by VanderWeele [18]. We pooled estimates when at least two studies reported harmonizable results on the same outcome. Due to the heterogeneous definitions and measurement methods of periodontal disease, we used random-effects meta-analyses with the inverse variance method to pool RRs (95% CI). Between-study heterogeneity was estimated with I^2. If heterogeneity was found to be significant ($p < 0.05$, $I^2 \geq 50\%$), we conducted sensitivity and subgroup analyses. In sensitivity analyses, we removed outliers and poor-quality studies. Subgroup analyses were performed based on study design. We did meta-regression analyses to explore how mean age and follow-up time might modify the associations found in the main analysis. We assessed reporting bias using Egger's test for funnel plot asymmetry and corrected the pooled effect estimates from the main analysis and sensitivity analysis using the trim and fill approach to account for potential reporting bias. We used Stata Version 16.0 (Stata Corp) and RevMan 5.4 software (Cochrane Collaboration Review Manager), for all statistical analyses.

Results

The preliminary systematic search of the literature yielded 7363 records. After excluding duplicates, and not relevant articles only 739 met the inclusion criteria and were included in the final qualitative analysis. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart illustrating the number of studies at each stage of the review was shown in Fig. 1. The endpoint of the literary skimming process resulted in 46 eligible articles which were included in the final qualitative analysis (Table 1) [19–64]. Figure 2 shows the percentage representation of each of the three outcomes (cognitive disorders, dementia, and depression) associated with PD based on the selected studies.

Details of the design (cohort or cross-sectional), sample size (*N*), and sex ratio (%), minimum age and mean (standard deviation, SD), setting (community, hospital, home care), and country of individual studies are shown in Table 1. Given the mixed shape of the recruitment settings for one of the selected studies (1 out of the 46), the distribution resulted as follows: 89.3% (*N*= 42) community, 10.7% (*N*= 5) hospital, while no study recognized nursing homes/home care as a setting. The Asian (36.9%, *N*= 17) continent led the geographical distribution of selected studies, followed by Europe (30.5%, *N*= 14), North America

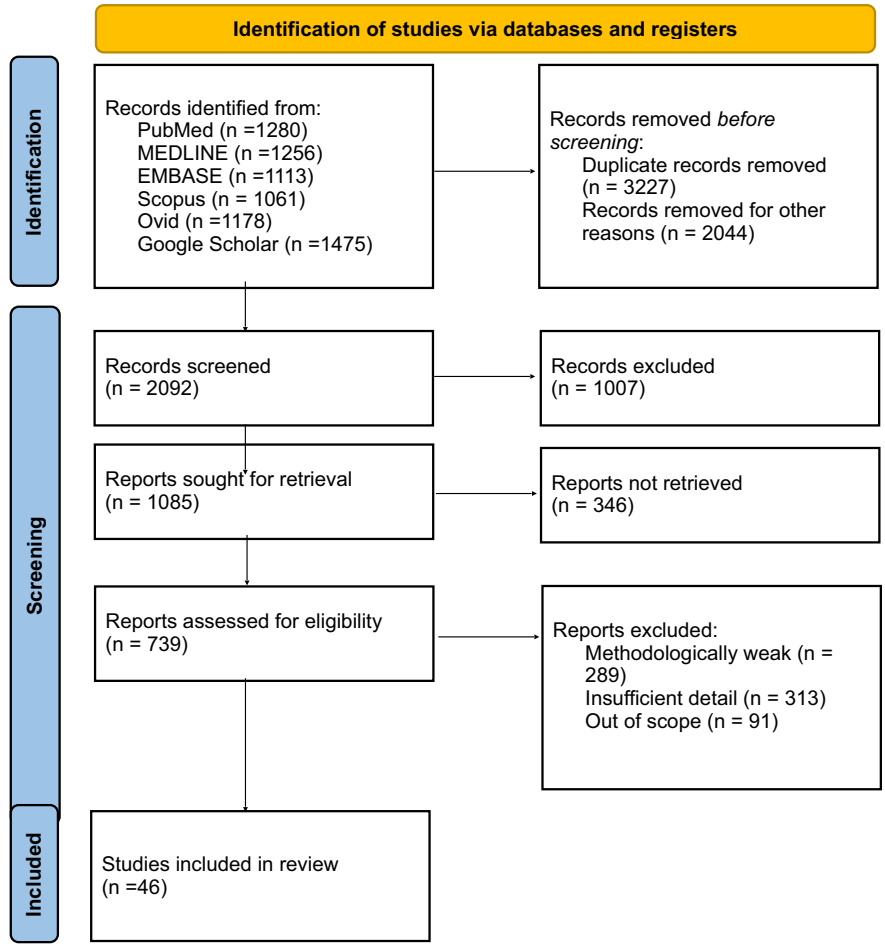


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020: flow chart illustrating the number of studies at each stage of the review

(26.08%, *N*= 12), and South America (6.52%, *N*= 3). This latter perspective pointed to both the lack of homogeneity in geographical distribution and the inadequate representativeness of all countries. Mean (SD) age and sex ratio of study participants were recorded if applicable. In the totality of 3,220,345 subjects, females accounted for the majority (about 55.2% vs 44.8%). Cross-sectional design (47.8%, *N*= 22) dominated the prospective cohort (23.9%, *N*= 11), the retrospective cohort one (15.2%, *N*= 7), and the case-control (13.1%, *N*= 6).

Diagnostic criteria for periodontal disease, assessment tools, and their distribution across studies

Several diagnostic criteria and classifications for PD were used in the selected studies (Table 1). The most commonly used classification was the Centre for Disease Control/American Academy of Periodontology case definitions, found in 11 studies [36, 37, 46, 49, 51, 58–61, 63, 64], followed by the International Classification of Diseases, Tenth Revision [48, 56, 57, 62] and the International Classification of Diseases, Ninth Revision [35, 39–41], each used in four studies. Less frequently used classification criteria for PD were the National Institute of Dental and Craniofacial Research epidemiological criteria, adopted in two studies [19, 23] and the Community Periodontal Index also found in two studies [28, 30]. Finally, represented only once each, other classification criteria were identified: established periodontitis by Machtei et al. criteria [20], the periodontal risk assessment by Lang and Tonetti [21], the Healthy People 2010 definition [31], the European Workshop in Periodontology Group C definition [46], and the Swedish Quality Registry for Caries and Periodontal Diseases [55].

Many studies did not provide one or more specific and validated classification criteria, but used clinical

Table 1 Selected studies investigating periodontal disease (PD) and cognitive disorders and depression (*N*=46) and quality appraisal summary

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Persson et al., 2003 [19]	National Institute of Dental and Craniofacial Research epidemiological criteria Standardized panoramic radiograph	Depression	GDS	Cross-sectional	701 (40.5% M, 59.5% F)	67.2 years (4.6)	Community	North America (USA)	Moderate	Evidence of depression (self-report or by GDS) was not associated with risk for PD in older subjects
Solis et al., 2004 [20]	Machtei et al. "established periodontitis"	Depression	Self-Report Screening Questionnaire-20 BDI	Case-control	47/106 (40% M, 60% F/33% M, 67% F)	42.9 years (10.45)/34.9 years (10.21)	Community	South America (Brazil)	Moderate	In this study, no evidence was found for an association between depression and established PD
Saletu et al., 2005 [21]	Periodontal risk assessment by Lang and Tonetti	Depression	Hamilton Depression Scale Zung Self-Rating Depression Scale	Case-control	40/41 (60% M, 40% F/56% M, 44% F)	32–64/23–70	Community	Europe (Austria)	Moderate	This clinical-psychometric study confirmed depressive mood as a relevant pathogenetic factor for PD

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Castro et al., 2006 [22]	Advanced periodontal disease: CAL ≥4 mm and BOP in at least 10 teeth, and PPD ≥6 mm in at least five teeth	Depression	BDI	Case-control	96/69 (52% M, 48% F/30% M, 70% F)	45.6 years (6.23)/41.70 years (5.13)	Community	South America (Brazil)	High	The authors did not find any significant association between PD and the psychosocial factors analyzed
Stewart et al., 2008 [23]	National Institute of Dental and Craniofacial Research epidemiological criteria	Cognitive impairment	Symbol Digit Substitution Test (20–59 years) Serial Digit Learning Test (20–59 years) Story Recall Test (>70 Years)	Cross-sectional	5138 (20–59 years) (49.1% M, 50.9% F) 1555 (>70 years) (41.6% M, 58.4% F)	(20–59 years) (>70 years)	Community	North America (USA)	High	Poor oral health was associated with worse cognitive function throughout adult life
Rosania et al., 2009 [24]	Number of sites with probing depth 5 to 7 or >7 mm; number of teeth with REC 2 to 4 or >4 mm; and number of teeth with CAL >5 to 7 or >7 mm	Depression	Center for Epidemiologic Studies Depression Scale	Cross-sectional	45 (31.1% M, 68.9% F)	45 to 82 years	Community	North America (USA)	Moderate	Depression may be associated with periodontal destruction through behavioral and physiologic mechanisms

