Research, Society and Development, v. 11, n. 5, e15811527931, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i5.27931

Is the history of periodontal disease a risk factor for cognitive decline? Systematic Review and Meta-analysis

A história de doença periodontal é um fator de risco para o declínio do estado cognitivo? Revisão Sistemática e Meta-análise

¿Es el antecedente de enfermedad periodontal un factor de riesgo para el deterioro del estado cognitivo? Revisión sistemática y metanálisis

Received: 03/10/2022 | Reviewed: 03/18/2022 | Accept: 03/26/2022 | Published: 04/01/2022

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Abstract
The aim of the study was to verify through a systematic review and meta-analysis whether the History of Periodontal Disease (HPD) is a risk factor for cognitive decline. Bibliographic searches in PubMed, Scopus, Web of Science and Cochrane databases totaled 378 records, after removing duplicates. Observational studies that verified HPD and/or tooth loss (≥22) resulting from HPD were selected to investigate an association with the decline in cognitive status. The quantitative synthesis resulted in two meta-analyzes (MA). MA1 (n=5) considered measures of association between HPD and decreased cognitive status; while MA2 (n=7) considered measures of association between tooth loss and decreased cognitive status. Meta-analyses were performed using the OpenMetaAnalyst software, using dichotomous random effects ($p<0.05$). Both meta-analyses showed that periodontal disease (OR=3.371; 95% CI=1.823-6.232; I^2=65.42%) and tooth loss (OR=1.875; 95% CI=1.355-2.596; I^2=56.74%) were related to the decline in cognitive status, as measured by the Mini-Mental State Examination. Patients with HPD and tooth loss resulting from periodontitis are more likely to deteriorate cognitive status, with possible association with Alzheimer's Disease.
Keywords: Alzheimer disease; Cognitive dysfunction; Periodontal diseases; Tooth loss.

Resumo
O objetivo do estudo foi verificar através de uma revisão sistemática e meta-análise se a História da Doença Periodontal (HPD) é um fator de risco para declínio cognitivo. As buscas bibliográficas nas bases de dados PubMed, Scopus, Web of Science e Cochrane totalizaram 378 registros, após a retirada das duplicatas. Estudos observacionais que verificaram HPD e/ou perda dentária (≥22) resultante de HPD foram selecionados para investigar uma associação com o declínio do estado cognitivo. A síntese quantitativa resultou em duas meta-análises (MA). MA1 (n=5) considerou medidas de associação entre HPD e diminuição do estado cognitivo; enquanto MA2 (n=7) considerou medidas de associação entre perda dentária e diminuição do estado cognitivo. As meta-análises foram realizadas no software OpenMetaAnalyst, usando efeitos aleatórios dicotômicos ($p<0,05$). Ambas as meta-análises mostraram que a doença periodontal (OR=3,371; IC 95%=1,823-6,232; I^2=65,42%) e a perda dentária (OR=1,875; IC 95%=1,355-2,596; I^2=56,74%) o declínio do estado cognitivo, medido pelo Mini-Exame do Estado Mental. Pacientes com HPD e

perda dentária resultante de periodontite são mais propensos a deteriorar o estado cognitivo, com possível associação com a Doença de Alzheimer.
Palavras-chave: Doença de Alzheimer; Declínio cognitivo; Doença periodontal; Perda de dente.

Resumen
El objetivo del estudio fue verificar a través de una revisión sistemática y un metanálisis si la Historia de la Enfermedad Periodontal (HPD) es un factor de riesgo para el deterioro cognitivo. Las búsquedas bibliográficas en las bases de datos PubMed, Scopus, Web of Science y Cochrane totalizaron 378 registros, después de eliminar los duplicados. Se seleccionaron estudios observacionales que verificaron HPD y/o pérdida de dientes (≥22) como resultado de HPD para investigar una asociación con la disminución del estado cognitivo. La síntesis cuantitativa resultó en dos metanálisis (MA). MA1 (n=5) consideró medidas de asociación entre HPD y disminución del estado cognitivo; mientras que MA2 (n=7) consideró medidas de asociación entre la pérdida de dientes y la disminución del estado cognitivo. Los metanálisis se realizaron utilizando el software OpenMetaAnalyst, utilizando efectos aleatorios dicotómicos ($p<0,05$). Ambos metanálisis mostraron que la enfermedad periodontal (OR=3,371; IC 95%=1,823-6,232; I^2=65,42%) y la pérdida de dientes (OR=1,875; IC 95%=1,355-2,596; I^2=56,74%) estaban relacionadas con el declive en el estado cognitivo, medido por el Mini-Examen del Estado Mental. Los pacientes con HPD y pérdida de dientes como resultado de la periodontitis tienen más probabilidades de deteriorar el estado cognitivo, con una posible asociación con la enfermedad de Alzheimer.
Palabra clave: Enfermedad de Alzheimer; Disfunción cognitiva; Enfermedad periodontal; Pérdida de diente.

1. Introduction

Periodontal diseases encompass a series of chronic and multifactorial inflammatory conditions of the gingiva, periodontal ligament and alveolar bone, which are the protective and supporting tissues of the periodontium (Kinane et al., 2017). It is one of the oral diseases that most contributes to the burden of chronic diseases. It can induce an aggressive immune response, which has been associated with increased systemic inflammation, indicated by high levels of C-reactive protein and interleukin-6 (Gargano & Hugues, 2014; Cardoso et al., 2018). As it is an infection with a high prevalence, affecting between 20 and 50% of the world population, it represents a major public health problem (Leyra et al., 2014). In addition to affecting a large portion of the population, periodontal disease is associated with about 50 systemic diseases, which can affect different groups and age groups (Beck et al., 2019).

Recent studies suggest that periodontal disease is associated with an increased severity of dementia and a faster cognitive decline in Alzheimer's disease (Ide et al., 2016). The relation between both diseases can be in the invasion of the brain tissue by periodontal bacteria such as *Porphyromonas gingivalis, Fornery of Tannerella, Aggregatibacter actinomycetemcomitans, Treponema denticola* and their products. This invasion can occur through the bloodstream or via peripheral nerves (Leyra et al., 2014).

Thus, both pathogenic microorganisms of periodontal disease, as well as the host's response to inflammation, cause an increase in the levels of pro-inflammatory cytokines. These pro-inflammatory molecules are able to compromise the blood-brain barrier (BBB) and enter the brain regions, leading to adverse repercussions that cause neuronal damage, causing or accelerating neuroinflammation, a process present in Alzheimer's disease (Abbayya et al., 2015).

Estimates show that by 2050, dementia will affect approximately 131.5 million people worldwide (Loughrey et al., 2018). With the aging of the world population, dementia and cognitive decline become more frequent and should be considered public health problems. Currently, approaches aimed at neuropathological processes, such as Alzheimer's disease, offer limited benefits, with only symptom-modifying effects. There are risk factors considered non-modifiable, such as age, genetic markers and family history. However, oral infections such as periodontal disease, for example, can be prevented in order to reduce the risk of developing cognitive decline (Cestari et al., 2016). Elucidating risk factors for the progression of this disease would facilitate the development of preventive strategies that may be more beneficial to the patient.

Therefore, the objective of this systematic review is to verify whether periodontal disease is shown to be a risk factor for the decline in cognitive status.

2. Methodology

2.1 Study design

This review was prepared according to the protocol established for Systematic Reviews and Meta-analyses proposed by the Preferred Reporting Items for Systematic Reviews (PRISMA) with a Patient or Population, Exposure, Control or Comparison, Result or Outcome (PECO) approach. The following research question was formulated to address the literature search strategy: Are patients with a history of periodontal disease more likely to have cognitive decline?

The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) CRD42019131839.

Bibliographic searches were performed on the bases PubMed, Scopus, Web of Science and Cochrane (Table 1), the records were downloaded and organized on the Mendeley platform, a desktop and web program produced by Elsevier to manage and share research documents and totaled 378 records, after removing duplicates.

Table 1: Search strategy in PubMed, Scopus, Web of Science and Cochrane.

Base de dados	**Chave de busca**
Medline-PubMed (n=106)	((Periodontitis[MeSH Terms]) OR (Periodontitides[Title/Abstract])) OR (Pericementitis[Title/Abstract])) OR (Pericementitides[Title/Abstract])) OR (Aggressive Periodontitis[MeSH Terms])) OR (Juvenile Periodontitis[Title/Abstract])) OR (Prepubertal Periodontitis[Title/Abstract])) OR (Early-Onset Periodontitis[Title/Abstract])) OR (Circumpubertal Periodontitis[Title/Abstract])) OR (Periodontosis[Title/Abstract])) OR (Periodontoses[Title/Abstract])) OR (Chronic Periodontitis[MeSH Terms])) OR (Chronic Periodontitides[Title/Abstract])) OR (Adult Periodontitis[Title/Abstract])) OR (Adult Periodontitides[Title/Abstract])) OR (Tooth Loss[MeSH Terms])) AND (Dementia[MeSH Terms])) OR (Dementias[Title/Abstract])) OR (Amentia[Title/Abstract])) OR (Amentias[Title/Abstract])) OR (Senile Paranoid Dementia[Title/Abstract])) OR (Senile Paranoid Dementias[Title/Abstract])) OR (Familial Dementia[Title/Abstract])) OR (Familial Dementias[Title/Abstract])) OR (Alzheimer Disease[MeSH Terms])) OR (Alzheimer's Disease[Title/Abstract])) OR (Dementia, Senile[Title/Abstract])) OR (Senile Dementia[Title/Abstract])) OR (Alzheimer Type Dementia[Title/Abstract])) OR (Alzheimer-Type Dementia (ATD[Title/Abstract]))) OR (Alzheimer Type Dementia (ATD[Title/Abstract]))) OR (Alzheimer Type Senile Dementia[Title/Abstract])) OR (Primary Senile Degenerative Dementia[Title/Abstract])) OR (Alzheimer Sclerosis[Title/Abstract])) OR (Alzheimer Syndrome[Title/Abstract])) OR (Alzheimer Dementia[Title/Abstract])) OR (Alzheimer Dementias[Title/Abstract])) OR (Dementia, Alzheimer[Title/Abstract])) OR (Senile Dementia, Alzheimer Type[Title/Abstract])) OR (Acute Confusional Senile Dementia[Title/Abstract])) OR (Presenile Dementia[Title/Abstract])) OR (Late Onset Alzheimer Disease[Title/Abstract])) OR (Focal Onset Alzheimer's Disease[Title/Abstract])) OR (Familial Alzheimer Disease (FAD[Title/Abstract]))) OR (Familial Alzheimer Diseases (FAD[Title/Abstract]))) OR (Early Onset Alzheimer Disease[Title/Abstract])) OR (Presenile Alzheimer Dementia[Title/Abstract])) OR (Neurocognitive Disorders[MeSH Terms])) OR (Neurocognitive Disorder[Title/Abstract])) OR (Nonpsychotic Organic Brain Syndrome[Title/Abstract])) OR (Traumatic Psychoses[Title/Abstract])) OR (Organic Mental Disorder[Title/Abstract])) OR (Organic Mental Disorders[Title/Abstract])) OR (Kandinsky Syndrome[Title/Abstract])) OR (Clerambault Syndrome[Title/Abstract])