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Noble et al., 2009 [25]	Serum P. gingivalis IgG	Cognitive impairment	Immediate and delayed logical verbal memory test from the East Boston Memory Test Three-word registration/memory task Five serial subtractions by intervals of three	Cross-sectional	2355 (42.7% M, 57.3% F)	≥60 years	Community	North America (USA)	High	A serological marker of PD was associated with impaired delayed memory and calculation
Ababneh et al., 2010 [26]	CAL > 1 mm PPD ≥ 3 mm	Depression	Zung Self-rating Depression Scale	Cross-sectional	666 (34% M, 66% F)	15 to 62 years (mean age 31.1)	Community Hospital (outpatients)	Asia (Jordan)	High	High susceptibility to depression did not play a significant role in the aetiology and severity of PD in the population studied
Kaye et al., 2010 [27]	Alveolar bone loss (percentage of root length in 20% increments) Maximum PPD	Cognitive decline	MMSE Spatial copying task	Prospective cohort study (32 years)	597 (100% M)	24 to 84	Community	North America (USA)	High	This study of community-dwelling men showed that rates of PD progression predicted subsequent decline in cognitive function

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Arrivé et al., 2011 [28]	Community Periodontal Index	Dementia	National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria Hachinski score	Prospective cohort study (14 years)	405 (45.4% M, 54.6% F)	65 years +	Community	Europe (France)	High	The authors did not find direct association between PD variables and dementias
Syrjälä et al., 2012 [29]	Teeth with deep periodontal pockets (≥ 4 mm)	Dementia	DSM-IV criteria McKeith's consensus criteria	Cross-sectional	354 (28.5% M, 71.5% F)	82 years (4.9)	Community	Europe (Finland)	Moderate	Among the older adults aged 75 years or older, patients with AD or other types of dementia are at increased risk of poor oral health and poor oral hygiene
Kamer et al., 2012 [30]	Modified Community Periodontal Index	Cognitive impairment	Digit span test Digit symbol test Picture completion test Block design test	Cross-sectional	152 (52% M, 48% F)	70 years	Community	Europe (Denmark)	High	The results of the study supported the hypothesis that periodontal inflammation may affect cognition

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Khambaty et al., 2013 [31]	Healthy People 2010 definition (one or more tooth sites with loss of attachment ≥4 mm)	Depression	World Health Organization Composite International Diagnostic Interview, auto version 2.1	Cross-sectional	1979 (45% M, 55% F)	29.1 years (5.8)	Community	North America (USA)	High	The authors did not find a significant association between major depressive disorder and PD
Gil-Montoya et al., 2015 [32]	Loss of attachment > 3 mm	Cognitive impairment	Spanish Society of Neurology Behavioral and Dementia Study Group criteria	Case-control	180/229 (32.8% M, 67.2% F/44.1% M, 55.9% F)	77.0 years (7.8)/78.5 years (7.9)	Hospital (outpatients)	Europe (Spain)	High	PD appears to be associated with cognitive impairment after controlling for confounders such as age, sex, and educational level
Iwasaki et al., 2015 [33]	Interproximal attachment loss ≥5 mm in ≥50% of teeth	Cognitive impairment	MMSE Hasegawa Dementia Scale-Revised scores	Cross-sectional	291 (34.7% M, 65.3% F)	80.9 years (4.5)	Community	Asia (Japan)	High	PD was significantly associated with cognitive impairment among community-dwelling older Japanese
Delgado-Angulo et al., 2015 [34]	Any tooth with pocket depths ≥4 mm	Depression	BDI	Cross-sectional	4673 (47% M, 53% F)	≥ 30 years	Community	Europe (Finland)	High	Depression was not significantly related to PD

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Hsu et al., 2015 [35]	International Classification of Diseases, Ninth Revision	Depression	International Classification of Diseases, Ninth Revision	Retrospective cohort study (11 years)	63,540 (51.5% M, 48.5% F)	> 20 years	Community	Asia (Taiwan)	High	PD may increase the risk of subsequent depression and was suggested an independent risk factor regardless of sex, age, and most comorbidities
Iwasaki et al., 2016 [36]	Centre for Disease Control/ American Academy of Periodontology case definitions	Cognitive decline	MMSE	Prospective cohort study (3 years)	85 (35.3% M, 64.7% F)	79.3 years (3.7)	Community	Asia (Japan)	High	Within the limitations related to its small sample size, the findings of the study suggested that severe PD was significantly associated with future decline in cognitive function among community-dwelling older Japanese subjects.

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Ide et al., 2016 [37]	Centre for Disease Control/ American Academy of Periodontology case definitions	Cognitive decline	MMSE (change ≥ −3)	Prospective cohort study (6 months)	59 (51% M, 49% F)	77.7 years (8.6)	Community	Europe (United Kingdom)	High	The authors found that PD was associated with an increase in cognitive decline in AD, independent to baseline cognitive state
Shin et al., 2016 [38]	RABL (≥2 interproximal sites with RABL ≥4 mm)	Cognitive impairment	MMSE	Cross-sectional	189 (51.8% M, 48.2% F)	60 years +	Community	Asia (South Korea)	High	PD was independently associated with cognitive impairment after controlling for various confounders
Tzeng et al., 2016 [39]	International Classification of Diseases, Ninth Revision	Dementia	International Classification of Diseases, Ninth Revision	Retrospective cohort study (10 years)	8828 (61.4% M, 38.6% F)	20 to > 70 years	Community	Asia (Taiwan)	High	Patients with chronic PD and gingivitis had a higher risk of developing dementia
Lee et al., 2016 [40]	International Classification of Diseases, Ninth Revision	Dementia	International Classification of Diseases, Ninth Revision	Prospective cohort study (12 years)	6056 (54% M, 46% F)	65 years +	Community	Asia (Taiwan)	High	PD was associated with greater risk of developing dementia

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Lee et al., 2017 [41]	International Classification of Diseases, Ninth Revision	Dementia	International Classification of Diseases, Ninth Revision	Retrospective cohort study (10 years)	182,747 (49.5% M, 50.5% F)	45 years +	Community	Asia (Taiwan)	High	Subjects who had more severe PD or did not receive periodontal treatment were at greater risk of developing dementia
Nilsson et al., 2017 [42]	Presence of periodontal pockets ≥ 5 mm at ≥ 30% of the teeth	Cognitive impairment	MMSE Clock drawing test	Cross-sectional	775 (45% M, 55% F)	60 years +	Community	Europe (Sweden)	High	A history of PD and tooth loss may be of importance for cognitive functions among older adults
Hwang and Park, 2018 [43]	Gingival bleeding, calculus, and presence of periodontal pockets	Depression	Patient Health Questionnaire	Cross-sectional	4328 (40.8% M, 59.2% F)	20 to 95 years (mean age 50.84 years)	Community	Asia (South Korea)	High	Neither self-reported nor diagnosed depression was associated with the presence of any PD or severe PD in the total sample

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Nilsson et al., 2018 [44]	Bone loss ≥4 mm at ≥30% of readable sites	Cognitive decline	MMSE	Prospective cohort study (6 years)	1402 (NA)	60 years +	Community	Europe (Sweden)	High	The present study demonstrated that a history of PD was associated with decline in cognitive functions after 6-year follow-up
Holmer et al., 2018 [45]	PPD ≥6 mm Marginal alveolar bone loss	Cognitive impairment Dementia	Petersen/Winblad criteria (CI) National Institute of Aging–Alzheimer's Association work group criteria (D)	Case-control	154/76 (47.8% M, 52.2% F/ 43.4% M, 56.6% F)	50 years +	Hospital (outpatients)	Europe (Sweden)	High	The results suggested that marginal PD was associated with early cognitive impairment and AD
Iwasaki et al., 2019 [46]	European Workshop in Periodontology Group C definition Centers for Disease Control/ American Academy of Periodontology definition	Cognitive decline	MMSE	Prospective cohort study (5 years)	179 (34.6% M, 65.4% F)	80.1 years (4.4)	Community	Asia (Japan)	High	Severe PD and periodontal inflammation were associated with incident MCI among older community-dwelling men and women.