Scopus (n=117)	TITLE-ABS-KEY(Periodontitis OR Periodontitides OR Pericementitis OR Pericementitides OR "Aggressive Periodontitis" OR "Juvenile Periodontitis" OR "Prepubertal Periodontitis" OR "Early-Onset Periodontitis" OR "Circumpubertal Periodontitis" OR Periodontosis OR Periodontoses OR "Chronic Periodontitis" OR "Chronic Periodontitides" OR "Adult Periodontitis" OR "Adult Periodontitides" OR "Tooth Loss") AND TITLE-ABS-KEY (Dementia OR Dementias OR Amentia OR Amentias OR "Senile Paranoid Dementia" OR "Senile Paranoid Dementias" OR "Familial Dementia" OR "Familial Dementias" OR "Alzheimer Disease" OR "Alzheimer's Disease" OR "Dementia, Senile" OR S"enile Dementia" OR "Alzheimer Type Dementia" OR "Alzheimer-Type Dementia (ATD)" OR "Alzheimer Type Dementia (ATD)" OR "Alzheimer Type Senile Dementia" OR "Primary Senile Degenerative Dementia" OR "Alzheimer Sclerosis" OR "Alzheimer Syndrome" OR "Alzheimer Dementia" OR "Alzheimer Dementias" OR "Dementia, Alzheimer" OR "Senile Dementia, Alzheimer Type" OR "Acute Confusional Senile Dementia" OR "Presenile Dementia" OR "Late Onset Alzheimer Disease" OR "Focal Onset Alzheimer's Disease" OR "Familial Alzheimer Disease (FAD)" OR "Familial Alzheimer Diseases (FAD)" OR "Early Onset Alzheimer Disease" OR "Presenile Alzheimer Dementia" OR "Neurocognitive Disorders" OR "Neurocognitive Disorder" OR "Nonpsychotic Organic Brain Syndrome" OR "Traumatic Psychoses" OR "Organic Mental Disorder" OR "Organic Mental Disorders" OR "Kandinsky Syndrome" OR "Clerambault Syndrome")
Web of Science (n=163)	TS=(Periodontitis OR Periodontitides OR Pericementitis OR Pericementitides OR "Aggressive Periodontitis" OR "Juvenile Periodontitis" OR "Prepubertal Periodontitis" OR "Early-Onset Periodontitis" OR "Circumpubertal Periodontitis" OR Periodontosis OR Periodontoses OR "Chronic Periodontitis" OR "Chronic Periodontitides" OR "Adult Periodontitis" OR "Adult Periodontitides" OR "Tooth Loss") AND TS=(Dementia OR Dementias OR Amentia OR Amentias OR "Senile Paranoid Dementia" OR "Senile Paranoid Dementias" OR "Familial Dementia" OR "Familial Dementias" OR "Alzheimer Disease" OR "Alzheimer's Disease" OR "Dementia, Senile" OR S"enile Dementia" OR "Alzheimer Type Dementia" OR "Alzheimer-Type Dementia (ATD)" OR "Alzheimer Type Dementia (ATD)" OR "Alzheimer Type Senile Dementia" OR "Primary Senile Degenerative Dementia" OR "Alzheimer Sclerosis" OR "Alzheimer Syndrome" OR "Alzheimer Dementia" OR "Alzheimer Dementias" OR "Dementia, Alzheimer" OR "Senile Dementia, Alzheimer Type" OR "Acute Confusional Senile Dementia" OR "Presenile Dementia" OR "Late Onset Alzheimer Disease" OR "Focal Onset Alzheimer's Disease" OR "Familial Alzheimer Disease (FAD)" OR "Familial Alzheimer Diseases (FAD)" OR "Early Onset Alzheimer Disease" OR "Presenile Alzheimer Dementia" OR "Neurocognitive Disorders" OR "Neurocognitive Disorder" OR "Nonpsychotic Organic Brain Syndrome" OR "Traumatic Psychoses" OR "Organic Mental Disorder" OR "Organic Mental Disorders" OR "Kandinsky Syndrome" OR "Clerambault Syndrome")
Cochrane (n=1)	#1 MeSH descriptor: [Periodontitis] in all MeSH products #2 Periodontitides OR Pericementitis OR Pericementitides #3 MeSH descriptor: [Aggressive Periodontitis] explode all trees #4 "Juvenile Periodontitis" OR "Prepubertal Periodontitis" OR "Early-Onset Periodontitis" OR "Circumpubertal Periodontitis" OR Periodontosis OR Periodontoses #5 MeSH descriptor: [Chronic Periodontitis] explode all trees #6 "Chronic Periodontitides" OR "Adult Periodontitis" OR "Adult Periodontitides" #7 MeSH descriptor: [Tooth Loss] explode all trees #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 MeSH descriptor: [Dementia] explode all trees
#10 Dementias OR Amentia OR Amentias OR “Senile Paranoid Dementia” OR “Senile Paranoid Dementias” OR “Familial Dementia” OR “Familial Dementias”
#11 MeSH descriptor: [Alzheimer Disease] explode all trees
#12 “Alzheimer's Disease” OR “Dementia, Senile” OR “Senile Dementia” OR “Alzheimer Type Dementia” OR “Alzheimer-Type Dementia (ATD)” OR “Alzheimer Type Dementia (ATD)” OR “Alzheimer Type Senile Dementia” OR “Primary Senile Degenerative Dementia” OR “Alzheimer Sclerosis” OR “Alzheimer Syndrome” OR “Alzheimer Dementia” OR “Alzheimer Dementias” OR “Dementia, Alzheimer” OR “Senile Dementia, Alzheimer Type” OR “Acute Confusional Senile Dementia” OR “Presenile Dementia” OR “Late Onset Alzheimer Disease” OR “Focal Onset Alzheimer's Disease” OR “Familial Alzheimer Disease (FAD)” OR “Familial Alzheimer Diseases (FAD)” OR “Early Onset Alzheimer Disease” OR “Presenile Alzheimer Dementia”
#13 MeSH descriptor: [Neurocognitive Disorders] explode all trees
#14 “Neurocognitive Disorder” OR “Nonpsychotic Organic Brain Syndrome” OR “Traumatic Psychoses” OR “Organic Mental Disorder” OR “Organic Mental Disorders” OR “Kandinsky Syndrome” OR “Clerambault Syndrome”
#15 #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16 #8 AND #15

Source: Authors.