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Kurushima et al., 2019 [47]	Self-reported (questionnaire)	Depression	Self-reported (Have you ever told by a doctor or other health professional that you had depression?)	Cross-sectional	4143 (100% F)	20 to 91 years	Community	Europe (United Kingdom)	Moderate	The results of the study suggested that the associations between mental health disorders and periodontal condition are strong even when controlling for potential risk factors
Choi et al., 2019 [48]	International Classification of Diseases, Tenth Revision	Dementia	International Classification of Diseases, Tenth Revision	Retrospective cohort study (12 years)	262,349 (53.1% M, 46.9% F)	60.3 years (7.5)	Community	Asia (South Korea)	High	Chronic PD may be associated with a higher risk of developing dementia
Sung et al., 2019 [49]	Centre for Disease Control/ American Academy of Periodontology case definitions	Cognitive impairment	Neurobehavioral Evaluation System 2	Cross-sectional	4663 (46.3% M, 53.7% F)	36.16 years (10.72)	Community	North America (USA)	High	Periodontal status was associated with cognitive impairment in a nationally representative sample of US adults

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Beydoun et al., 2020 [50]	Attachment loss and PPD Periodontal pathogens (serum immunoglobulin G titers against 19 periodontal bacteria	Dementia	International Classification of Diseases, Ninth Revision	Retrospective cohort study (26 years)	6823 (44.9% M, 55.1% F)	45 years +	Community	North America (USA)	Moderate	This study provides evidence for an association between periodontal pathogens and AD, which was stronger for older adults
Demmer et al., 2020 [51]	Periodontal Profile Class Centre for Disease Control/ American Academy of Periodontology case definitions	Dementia	National Institute of Aging–Alzheimer's Association work group criteria	Prospective cohort study (20 years)	8275 (45%M, 55% F)	63 years (6)	Community	North America (USA)	High	PD was modestly associated with incident MCI and dementia in a community-based cohort of black and white participants
Bumb et al., 2021 [52]	Loss of attachment > 3 mm	Cognitive decline	MMSE	Prospective cohort study (5 years)	288	70.9 years (4.3) NA	Community	Asia (India)	Moderate	In older population of India, severe PD was independently associated with the development of cognitive decline within 5 years

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
de Oliveira Araújo et al., 2021 [53]	Two or more inter-proximal sites with probing depth ≥ 5 mm and CAL ≥ 5 mm, not on the same tooth, which bled after probing	Dementia	Clinical Dementia Rating MMSE	Case-control	50/52 (48% M, 52% F/21.2%M, 78.8% F)	72.6 years (1.1)/69.8 years (1.0)	Hospital (outpatients)	South America (Brazil)	High	The results of the study suggested that PD was associated with AD
Kim et al., 2021 [54]	Biofilm-gingival interface-index	Cognitive impairment	MMSE	Cross-sectional	140 (34.3% M, 65.7% F)	65 years +	Community	Asia (South Korea)	High	PD was strongly associated with cognitive ability
Holmer et al., 2021 [55]	Swedish Quality Registry for Caries and Periodontal Diseases	Dementia	International Classification of Diseases Tenth Revision	Prospective cohort study (8 years)	37,174 (56.2% M, 43.8% F)	40 years +	Community	Europe (Sweden)	High	In the examined sample, no association was revealed between deep probing pocket depths and the incidence of dementia

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Kim et al., 2022 [56]	International Classification of Diseases, Tenth Revision	Dementia	International Classification of Diseases, Tenth Revision	Retrospective cohort study (13 years)	17,248 (34.1% M, 65.9% F)	60 years +	Community	Asia (South Korea)	High	The authors found a strong association between severe chronic PD and dementia
Kim et al., 2022 [57]	International Classification of Diseases, Tenth Revision	Depression	GDS	Cross-sectional	18,713 (44.7% M, 55.3% F)	66 years	Community	Asia (South Korea)	High	This study confirmed a significant association between depressed mood and chronic PD
Luo et al., 2023 [58]	Centre for Disease Control/ American Academy of Periodontology case definitions	Cognitive impairment	National Institute of Aging–Alzheimer's Association work group criteria	Cross-sectional	5709 (41.9% M, 58.1% F)	50 to 74 years	Community	North America (USA)	High	Severe PD was not associated with MCI after controlling for various confounders

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Marruganti et al., 2023 [59]	Centre for Disease Control/ American Academy of Periodontology case definitions	Cognitive impairment	Word Learning and recall modules from the Consortium to Establish a Registry for Alzheimer's Disease Animal fluency test Digit symbol substitution test Global cognition score	Cross-sectional	2086 (46.7% M, 53.3% F)	68.6 years (0.25)	Community	North America (USA)	High	The findings of the present study suggested the existence of an independent association between PD and low cognitive performance among older adults (≥60 years old)
Carballo et al., 2023 [60]	Centre for Disease Control/ American Academy of Periodontology case definitions	Cognitive decline	Addenbrooke's Cognitive Examination MMSE	Prospective cohort study (2 years)	101 (42.5% M, 57.5% F)	60 years +	Community	Europe (Spain)	High	PD was associated with cognitive decline and its progression in elderly patients with a previous history of hypertension

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Gu et al., 2023 [61]	Centre for Disease Control/ American Academy of Periodontology case definitions	Cognitive impairment Dementia	MMSE Montreal Cognitive Assessment	Cross-sectional	677 (43.7% M, 56.3% F)	66 years (63.68)	Community	Asia (China)	High	Poor periodontal status was strongly associated with worse global cognition performance, especially in the short-term memory and executive domain for the aging population
Yoo et al., 2023 [62]	International Classification of Diseases, Tenth Revision	Dementia	International Classification of Diseases Tenth Revision	Retrospective cohort study (10 years)	2,555,618 (64.5% M, 35.5% F)	55.7 years (10.9)	Community	Asia (South Korea)	High	PD was independently associated with a higher risk of dementia
Gao et al., 2023 [63]	Centre for Disease Control/ American Academy of Periodontology case definitions	Cognitive impairment	Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest Digit Symbol Substitution test Animal fluency test	Cross-sectional	2508 (50.1% M, 49.9% F)	69.3 years (6.7)	Community	North America (USA)	High	This study found a robust bidirectional associations between PD and cognitive function using various modelling approaches among the aging population

Table 1 (continued)

Authors, year (reference)	Periodontal disease assessment tool(s)	Outcome(s)	Outcome assessment tool(s)	Design (follow-up)	*N*	Age (SD)	Setting(s)	Country	Quality assessment	Main findings
Walther et al., 2023 [64]	Centre for Disease Control/ American Academy of Periodontology case definitions	Depression	9-item Patient Health Questionnaire	Cross-sectional	5591 (50% M, 50% F)	62 years (55.69)	Hospital (outpatients)	Europe (Germany)	High	The authors identified a significant association between severe PD and depression severity

SD, standard deviation; *M*, males; *F*, females; *GDS*, Geriatric Depression Scale; *BDI*, Beck Depression Inventory; *CAL*, clinical attachment level; *BOP*, bleeding on probing; *PPD*, probing pocket depth; *REC*, recession; *P. gingivalis*, Porphyromonas gingivalis; *MMSE*, Mini-Mental State Examination; *AD*, Alzheimer's disease; *RABL*, radiographic alveolar bone loss; *MCI*, mild cognitive impairment

parameters for the assessment of PD, such as probing depth, clinical attachment level, and bleeding on probing, with arbitrary cut-off values [22, 24, 26, 27, 29, 32–34, 42–45, 52, 53]. Radiographic alveolar bone loss as an identifying criterion for PD was examined in two studies [19, 38], while two other studies used laboratory data, respectively serum *Porphyromonas gingivalis* (*P. gingivalis*) IgG [25] and serum immunoglobulin G titers against 19 periodontal bacteria [50], to capture evidence of systemic exposure to common PD-causing pathogenic bacterium with well described pathogenicity. Finally, one study used a questionnaire for a self-reported assessment of PD [47].

Assessment tools for adverse health-related outcomes and their distribution across studies

The percentage distribution of the different investigated outcomes is shown in Fig. 2. Given the multiplicity of adverse health-related events observed in two of the 46 selected studies, a total of 48 outcomes were recorded as denominators when calculating the representativeness of each adverse health-related outcome. More specifically, both studies were found to evaluate cognitive impairment and dementia [45, 61]. Overall, cognitive impairment (43.8%, *N*= 21 out of 48) was found to be the most represented outcome, followed by dementia (29.2%, *N*= 14 out of 48) and depression (27.1%, *N*= 13 out of 48).

Regarding the different types of assessment tools, several studies used two or even more instruments to assess the respective outcome(s) (Table 1). For the outcome cognitive impairment, the Mini-Mental State Examination was most frequently adopted (32.5%, *N*= 12) [27, 33, 36–38, 42, 44, 46, 52, 54, 60, 61], followed by the Digit Symbol Substitution Test (10.5%, *N*= 4) [23, 30, 59, 63]. Less represented was the animal fluency test (5%, *N*= 2) [59, 63]. Finally, each of the following assessment tools was used only once (2.6%, *N*= 1, each): the Serial Digit Learning Test and the Story Recall Test [23]; the Immediate and delayed logical verbal memory test, the three word registration/memory task, and the five serial subtractions by intervals of three [25]; the spatial copying task [27]; the digit span test, the picture completion test, and the block design test [30]; the Spanish Society of Neurology Behavioral and Dementia Study Group criteria [32]; the Hasegawa

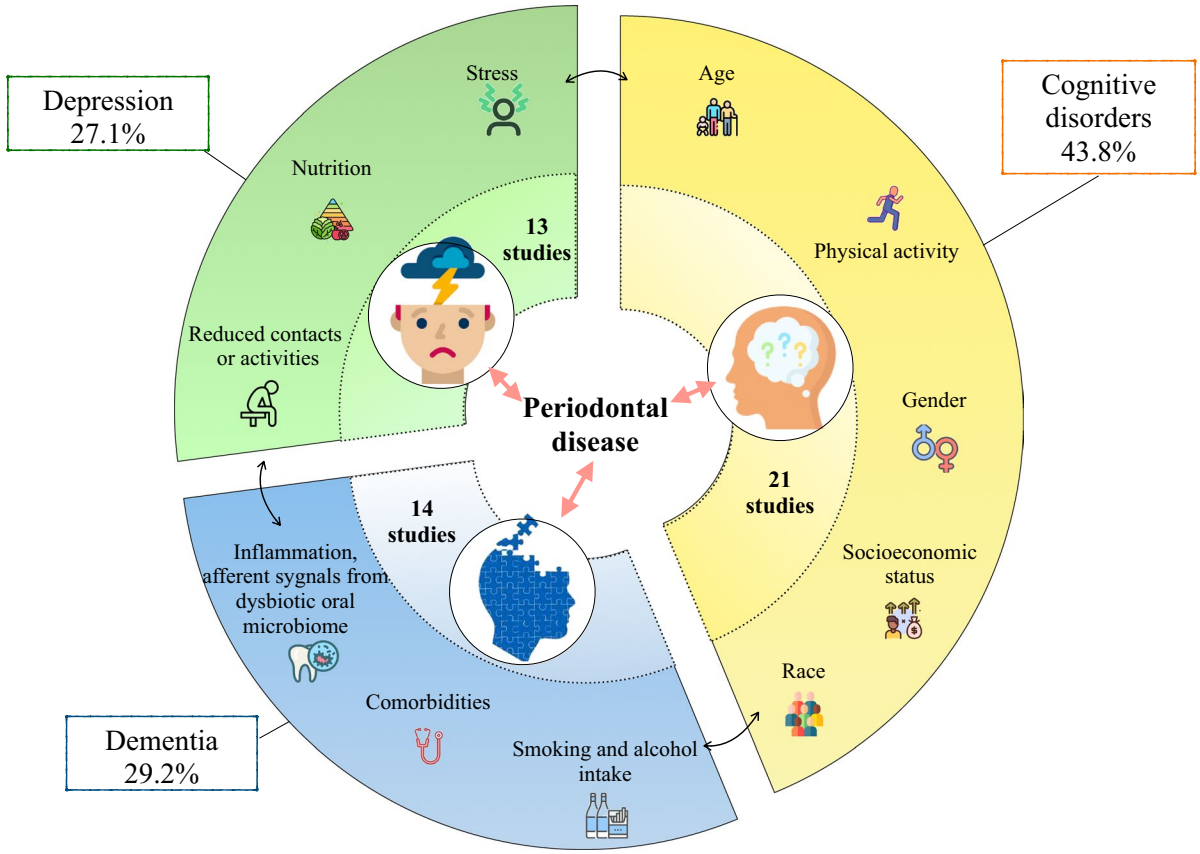


Fig. 2 Percentage distribution of the three different adverse health-related outcomes investigated in the selected studies

Dementia Scale-Revised scores [33]; the clock drawing test [42]; the Petersen/Winblad criteria [45]; the Neurobehavioral Evaluation System 2 [49]; the National Institute of Aging–Alzheimer's Association work group criteria [58]; the Word Learning and recall modules from the Consortium to Establish a Registry for Alzheimer's disease and the global cognition score [59]; the Addenbrooke's Cognitive Examination [60]; the Montreal Cognitive Assessment [61]; and the Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest [63].

For the 14 studies focusing on dementia, the most used assessment tools were the International Classification of Diseases, Ninth Revision [39–41, 50] and the International Classification of Diseases, Tenth Revision [48, 55, 56, 62] (22%, *N*= 4 each), followed by Mini-Mental State Examination [53, 61], and the National Institute of Aging–Alzheimer's Association work group criteria [45, 50] (11.5%, *N*= 2 each). Finally, each used in a single study, the following assessment tools were identified for the diagnosis of dementia (5.5%, *N*= 1 each): the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria and the Hachinski score [28]; DSM-IV criteria and McKeith's consensus criteria [29]; the Montreal Cognitive Assessment [61]; and the Clinical Dementia Rating [53].

For the assessment of depression, the most frequently used tool was the Beck Depression Inventory (20%, *N*= 3) [20, 22, 34], followed by the Geriatric Depression Scale [19, 57], and the Zung Self-Rating Depression Scale [21, 26] (13.2%, *N*= 2 each). The least used tools (6.7%, *N*= 1 each), each adopted in a single study, were the Self-Report Screening Questionnaire-20 [20]; the Hamilton Depression Scale [21]; the Center for Epidemiologic Studies Depression Scale [24]; the World Health Organization Composite International Diagnostic Interview, auto version 2.1 [31]; the International Classification of

Diseases, Ninth Revision [35]; the Patient Health Questionnaire [43]; a self-reported questionnaire [47]; and the 9-item Patient Health Questionnaire [64].

Risk of *bias* across studies and overall quality of evidence for adverse age-related outcomes associated to periodontal disease

Examining all the 46 included studies, we found a moderate (n = 8) to high (n = 38) methodological quality (Table 1). An overview of quality ratings within (panel A) and across studies (panel B) was provided in Fig. 3, highlighting areas with higher or lower risk ratings. Bias was detected predominantly in the domain of blinded assessors (detection bias) (46/46 studies, 100% of studies with a higher risk of bias) and sample size justification (selection bias) (39/46 studies, 85% of studies with a higher risk of bias) and, to a lower extent, in the domains of participation rate (16/46 studies, 35% of studies with a higher risk of bias), multiple exposure (8/46 studies, 17% of studies with a higher risk of bias), and confounding (6/46 studies, 13% of studies with a higher risk of bias) (Fig. 3, panels a–B). Using the GRADE approach, the overall quality of evidence of the three adverse cognitive and depressive outcomes associated to PD was judge moderate for each of the three categories, i.e., cognitive disorders (cognitive impairment and cognitive decline) (n= 21), dementia (n= 14), and depression (n= 13); this is mainly due to the large participation of subjects examined in the various studies and the discrete number of studies conducted for each of the assessed outcomes (Table 2).

Meta-analysis results

Periodontal disease and cognitive disorders

Ten cross-sectional studies, with an overall population of 10,952 subjects, showed a significant association between PD and cognitive impairment (RR 1.25, 95% CI 1.11 to 1.40) with low heterogeneity between the studies (I^2= 20%, p= 0.12) (Fig. 4A), but evidence of small study effect at Egger's test (p=0.01) and asymmetry at funnel plot (Fig. S1A). The trim-and-fill analysis reported that three hypothetical studies were estimated to be missing, when imputed and added to the meta-analysis the overall risk of cognitive impairment associated with the presence of PD was slightly reduced, but still significantly high (RR 1.19, 95% CI 1.06 to 1.34).

Six prospective studies, with an overall population of 1123 subjects, explored the association between PD and risk of cognitive decline during a mean follow-up of 3.5 years (range: 0.5–6 years). PD was associated to higher risk of cognitive decline (RR 3.01, 95% CI 1.52 to 5.95) with significant heterogeneity across the studies (I^2= 84%, p< 0.001) (Fig. 4B), but no evidence of small study effect at Egger's test (p=0.898), neither asymmetry at funnel plot (Fig. S1B). Adjusting the model for mean age at the inclusion and the duration of follow-up, the remaining between-study residual heterogeneity is roughly 60%. We found that there is a significant negative relationship between estimated effect size and age of the population (z= −2.41, p=0.016) (Fig. S2).