2.2 Data extraction and quality assessment

The studies were then selected by assessing the titles and abstracts identified in the initial search. This selection was carried out by two researchers, independently and blindled (M.L.B.R. and R.O.S), strictly obeying the inclusion and exclusion criteria defined in the research protocol. When the title and abstract were not clarified, it was necessary to seek the entire article for reading. Observational studies that verified PDH and/or tooth loss (≥22) were included to investigate an association with decline in cognitive status, when assessed by MMSE. Literature reviews, editorials, case reports, case series and analytical studies were excluded.

In sequence, the methodological quality and the risk of bias in the studies were evaluated, using the list of guidelines described by Fowkes and Fulton (Fowkes; Fulton, 1991), which allows the classification of cross-sectional studies, cohort, clinical trials and case-control studies, in addition to containing questions about the study design, sample, control group, quality of evaluation and results, integrity and distortion of influences.

For data extraction, a standardized form was used, and included the following information about the studies: author (s) and year of publication, type of study, period of collection, country or place of collection, sample size, method of evaluation of periodontal disease (tooth loss or probing depth) and method of assessing dementia/cognitive decline, results obtained (OR, RR, RP), and the method of statistical analysis used.

Methodological quality analysis was performed to determine the articles that would be used for quantitative analysis (meta-analysis).

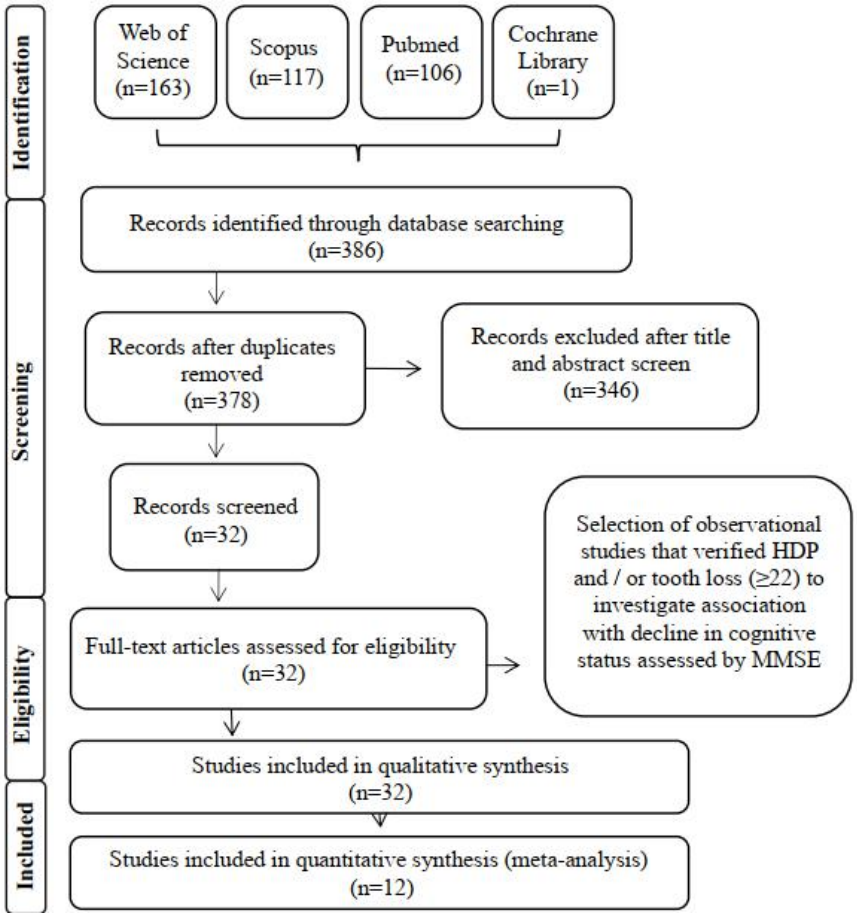
2.3 Statistical analysis

In the meta-analysis, measurements of accuracy, sensitivity and specificity were extracted. To do so, the heterogeneity of the studies was first investigated (Cochran's Q). Quantitative synthesis with a random effect was performed. All statistical analyses were performed using the Open Meta Analyst software, adopting a significance level of 5%.

3. Results

The study selection process is presented in the flowchart of the research results in the databases (Figure 1). A total of 387 records were identified in the databases (PubMed, Scopus, Web of Science and Cochrane) and 378 remained after removing duplicates. Subsequently, after reading the title and abstract, the number was reduced to 32 studies. The full texts of these 32 studies were assessed for eligibility. All 32 studies were included in the qualitative synthesis and 12 articles were included in the quantitative synthesis. Table 2 shows the descriptive extraction of data from the studies included in the review.

Figure 1: PRISMA flow diagram of literature searches.



Source: Authors.

Table 2: Data collection of the eligible articles.

Reference	Study design	Sample	Periodontitis evaluation method	Cognitive evaluation method	Statistical Analysis	Results	Conclusions
Grabe et al (2009)	Cross-sectional	1059	Tooth loss	Mini-mental State Examination (MMSE)	Mann-Whitney Tobit regression	Female: B= 0.045 (0.017); (95% CI 0.011–0.079); p<0.010 Male: B= 0.011 (0.017); (95% CI -0.023–0.045); p<0,521	The hypothesis must be investigated in prospective studies.

Okamoto et al (2010)	Cross-sectional	4061	Tooth loss	Mini-mental State Examination (MMSE)	Chi-square and Mann-Whitney tests	OR=2.177; (95% CI 1.510-3.140)	Tooth loss is associated with cognitive function.
Saito et al (2013)	Cross-sectional	462	Tooth loss	Mini-mental State Examination (MMSE)	Chi-square and T-test, logistic regression analysis	OR=20.21; (95% CI 2.20-185.47); p<0.01	Study revealed links between tooth loss and cognitive function.
Stewart et al (2013)	Cohort	1171	Number of teeth; number of pairs of occlusive teeth and periodontal evaluation.	Modified Mini-Mental State Examination (3MS)	Logistic regression model	OR=1.18; (95% CI 0.95-1.45)	Association between gingival inflammation and confirmed cognitive decline as a potentially important risk factor
Elsig et al (2015)	Cross-sectional	51	Tooth loss	Mini-mental State Examination (MMSE)	Student's t-test, Mann-Whitney U test or Fisher's exact test. Univariate and multiple logistic regression models.	OR=1.091; (95% CI 0.4814-2.472	Masticatory efficiency seems stronger associated with cognitive impairment than the number of teeth.
Iwasaki et al (2015)	Cross-sectional	291	Tooth loss and probing depth	Mini-mental State Examination (MMSE) and HDS-R	Univariate and multivariate logistic regression.	OR=2.28; (95% CI 1,06-4.9)	Periodontal disease and tooth loss are significantly associated with cognitive impairment
Okamoto et al (2015)	Cohort	2335	Tooth loss	Mini-mental State Examination (MMSE)	Chi-square, Mann-Whitney, and Kruskal-Wallis tests	OR=2.39; (95% IC 1.48-3.86); p<0,001	Tooth loss can be an independent risk factor for decline mental.
Shin et al (2016)	Cross-sectional controlled	186	Digital Panoramic X-rays	MMSE-KC (MMSE version)	Chi-square, T-test, Fisher's exact test, Mann-Whitney, logistic regression	OR=2.14; (95% CI 1.04-4.41)	These results show that periodontitis is independently associated with cognitive impairment
Iwasaki et al (2016)	Two separate collections	85	Loss of clinical attachment and probing depth	Mini-mental State Examination (MMSE)	Chi-square, T test, Poisson regression, Linear regression	RR=2.21; (95% CI 1.1-4.5)	Severe periodontitis is significantly associated with future decline in cognitive function.
Iwasaki et al (2018)	Cohort	179	Pocket depth and bleeding on probing	Mini-mental State Examination (MMSE)	Logistic Regression	OR=3.51; (95% CI 1.45-8.87)	Severe periodontitis and periodontal inflammation are associated with cognitive decline

Saito et al (2018)	Prospective Cohort	140	Multiple tooth losses	Mini-mental State Examination (MMSE)	T-test, Willcoxon, Multiple logistic regression	OR=3.31; (95% CI1.07-10.2); p<0,037	Multiple tooth loss is associated with the development of cognitive impairment.
Holmer et al (2018)	Case-control	230	Probing depth and bleeding on pocket probing, suppuration, tooth mobility and furcal involvement	Mini-mental State Examination (MMSE)	Logistic regression	OR=15.12; (95% CI 5.93-38.58)	The periodontitis-dementia interaction seems biologically plausible.
Jae-Min et al (2007)	Cross-sectional	686	Tooth loss	Mini-mental State Examination (MMSE)	Mann–Whitney Kruskal–Wallis	OR=1,4 (95% CI 1,1–1,7) in all of the participants OR=1,2 (95% CI 0,9–1,6) in those who used dentures OR=2,0 (95% CI 1,3–2,9) in those who did not use dentures.	Periodontal disease characteristics can also increase the risk of dementia, and, particularly, Alzheimer's disease
Chen et al (2010)	Longitudinal retrospective study	491	Tooth loss	Patient's medical history	Chi-square tests, variance analysis, Cox, Poisson and negative binomial regressions	RR=1,00 (95% CI 0,62 - 1,39)	Dementia was not associated with Tooth loss.
Rai et al (2012)	Case-control	107	Periodontal evaluation	Diagnosed with dementia	Covariance analysis	Dental plaque: (SD)= 0,38 (0,15); Gingival inflammation: (SD)= 0,98 (0,38); Bleeding on probing: (SD)= 89,12 (15,6); Probing depth: (SD)=4,81 (0,78); Clinical attachment level: (SD)=4,02 (0,23)	Further exploration of the relationship between periodontitis and cognition is needed.
Kamer et al (2012)	Cohort	152	Modified Community Periodontal Index (MCPI)	DST e BDT	t-test (T), Mann-Whitney U test (MW), ANOVA (A) or Kruskal-Wallis (KW).	OR=3,26 (95% CI 1,26-8,38); p<0,01	Periodontal inflammation can affect cognition.
Del Brutto et al (2014)	Cross-sectional	274	Tooth loss	Spanish version of the Montreal Cognitive Assessment (MoCA) test	Kruskal-Wallis and linear regression analysis	MoCA score (mean ± SD): 19.4 ± 4.5; p<0.0001 Significantly lower MoCA scores for persons with \10 remaining teeth (b = -1.06, p = 0.03)	Severe edentulism is associated with worse cognitive performance in the elderly.