Periodontal disease and dementia

Eight studies with an overall population of 3,076,684 subjects, free of dementia at baseline, explored the association between PD and risk of incident dementia during a mean follow-up of 11 years (range 6.6–18.4 years). PD was associated to higher risk of incident dementia (RR 1.22, 95% CI 1.10 to 1.36) with significant heterogeneity across the studies (I^2= 95%, p< 0.001) (Fig. 4C), but no evidence of small study effect at Egger's test (p=0.473) (Fig. S1C). Results did not significantly change in a subgroup analysis by study design, neither adjusting the model for mean age at the inclusion and the duration of follow-up, but heterogeneity reduced among the three prospective studies (I^2= 60%, p= 0.08) (Fig. 4D). The trim-and-fill analysis reported that two hypothetical studies were estimated to be missing. When these two studies were imputed and added to the meta-analysis, the overall risk of dementia associated with the presence of PD further increased (RR 1.29, 95% CI 1.16 to 1.43). One cross-sectional study carried out among 102 subjects (43 with PD) showed significant association between periodontal disease and Alzheimer's disease (AD) (RR 2.92, 95% CI 1.87 to 4.55) [53].

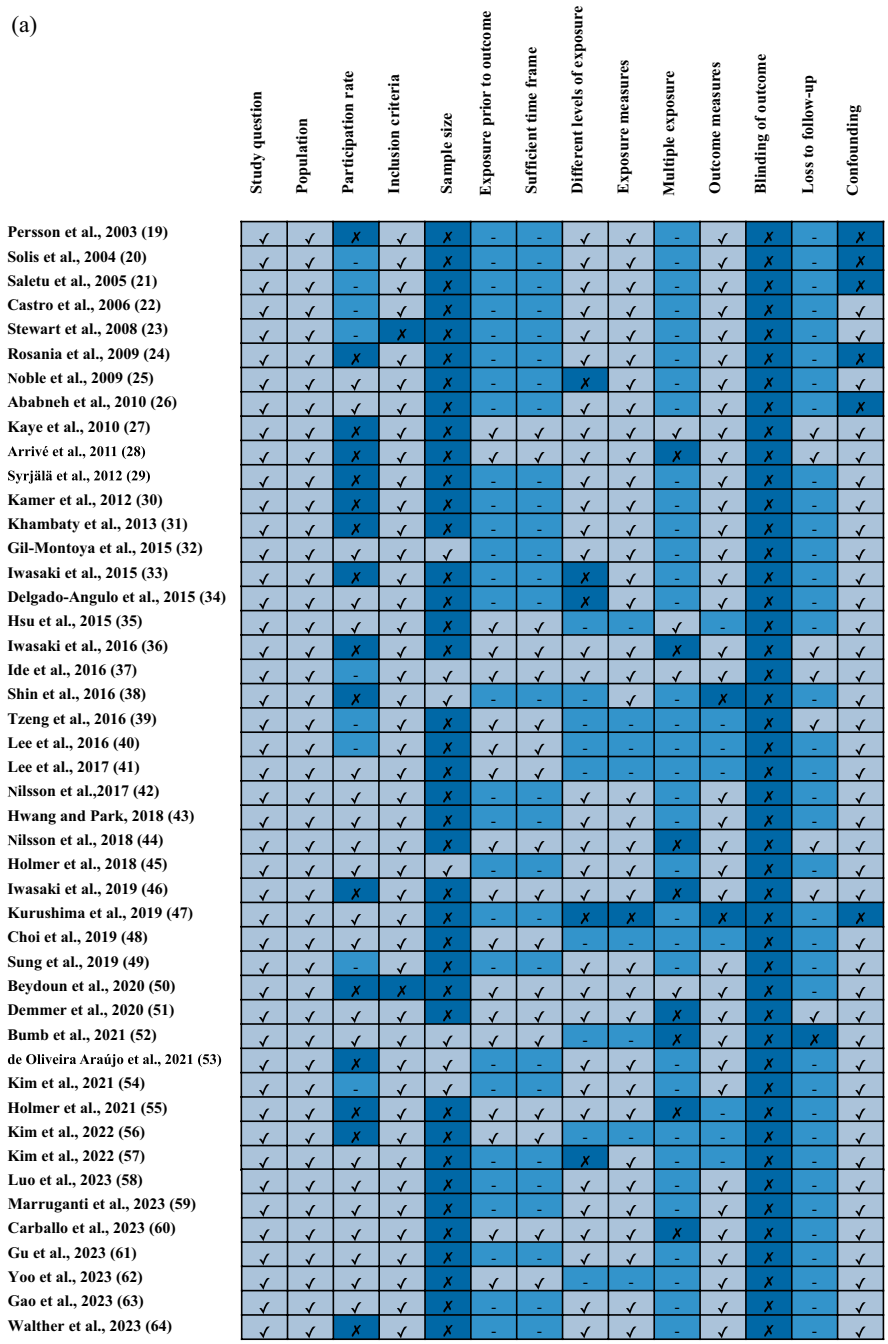
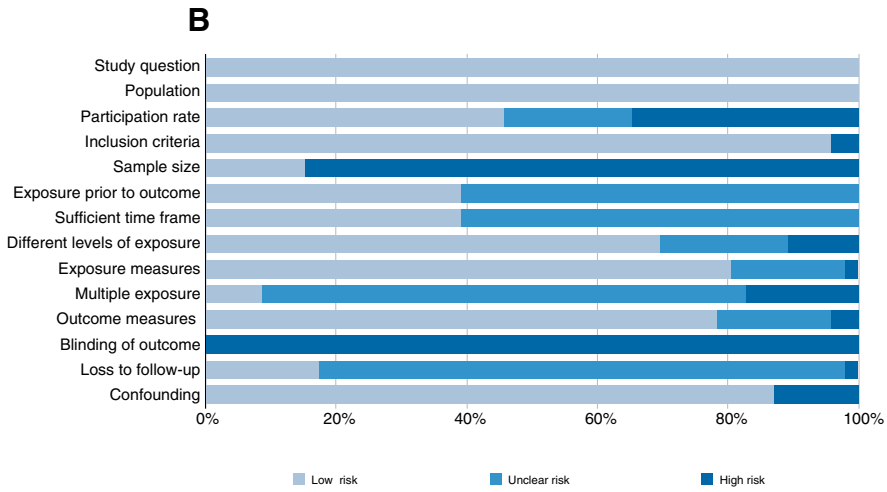


Fig. 3 Methodological quality assessment within studies (panel **a**), and overall quality assessment across studies (panel **B**)

Periodontal disease and depression

Five studies, with an overall population of 29,266 subjects, explored the association between PD and depression. Any significant increased risk of depression was observed among subjects with PD (RR 1.07, 95% CI 0.95 to 1.21) with significant heterogeneity between the studies (I^2= 74%, p= 0.004) (Fig. 4E), but no evidence of small study effect at Egger's test (p=0.944). Mean age difference did not explain such heterogeneity at meta-regression analysis. In a sensitivity analysis, we removed the study by Kurushima et al., which had poorer quality and determined asymmetry at funnel plot (Fig. S1D), and the results did

Fig. 3 (continued)



not change (RR 1.01, 95% CI 0.93 to 1.10), but heterogeneity was reduced (I^2= 43%, p= 0.16). A single retrospective study, with 11 years of follow-up including 63,540 subjects (> 20 years old), found a significant association between periodontal disease and risk of incident depression (HR 1.73, 95% CI 1.58–1.89) [35].

Discussion

In the present systematic review and meta-analysis, we analyzed studies investigating the impact of PD on cognitive disorders (cognitive impairment and cognitive decline), dementia, and depression. Overall, cognitive disorders were the most common outcome related to PD (43.8%), followed by dementia (29.2%), and depression (27.1%). We found that PD was associated with a significantly increased risk of cognitive impairment of 25% in cross-sectional studies and a higher risk of cognitive decline up to threefold during a mean follow-up of 3.5 years. Furthermore, PD was significantly associated with 22% higher risk of incident dementia during a mean follow-up of 11 years. However, we found no significant association between PD and depression.

A number of systematic reviews and meta-analyses have already examined the association of PD with cognitive and depressive disorders [8, 9, 65–77], although none of these studies investigated all the outcomes. For cognitive disorders, in the present study, we found that PD was associated to both cognitive impairment and cognitive decline, with a low heterogeneity in the first case (I^2= 20%), and a significant one in the second (I^2= 84%) even when adjusting the model for mean age at inclusion and duration of follow-up (I^2= 60%). A recent systematic review also found that patients with chronic PD with at least 8 years of exposure were at higher risk of developing cognitive decline and dementia [76]. Another meta-analysis on eight studies showed that subjects with PD had higher risk of MCI, especially those with severe PD [72].

For dementia, in the present study, we found that PD was associated with increased risk of incident dementia, without examining dementia subtypes, i.e., AD or vascular dementia, and there was a remarkable heterogeneity across the studies (I^2= 95%). A previous systematic review including neurodegenerative disease (Parkinson's disease and AD) as the outcome, suggested that all the included studies reported an association between neurodegenerative diseases and PD, although the level of evidence was assessed as very low [70]. Furthermore, previous meta-analyses have confirmed a significant association between poor periodontal health and the incidence of dementia; however, studies with a follow-up period of at least 10 years have suggested that this association may be explained by reverse causality [9, 77]. In other words, poor periodontal health may not necessarily cause dementia, but rather results from it. This finding was reported by Asher and colleagues, and sheds light on the potential limitations of previous studies [9].

Table 2 Summary of findings on periodontal disease (PD) associated with cognitive disorders, dementia, and depression

Cognitive outcomes and depression	Evidence base	Strength of association	Strength of evidence (GRADE)	Comments
Cognitive disorders [23, 25, 27, 30, 32, 33, 38, 42, 44-46, 52, 54, 58-61, 63 36-49,]	Twenty-one studies *n*= 29588	Gingival bleeding vs. Serial Digit Learning Test Score (participants aged 20–59 years): β=0.017, CI=0.002–0.032 Gingival bleeding vs. DSST Score (participants aged 20–59 years): β=0.003, CI=0.001–0.005; Loss of periodontal attachment vs. DSST Score (participants aged 20–59 years): β=0.003, CI=0.001–0.005; Loss of periodontal attachment vs. Serial Digit Learning Test Score (participants aged 20–59 years): β=0.001, CI=0.012–0.012; Gingival bleeding vs. Story Recall score (participants aged >70 years): β=0.002, CI=0.009–0.013; Loss of periodontal attachment vs. Story Recall score (Participants aged >70 years): β=0.003, CI=0.004–0.010 (23) PD (*P. gingivalis* IgG (EU) (>119) vs. cognitive impairment (Immediate verbal memory/ registration): OR=2.57, 95% CI=0.75–8.85; PD (*P. gingivalis* IgG (EU) (>119) vs. cognitive impairment (Delayed verbal memory): OR=3.01, 95% CI=1.06–8.53; PD (*P. gingivalis* IgG (EU) (>119) vs. cognitive impairment (Serial subtraction): OR=2.00, 95% CI=1.19–3.36 (25) Risk per additional tooth lost with alveolar bone loss progression per decade vs. Low MMSE Score: aHR=1.03, 95% CI=1.00–1.07; Risk per additional tooth lost with pocket depth progression per decade vs. Low SCT Score: aHR=1.04, 95% CI=1.01–1.06 (27) Periodontal inflammation status vs. low versus high DSST score: OR=7.00, 95% CI=1.74–28.16; Periodontal inflammation (among participants with 0–10 and 11+ missing teeth) vs. low versus high Block Design score: OR=7.62, 95% CI=1.29–44.89 (30) PD (CAL > 3mm; 33–66% - moderate) vs. cognitive impairment: OR=2.64, 95% CI=1.18-5.92; PD (CAL > 3 mm; 67–100%—severe) vs. cognitive impairment: OR=2.31, 95% CI=1.15–4.66 (32) PD vs. cognitive performance (Hasegawa Dementia Scale-Revised score): OR=4.85, 95% CI=1.29–18.15; PD vs. cognitive performance (MMSE): OR=2.21, 95% CI=1.01–4.84 (33) Severe PD (vs. no severe PD) vs. MMSE score decline: RR=2.1, 95% CI=1.03–4.5 (36) PD vs. change in ADAS-COG, points: r= 4.9, 1.2 to 8.6, p = 0.01; PD vs. change in standardized MMSE, points: r= −1.8, −3.6 to 0.04, p = 0.06 PD vs. cognitive impairment: OR=2.14, 95% CI=1.04–4.41 (37) PD *vs*. cognitive impairment: OR=2.14, 95% CI=1.04–4.41 (38) Number of teeth (1−19) + PD vs. cognitive impairment (MMSE < 25): OR=2.7, 95% CI=1.2–5.9; Number of teeth (1−19) + PD vs. cognitive impairment (MMSE=25–27): OR=1.7, 95% CI=1.0–2.8 (42) Periodontal bone-loss vs. cognitive decline: OR=2.2, 95% CI=1.2−3.8 (44)	⊕⊕⊕ Moderate	Strong association with cognitive disorders (cognitive impairment and cognitive decline), with estimates provided; large sample size and multiple studies included

Table 2 (continued)

Cognitive outcomes and depression	Evidence base	Strength of association	Strength of evidence (GRADE)	Comments
		Number of teeth with probing pocket depth ≥6 mm (≥1) vs. SCD: OR=9.48, 95% CI=3.55–25.33; Number of teeth with probing pocket depth ≥6 mm (≥1) vs. MCI: OR=5.22, 95% CI=2.19–12.44; Marginal alveolar bone loss (generalized) vs. SCD: OR=12.32, 95% CI=1.65–92.19; Marginal alveolar bone loss (generalized) vs. MCI: OR =2.17, 95% CI=0.27–17.58 (45) PD status (EWP definition) (severe) vs. MCI: OR=3.88, 95% CI=2.16−10.86 PD status (CDC/AAP definition) (severe) vs. MCI: OR=2.61, 95% CI=1.08−6.28 (46) Moderate + Severe PD vs. DSST: β= 0.021 (p values for trend = 0.014); Moderate + Severe PD vs. serial digit learning test: β= 0.146 (p values for trend = 0.038) (49) Severe PD vs. cognitive decline: OR=2.31, 95% CI=1.15−4.66 (52) BGI (deep lesion/moderate bleeding) vs. cognitive impairment: $\beta = -0.229$ (p= .030); BGI (deep lesion/severe bleeding) vs. cognitive impairment: $\beta = -0.085$ (p= .387); BGI (deep lesion/low bleeding) vs. cognitive impairment: $\beta = -0.043$ (p= .666) (54) Severe PD vs. MCI: OR=1.00, 95% CI=0.66–1.51 (58) Moderate PD vs. low cognitive performance (DSST < 36): OR=1.66, 95% CI=1.10–2.52; Severe PD vs. low cognitive performance (DSST < 36): OR=2.97, 95% CI=1.56–5.65 (59) PD vs. progression of cognitive impairment: HR=1.8, 95% CI=1.0–3.1; PD vs. poor cognitive performance (MMSE): β= −1.5 (0.6) ($p < .05$) (60) Severity of PD vs. cognitive impairment: OR=0.79, 95% CI=0.57–1.10; Severity of PD vs. MCI: OR=0.80, 95% CI=0.56–1.14 (61) PD vs. memory: OR=0.93, 95% CI=0.87–1.00; PD vs. processing speed: OR=0.88, 95% CI=0.81–0.96; PD vs. global cognitive score: OR=0.95, 95% CI=0.92–0.99(63)		

Table 2 (continued)

Cognitive outcomes and depression	Evidence base	Strength of association	Strength of evidence (GRADE)	Comments
Depression [19–22, 24, 26, 34, 35, 47, 57, 64 31, 43,]	Thirteen studies *n*= 104778	PD vs. depression: OR=1.377, 95% CI=0.869–2.180 (19) Established PD vs. depression (SRQ-20 scores): OR=1.25, 95% CI=0.33–4.78; Established PD vs. depression (BDI scores): OR=057, 95% CI=0.15–2.21 (20) PD vs. Hamilton Depression Scale: *p*= 0.002 (multifactorial analysis of variance); PD vs. Zung Self-Rating Depression Scale: *p*= 0.002 (multifactorial analysis of variance) (21) PD vs. depression (BDI scores): OR=0.963, 95% CI=0.88–1.05 (22) PD (probing depth 5 to 7 mm) vs. depression (CES-D scores): *R*= −0.12; PD (probing depth >7 mm) vs. depression (CES-D scores): *R*= –0.06; PD (CAL >5 to 7 mm) vs. depression (CES-D scores): *R*= 0.08 (24) PD (clinical attachment level > 1 mm) vs. susceptibility to depression (low versus high): OR=0.71, 95% CI=0.48–1.05; PD (probing pocket depth ≥ 3 mm) vs. susceptibility to depression (low versus high): OR=0.87, 95% CI=0.56–1.34 (26) PD vs. major depressive disorder: OR=0.92, 95% CI=0.42–2.02 (31) PD vs. depression: OR=0.96, 95% CI=0.88,1.05 (34) PD status vs. depression: HR=1.73, 95% CI=1.58–1.89 (35) Any PD vs. self-report depression: OR=0.893, 95% CI=0.667–1.196; Severe PD vs. diagnosed depression: OR=0.960, 95% CI= 0.705-1.308 (43) PD vs. depression: OR=1.50, 95% CI=1.18, 1.91 (47) Chronic PD vs. depressive mood: OR=1.12, 95% CI=1.06–1.19 (57) Severe PD vs. depression severity: *β*= −0.01 (−0.02–0.00) (*p* =.006) (64)	⊕⊕⊕ Moderate	Strong association with depression, with estimates provided; very large sample size and multiple studies included