Gil-Montoya et al (2014)	Case-control	409	Plaque index, bleeding index, loss of clinical attachment and pocket depth.	General/neurological examination and neuropsychological behavioral assess-ment (Neuropsy-chiatric Inventory Scale) and function-nal (Barthel,Lawton & Brodie Scale) and global staging (Glo-bal Deterioration Scale and Clinical Dementia Rating Scale).	Multiple logistic regression	OR = 3,04 (IC 95% 1,69-5,46).	Periodontitis seems to be associated with cognitive impairment.
Stewart et al (2015)	Cohort	697	Tooth loss/number of teeth	Medical records	Logistic regression model	OR=1.81 (95% CI = 0.77–4.25)	There is a relationship between dementia and oral health.
Tsakos et al (2015)	Longitudinal	3166	Tooth loss	Word memorization Test	Logistic regression model	OR=0,88 (95% IC = 0,66-1,10)	There is an association between edentulism and cognitive decline.
Cestari et al (2016)	Cross-sectional controlled study	65	Gingival bleeding index (BI), probing depth (PPD) and clinical attachment level (CAL)	Mini-mental State Examination (MMSE)	ANOVA, Pearson's correlation, Chi-squared	Gingival bleeding (BI) = 44.61 ± 34.26 (0–87) Probing depth (PPD) = 4.30 ± 1.88 (2.00–8.00) Clinical attachment level (CAL) = 5.66 ± 3.84 (0.00–11.00)	There is an association between inflammation (periodontitis) and Alzheimer's disease.
Tzeng et al (2016)	Combined Retrospective Cohort	8828	Diagnosis of chronic periodontitis and gingivitis by a dentist	Diagnosis by psychiatrists and neurologists according to the Diagnostic and Statistical Manual of Mental Disorders	Chi-square test, t-test, fisher's exact test, COX proportional risk regression.	OR=2.540 (95% CI 1.589–4.242)	Patients with chronic periodontitis and gingivitis have a higher risk of developing dementia than those without.
Naorungroj et al (2013)	Cross-sectional	5.942	BGI index	Delay Word Recall (DWR), Digit Symbol Substitution (DSS) and Word Fluency (WF)	Bivariate analysis	DWR: b=0,047; SE= (0,076) DSS: b=-0,44; SE= (0,48); p<0,0464 WF: b=-0,78; SE= (0,59); p<0,0015	Complete loss of teeth or low number of teeth and the inflammatory stage of periodontal disease are associated with lower cognitive performance.

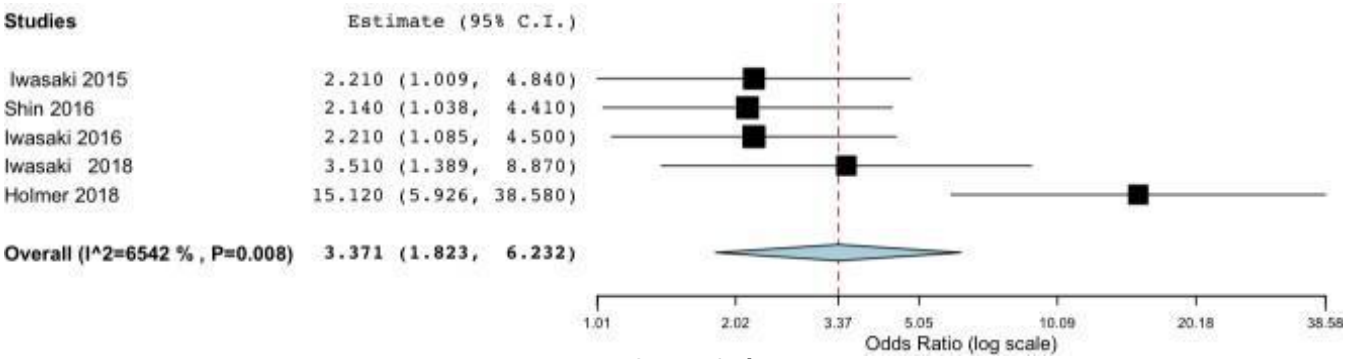
Ide et al (2016)	Cohort	52	Presence of plaque, probing depth and gingival bleeding.	Alzheimer's disease evaluation scale (ADAS-cog) (PRIMARY) and Standardized Mini-mental State Exam (sMMSE) (SECONDARY)	Chi-square, T-test, Mann-Whitney, Linear regression	1.5 (95% CI -1.2 to 4.2), p = 0.3	There is a direct relationship between periodontitis and cognitive decline.
Chen et al (2017)	Combined Retrospective Cohort	323	Diagnosis of chronic periodontitis by a dentist	DA diagnosis	Chi-square, T-test, Cox regression	OR=1,707 (95% CI 1.152–2.528) p<0.0077	Exposure to Chronic Periodontitis was associated with an increased risk of developing AD.
Takeuchi et al (2017)	Prospective Cohort	1.566	Tooth loss	Diagnostic and Statistical Manual of Mental Disorders	Logistic regression and Cox proportional hazards model	10 to 19 teeth (HR = 1,62, IC 95% = 1,06–2,46), 1 to 9 teeth (HR = 1,81, IC95% = 1,11–2,94) 0 teeth (HR = 1,63, IC95% = 0,95–2,80)	Tooth loss is a risk factor for development of dementia.
Lee et al (2017)	Cohort	6056	Diagnosis of chronic periodontitis by a dentist	DA diagnosis	T-test and Chi-square test, COX regression	HR=1,16 (95% CI 1,01-1,32)	The risk of dementia in elderly adults is greater than in those without periodontitis.
Yau-Hua et al (2008)	Cross-sectional	803	Probing depth	DSST	The DSST SD scores were related to the periodontal disease status using multiple logistic regression.	OR=0,69 (95% CI 0,51-0,94); p<0,02	There is an association between periodontal disease and cognitive decline.
Dintica et al (2018)	Longitudinal	2715	Tooth loss	MMSE, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM–IV)	Linear regression	B=0,08 (95% CI 0,21 - 0,38)	There is an association between tooth loss and cognitive decline
Hatta et al (2018)	Longitudinal	515	Tooth loss and posterior occlusal support	MoCA-J	Logistic regression	OR=1.32 (95% CI 1.22–1.44); p<0.001	Lack of superior occlusal support can increase the incidence of cognitive decline

Sochoka et al (2017)	Cross-sectional	128	Tooth loss and periodontal evaluation .	Mini-mental State Examination (MMSE)	R Pearson s' correlation between U and V	OR = 2.8 (95% 0.9 - 6.5)	Pro-inflammatory mediators of periodontal disease can exacerbate systemic inflammation and deepen the neurodegenerative status.
Gil-Montoya et al (2017)	Case-control	288	Number of teeth present, Löe and Silness plaque index, clinical attachment loss and probing depth.	Medical diagnosis, diagnosis criteria and Statistical Manual of Mental Disorders DSM-IVR and Mini-mental	Logistic regression	OR=1,9; (95% CI 2,7-53,1); p<0.001	Periodontitis influences cognitive decline

Source: Authors.