Table 2 (continued)

Cognitive outcomes and depression	Evidence base	Strength of association	Strength of evidence (GRADE)	Comments
Dementia [28, 29, 39–41, 45, 50, 53, 56, 62 48, 51, 55, 61,]	Fourteen studies *n*= 3086886	Periodontal status (bleed/calculus) vs. dementia (higher school level): HR=0.71, 95% CI=0.31–1.63; Periodontal status (pockets) vs. dementia (higher school level): HR=0.42, 95% CI=0.15–1.15; Periodontal status (no eligible sextant) vs. dementia (higher school level): HR=1.51, 95% CI=0.63–3.57; Periodontal status (bleed¢alculus) vs. dementia (lower school level): HR=1.24, 95% CI=0.39–3.88; Periodontal status (pockets) vs. dementia (lower school level): HR=0.97, 95% CI=0.29–3.19; Periodontal status (no eligible sextant) vs. dementia (lower school level): HR=1.02, 95% CI=0.28–3.66 (28) Number of teeth with deep periodontal pockets (≥ 4 mm) vs. AD: RR=1.4, 95% CI=0.9–2.1; Number of teeth with deep periodontal pockets (≥ 4 mm) vs. other types of dementia: RR=2.5, 95% CI=1.5–4.1 (29) Chronic gingivitis/chronic periodontitis vs. dementia: HR=2.540, 95% CI=1.552–4.156 (39) PD vs. dementia: HR=1.16, 95% CI=1.01–1.32 (40) PD with tooth extraction vs. dementia: HR=1.10, 95% CI=1.04–1.16 (41) Number of teeth with probing pocket depth ≥6 mm (≥1) vs. AD: OR=15.12, 95% CI=5.93–38.58; Marginal alveolar bone loss (generalized) vs. AD: OR=5.99, 95% CI=1.02–35.13 (45) Chronic PD vs. dementia: aHR=1.06, 95% CI=1.01–1.11; Chronic PD vs. AD: aHR==1.06, 95% CI=1.01–1.12; Chronic PD vs. vascular dementia: aHR=1.09, 95% CI=0.97–1.22 (48) Composite of *Campylobacter rectus* and *P. gingivalis* titers (per SD) vs. AD incidence: aHR=1.22, 95% CI=1.04–1.43 (50) Severe tooth loss and PD (by periodontal profile classes classification) vs. incident dementia: HR=1.25, 95% CI=1.11–1.42 (51) PD vs. AD diagnosis: OR=11.08, 95% CI=3.99–30.75 (53) Deep probing pocket depths vs. dementia: HR=1.13, 95% CI=0.39–3.24 (55) Severe chronic periodontitis vs. dementia: HR=1.15, 95% CI=1.04, 1.27 (56) Severity of PD vs. dementia: OR=0.86, 95% CI=0.40–1.83 (61) PD vs. all-cause dementia: HR=1.07, 95% CI=1.04–1.09; PD vs. AD: HR=1.09, 95% CI=1.06–1.13 (62)	⊕⊕⊕ Moderate	Strong association with dementia, with estimates provided; very large sample size and multiple studies included

CI, confidence interval; *OR*, odds ratio; *HR*, hazard ratio; *EU*, ELISA Units; *P. gingivalis*, Porphyromonas gingivalis; *MMSE*, Mini-Mental State Examination; *SCT*, spatial copying task; *CAL*, clinical attachment loss; *SCD*, subjective cognitive decline; *MCI*, mild cognitive impairment; *EWP*, European Workshop in Periodontology; *CDC/AAP*, Centers for Disease Control/American Academy of Periodontology; *BGI*, Biofilm-Gingival Interface; *DSST*, Digit Symbol Substitution Test; *SRQ-20*, Self-Report Screening Questionnaire-20; *BDI*, Beck Depression Inventory; *PD*, probing depth; *CES-D*, Center for Epidemiologic Studies Depression Scale; *ADAS-cog*, Alzheimer's Disease Assessment Scale; *AD*, Alzheimer's disease

However, some systematic reviews and meta-analyses including a few longitudinal studies indicated that exposure to PD was not related to the risk of incident AD [66, 72]. It is possible that the partially conflicting results regarding the link between PD and AD are due to variations in the number of studies included. Additionally, observational studies examining this relationship often had a high level of heterogeneity and may be affected by confounding factors. In fact, a recent meta-analysis suggested that confounding factors were not adequately considered in over 50% of the articles that investigating this connection [75].

For depression, in the present meta-analysis of cross-sectional studies, we found that PD was not associated with an increased risk of depression. The present high heterogeneity could not be explained by population age, but probably related to difference in residual confounders as assessment tools for depression and onset of depressive disorders (young adults vs. late-life). Previous studies have mainly explored the inverse relationship, showing conflicting results on PD risk between subjects with or without depression, but confirming a great heterogeneity among the studies [8, 69]. Moreover, a recent systematic review provided a novel perspective to evaluate the impact of stress-related disorders on the progression of PD, examining the growing body of evidence of stress as a risk indicator for PD progression and assessing the presence of biomarkers [68]. According to this systematic review, the use of salivary pro-inflammatory cytokines alone was found to be inadequate for identifying the severity or progression of PD, with or without the presence of stress-related diseases. However, this study did observe a positive qualitative correlation in the selected study between stress-related biomarkers and the severity of PD [68].

The mechanisms underlying the possible associations between PD and different cognitive and depressive disorders are, at present, not fully understood. The association of PD with cognitive disorders/dementia may be explained by neuropathology and the biological mechanism triggered by PD. In fact, this disorder can challenge the brain with intact bacteria and inflammatory mediators due to daily, transient bacteremias, and chronic periodontitis of 10 years' duration was reported to double the risk of AD [39]. Studies have shown that the bacteria involved in periodontal disease can enter the bloodstream and travel to the brain [12, 78], triggering an immune response that may contribute to the development of dementia. The best-known bacterial species comprise the so-called "red complex," *P. gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, which are associated with diseased sites in the mice [79, 80]. Periodontal diseases may also affect the brain via neural pathways [13]; moreover, inflammatory molecules induced by periodontal diseases may affect the blood and brain [14], and, finally, tooth loss due to periodontal diseases and reduced masticatory function may affect cognitive function [11]. Furthermore, chronic inflammation caused by periodontal disease has been linked to the formation of amyloid-β plaques in the brain [81], which are a hallmark of AD. A recent systematic review of only preclinical studies exploring the biological links between periodontal disease and AD pathology suggested that oral or systemic exposure to periodontopathogens or their byproducts may be responsible for both in situ brain manifestations and systemic effects contributing to neuroinflammation, amyloidosis, and tau phosphorylation, leading to brain damage and subsequent cognitive impairment [82]. In addition to the direct biological mechanisms, PD has also been associated with risk factors for dementia, such as cardiovascular disease and diabetes. Poor oral health can exacerbate these conditions, further increasing the risk of cognitive decline and dementia. Finally, also gender and socioeconomic status can be common risk factors associated with both dementia and PD and can underlie and partially explain the associations between these two conditions [77, 83]. In fact, people with a lower socioeconomic status and those with a poor education level and women [83, 84] have poorer cognitive functioning in later life [85]. At the same time, the prevalence and risk estimates of cognitive disorders in association with PD can be influenced by gender [77]. Low socioeconomic status also leaded to the adoption of unhealthy behaviors, such as smoking and drinking [83, 86], and these lifestyle behaviors increased PD manifestation [83, 87].