The first meta-analysis (Figure 2) included five studies (n=5) (Iwasaki et al., 2015; Shin et al., 2016; Iwasaki et al., 2016; Iwasaki et al., 2018; Holmer et al., 2018), that assessed the association between Periodontal Disease History (HPD) and cognitive decline, its heterogeneity was superior to 50% (I^2=65.42%). The result associated HPD as a risk factor for increased cognitive decline, OR=3.371 (95% CI: 1.823-6.233), *p*=0.008.

Figure 2: Forest plot of the association between HPD and cognitive decline.



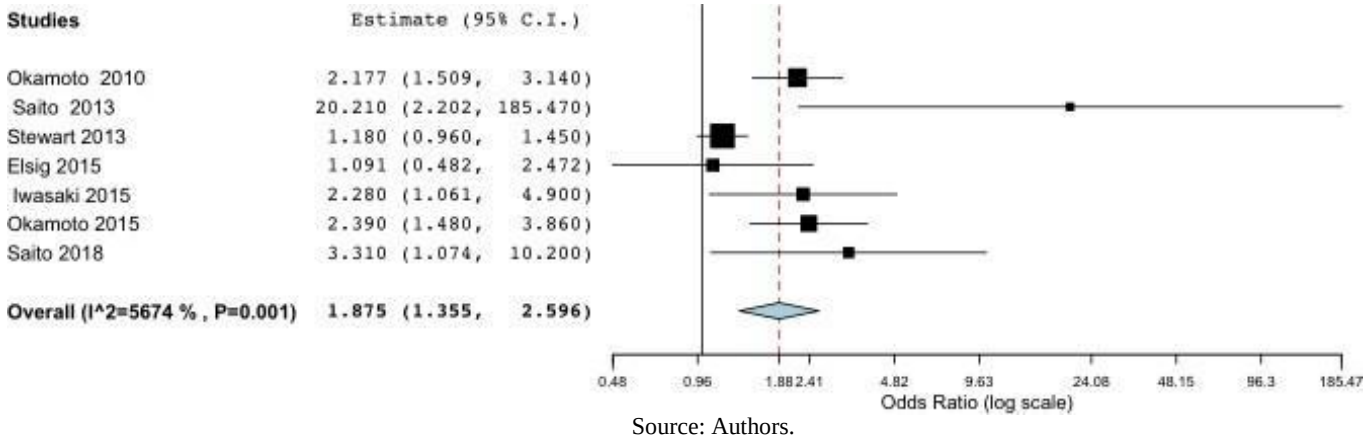
Source: Authors.

In the second meta-analysis (Figure 3), seven studies were included (n=7) (Stewart et al., 2013; Okamoto et al., 2015; Saito et al., 2018; Okamoto et al., 2010; Saito et al., 2013; Elsig et al., 2015; Iwasaki et al., 2015) that evaluated the association between tooth loss and cognitive decline, their heterogeneity was greater than 50% (I^2= 56.74%). The result showed tooth loss as a risk factor for increased cognitive decline, OR=1.875 (95% CI: 1,355, 2,596), *p*=0.001.

The analysis of the risk of bias (table 3) shows all the studies included in the systematic review, which scored between high and low risk of bias. Of the 5 studies included in the first meta-analysis, two studies were not at risk of bias (Iwasaki et al.,

2016; Iwasaki et al., 2015), while the other three were at high risk of bias (Iwasaki et al., 2019; Shin et al., 2016; Holmer et al., 2018). In the second meta-analysis, of the seven included studies, only one presented a high risk of bias (Saito et al., 2018).

Figure 3: Forest plot of the association between tooth loss and cognitive decline.



Source: Authors.

Table 2: Fowkes and Fulton criteria classification determined by the authors.

Guideline	Checklist	Kim, et al (2007)	Yu, et al (2008)	Grabe, et al (2009)	Chen, et al (2010)	Okamoto, et al (2010)	Rai, et al (2012)	Kamer, et al (2012)	Saito, et al (2013)	Stewart, et al (2013)	Del Brutto, et al (2014)	Rai, et al (2012)	Kamer, et al (2012)	Gil-Montoya, et al (2014)	Elsig, et al (2015)	Iwasaki, et al (2015)	Okamoto, et al (2015)	Stewart, et al (2015)	Tsakos, et al (2015)	Tzeng, et al (2016)	Ide, et al (2016)	Iwasaki, et al (2016)	Shin, et al (2016)	Cestari, et al (2016)	Naorungroj, et al (2016)	Gil-Montoya, et al (2017)	Takeuchi, et al, (2017)	Chen, et al (2017)	Sochocka, et al (2017)	Lee, et al (2017)	Hatta, et al (2018)	Dintica, et al (2018)	Holmer, et al (2018)
Study design appropriate?	Cross-sectional (prevalence)	X	X	X		X			X						X	X													X				
	Cohort (prognosis)				X			X		X			X				X	X	X		X	X						X	X		X	X	X	
	Controlled Trial (treatment)										X																						
	Case-control, cross-sectional (cause)						X					X		X						X			X	X	X	X							X
Study sample representative?	Source of sample	0	0	0	+	0	+	+	0	0	0	+	+	++	+	0	0	0	0	0	++	0	+	++	+	+	0	0	++	0	+	0	+
	Sampling method	+	+	0	++	0	++	++	++	0	0	++	++	++	0	0	0	0	0	+	++	++	++	+	++	+	+	0	+	0	+	+	++
	Sample size	+	0	0	+	0	++	++	++	0	+	++	++	+	+	+	0	0	0	0	++	++	+	++	0	++	0	0	++	0	+	0	++
	Entry criteria and exclusions	0	0	0	+	0	++	0	++	++	++	++	0	0	0	++	++	++	++	+	++	0	0	0	0	0	0	0	++	0	0	0	+
Control group acceptable?	Definition of control	++	0	++	0	++	0	0	++	++	0	0	0	++	++	++	++	++	++	+	0	0	++	++	0	0	0	0	++	0	0	0	++
	Source of control	0	0	0	0	0	+	0	0	+	0	+	0	0	++	0	++	++	++	0	0	0	++	++	0	0	0	0	++	0	0	0	++
	Matching/randomization	++	++	++	++	++	0	0	++	++	+	0	0	++	++	++	++	++	++	0	0	0	++	++	++	++	+	0	++	+	0	0	++
	Comparable characteristics	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	++	++	++	++	++	++	++	0	++	0	++	++	++
Quality of measurements and outcomes?	Validity	0	0	0	++	0	++	0	0	0	0	++	0	0	0	0	0	0	++	++	0	+	0	0	0	0	0	+	0	+	0	+	0
	Reproducibility	+	0	0	++	0	++	0	0	0	0	++	0	0	0	0	0	++	++	++	0	+	0	0	0	0	0	+	0	+	0	+	0
	Blindness	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Quality control	+	+	+	++	+	++	+	+	++	0	++	+	+	+	+	+	+	+	++	+	++	+	0	+	+	+	+	0	+	+	+	+
Completeness?	Compliance	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Drop out	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Death	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Missing data	++	++	+	0	+	0	++	0	++	+	0	++	0	++	++	++	++	++	++	+	++	++	0	+	0	+	++	0	0	++	++	0
Distorting influence?	Extraneous treatments	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Contamination	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Changes over time	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Confounding factors	0	0	0	+	+	0	+	++	++	++	0	+	0	0	0	+	+	0	0	+	+	0	0	0	++	0	0	++	0	0	+	++
	Distortion reduced by analysis	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	++	0	0	++	0	++	0	0	++	0	0	0	+

Source: Authors.

4. Discussion

In this systematic review, 14 studies were evaluated associating tooth loss with cognitive decline, of which 7 proved the association (p=0.001), considering that, although the patient has received specialized care and treatment for periodontal disease, it is still shown as the main reason for tooth loss in elderly patients (Ide et al., 2015; Renvert et al., 2013).

Alzheimer's disease (AD) is the most frequent type of dementia characterized by a progressive decline in memory, thinking, language and learning ability, which ends in death (Lance; Hardy; Schott, 2018). It must be taken into account that more than 37 million people are affected by it globally, with the highest prevalence in the elderly aged ≥ 65 years and that, according to the World Health Organization, approximately 5 to 20% of older adults (age ≥ 65 years) suffer from severe forms of periodontitis (Gaur & Agnihotri, 2015).

There are many other factors that strongly influence the etiology, development, and progression of cognitive decline in old age. These factors include not only different personality and mood traits, but also lifestyle patterns (for example, exercise and diet) and levels of awareness that lead to cognitive decline in old age (Jaroud et al., 2017).

It is worth highlighting the five main preventable risk factors for Alzheimer's, such as smoking, depression, hypertension, diabetes mellitus and obesity, which have a common association with a systemic pro-inflammatory phenotype. This association further supports the hypothesis that systemic inflammation may play a key role in the development and progression of dementia or cognitive loss (Teixeira et al., 2017; Dally., ,2017).

Systemic inflammation caused by inflammation resulting from periodontal disease as a risk factor for Alzheimer's disease has biological plausibility, as periodontal disease increases the level of inflammatory markers that are also present in dementia or Alzheimer's (Teixeira et al., 2017).

The evidence for the association between history of periodontal disease and AD has been established through studies in humans and animals (Jaroudi et al., 2017). In the studies used in the second meta-analysis of the present study, the relationship between cognitive impairment (a preclinical stage of AD), assessed through the MMSE, and history of periodontal disease (OR=3,371) was considered, with HPD as a risk factor.

The meta-analyses showed heterogeneity ranging from high to moderate between the study samples, which probably refers to the degree of differences between the results of individual studies. Despite the application of eligibility criteria, this variation can be explained by the differences between the methodologies (Walker et al., 2008).

Over the years and with increasing age, maintenance and oral health problems are secondary, as concerns and general health conditions increase (Singhrao et al., 2014). Although this systematic review and meta-analysis show that the history of periodontal disease may be associated with the decline in cognitive status, further studies are needed, as few studies follow the same methodology and this contributes to increasing the heterogeneity of the meta-analyses. These future studies in the area would contribute to elucidate the veracity of the history of periodontal disease as a risk factor for the progression of cognitive decline.

5. Conclusion

Based on the results of this systematic review and meta-analysis, the following conclusions were drawn:

1. Individuals with a history of periodontal disease are at increased risk of developing cognitive decline.
2. Individuals with tooth loss due to periodontal disease are also at a higher risk of developing cognitive decline.
3. The relation between the two pathologies is due to the systemic inflammation caused by periodontal disease, which increases levels of inflammatory markers that are also present in individuals with cognitive impairment.
4. New studies with standard methodologies need to be carried out.

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