For the links between PD and depression, chronic stress and depressive symptoms have been hypothesized to reduce immune responsiveness, resulting in a higher rate of infection with pathogenic organisms and a greater degree of periodontal tissue destruction [8]. In general, the evidence was consistent with

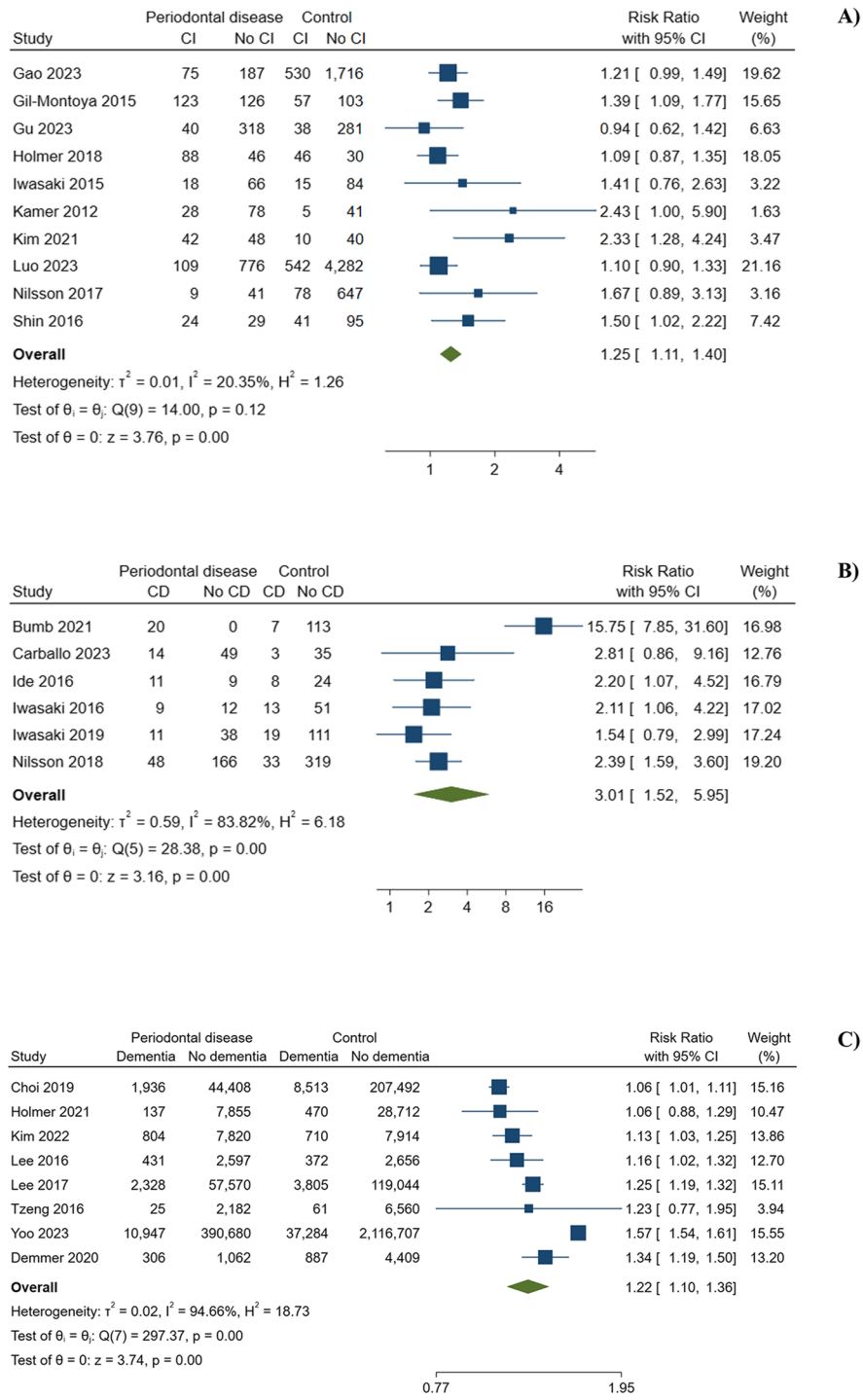
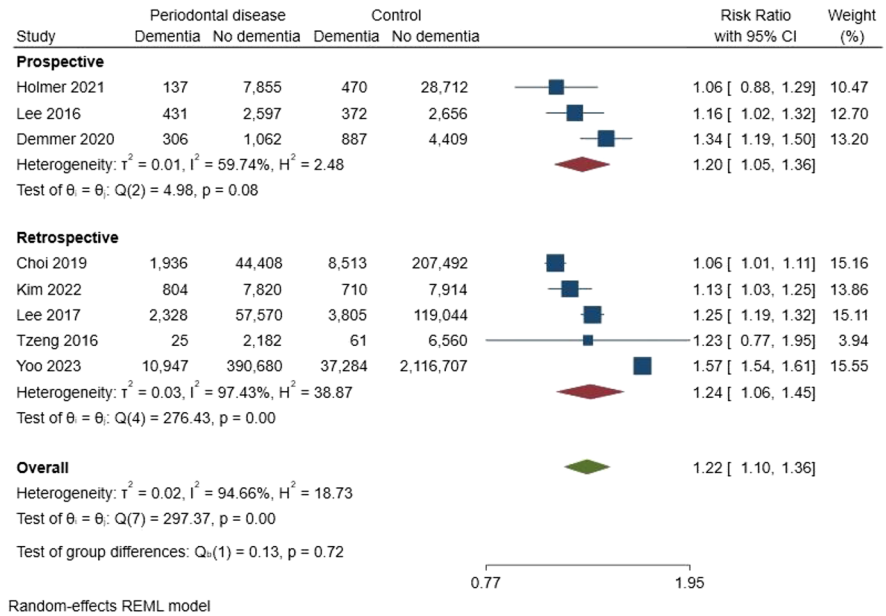


Fig. 4 Meta-analysis for association between periodontal disease, depression, and cognitive-related outcomes: forest plot of the association between periodontal disease and cognitive impairment in cross-sectional studies (**A**); forest plot of the association between periodontal disease and cognitive decline in longitudinal studies (**B**); forest plot of the association between periodontal disease and dementia (**C**); forest plot of the subgroup analysis by study design of the association between periodontal disease and dementia (**D**); forest plot of the subgroup analysis by study design of the association between periodontal disease and depression (**E**)

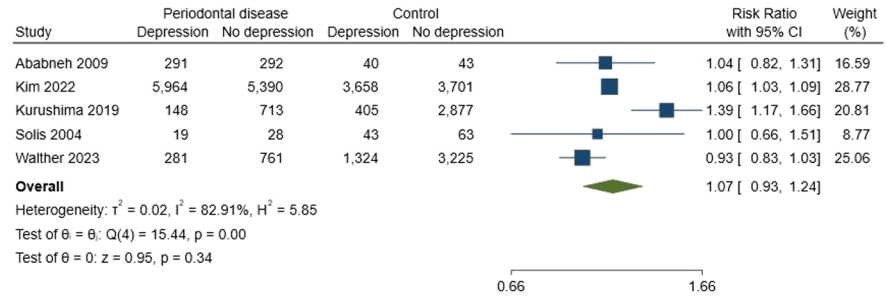
the hypothesis that stress in patients susceptible to PD can modify the host immune defense and permit the progression of periodontal infections [88]. However, substantial evidence also indicated that these conditions can mediate risk for disease, including PD, through changes in health-related behaviors, such as oral hygiene, smoking, and diet [89, 90]. The immune-inflammatory contribution of PD to

Fig. 4 (continued)

D)



E)



depression, but whether biomarkers may mediate the associations between PD and major depression, was unclear [91].

The present article covered the whole spectrum of cognitive deterioration including depression and excluding from the definition of PD the tooth loss that may be related to reasons other than PD. We must also acknowledge some limitations. Statistical heterogeneity may be a consequence of clinical heterogeneity, considering how a variety of clinical and classification criteria have been used in the various studies in the evaluation of PD. For example, the cut-off levels adopted for clinical attachment level, probing depth, and bleeding on probing were often arbitrary. In the same way, numerous tests, tools, and classifications were used for the assessment of the three explored outcomes. Furthermore, only a single longitudinal study with retrospective design and not exploring specifically late-life depression was found on the association between PD and incident depression. Therefore, further studies are needed to verify the potential impact of PD on late-life depression. Finally, we did not have subgroup analyses taking into account PD-causing pathogens or including only older subjects, given that some of the selected studies had a broader age range.

In conclusion, the present systematic review and meta-analysis suggested a significant association between PD and cognitive impairment and decline. Furthermore, PD was significantly associated with

a higher risk of incident dementia. Conversely, evidence on the relationship between PD and depression was still inconclusive. Future studies should utilize bias-reducing selection methods, i.e., inverse probability weighting and random sampling, of large and representative study populations with validated PD assessment tools and more specific criteria for disorders in different cognitive domains to reduce the current heterogeneity.

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Declarations

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Competing interests The authors declare no competing interests.

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