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Research article

Confounding in observational studies evaluating the association between Alzheimer's disease and periodontal disease: A systematic review

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ABSTRACT

Background: Studies investigating the association between periodontitis and Alzheimer's disease (AD) suggested indirect (periodontitis would increase the circulation of inflammation-inducible molecules) and direct (periodontopathogens might colonize brains affected by Alzheimer's disease) pathways. While there seems to be a positive relationship between periodontitis and AD, concerns have been raised about the role of confounding.

Aim: To systematically review the literature to assess confounding and their level of heterogeneity in the association between periodontitis and AD. Also, to examine data reporting and interpretation regarding confounding bias.

Methods: This review followed the PRISMA guidelines and was registered within PROSPERO. Electronic searches were performed in seven main databases and three others to capture the "grey literature". The PECO strategy was used to identify observational studies (cross-sectional, case-control, or cohort studies) assessing the association between periodontal disease and AD without restricting publication language and year. Critical appraisal was performed according to the Joanna Briggs Institute guidelines. Confounders were evaluated following a two-step approach.

Results: A total of 3255 studies were found, of which 18 (13 case-control, four cross-sectional, and one cohort) met the eligibility criteria. Participants with AD were 1399 (mean age 64 ± 9 to 84.8 ± 5.6 years), whereas those without AD were 1730 (mean age 62.6 ± 7.1 to 81.4 ± 4.6). Female patients composed most of the sample for both groups. The confounding variables "age" and "sex" were present in all studies. Four studies used the 2017 AAP/EFP periodontal classification. Most studies had a low risk of bias. Fifty percent of the articles did not consider confounding; variation in the adjustment approaches was observed. Additionally, 62% of the studies did not mention bias, and 40% did not discuss any limitations about confounders.

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Conclusions: Given the study's limitations, caution must be taken to properly interpret the association between periodontitis and AD.
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1. Introduction

Studies investigating the association between oral and systemic diseases have become increasingly popular over the past decades. Periodontitis has been characterized by the progressive destruction of the tissues supporting the teeth, with clinical manifestations varying from mild to severe damage resulting from an exacerbated immune response. Understanding periodontitis etiology is challenging given its multicausal nature that involves complex and dynamic interactions between the host's immune system [1], microbiome [2,3], genomics, lifestyle and environmental factors [4,5]. According to the Global Burden of Diseases, severe periodontitis affects approximately 11% of the adult population worldwide [6]. In 2018, periodontitis cost about US$ 154 billion in the US and €159 billion in Europe, posing a heavy burden on individuals and societies [7].

Over the years, periodontitis has been associated with several systemic conditions, including diabetes, cardiovascular diseases, and mortality. More recently, studies have investigated the association between periodontitis and Alzheimer's disease (AD), a complex neurodegenerative disorder defined by a progressive accumulation of cerebral parenchymal β-Amyloid (Aβ) plaques and intraneuronal tau neurofibrillary tangles, associated with extensive brain inflammatory processes, leading to a gradual cognitive decline with progressive memory impairment [8,9]. It is estimated that there will be approximately 152 million people with AD and other forms of dementia by 2050 [10]. In 2019, the global cost of AD was estimated at US$ 2.8 trillion, while in 2050, this value must reach US$ 16.9 trillion. Low- and middle-income countries will account for 65% of the global AD by 2050, thus, showing the enormous and inequitable burden of AD for the future [11].

Studies have suggested an indirect inflammatory pathway through which periodontitis would increase the circulation of inflammation-inducible molecules [12] and a direct infectious path, as periodontopathogens have been found in brains affected by Alzheimer's disease [13,14]. Additionally, based on the "gut-brain" axis approach [15], a hypothesis about the role of the oral microbiome on the development of mental disorders through the "oral-brain" axis has been postulated, but more studies are still necessary to further elucidate this potential path [16].

After gaining widespread attention in the media and the scientific community, such findings can influence patients and clinicians and may create dubious notions regarding the role of oral health in the onset of systemic diseases [17]. However, most of the evidence originates from observational studies, which have methodological characteristics that, if not accounted for, generate bias and misleading results. Thus, it becomes evident to critically appraise the evidence prior to making further clinical recommendations, such as routine dental visits to prevent AD. This is of relevance, as while direct and indirect paths have been hypothesized to explain the periodontitis-AD relationship, the influence of common risk factors shared by both diseases is yet to be explored. Among the most critical common risk factors, and therefore confounders of this association, one may highlight age, sex, and socioeconomic position, in addition to behavioral factors, such as smoking and alcohol consumption, and the presence of other systemic conditions, such as depression, diabetes, hypertension, and obesity [5,18].

Confounding is one of the primary sources of bias inherent to observational studies [19]. Confounding bias results from the presence of causes (risk factors) common to exposure and outcome, hence having the ability to distort potential exposure-outcome associations [20]. Despite the various approaches and strategies to deal with confounding in observational studies, it is a mammoth task to ensure the complete exclusion of residual confounding. Residual confounding may arise from different sources, including poor-quality confounder information or unmeasured confounders [21]. The former refers to the challenges regarding operationalizing complex information into single variables or the absence of proper measures for the confounder. Smoking, for instance, is a variable with several dimensions, including type, frequency, duration, metabolization, and damage susceptibility. However, observational studies usually categorize smoking as current, former, or never-smoking, thus, neglecting the several dimensions of such a confounder [22]. Lack of proper measure refers to the use of information that may not be valid to accurately assess the potential confounder, such as self-reported information on health conditions. Finally, unmeasured confounders, as explicit, might be confounders known by the researcher yet not collected or unknown confounders according to the current scientific knowledge [23].

Another interesting aspect concerning confounding refers to confounder selection. While a theoretical background might be the ideal approach for confounder selection, not rarely oral health researchers still rely on statistical significance to select confounders (e.g., "stepwise" regression approach) [24]. Hence, it is not surprising that among the researchers investigating the same topic, e.g., periodontitis and AD, there is a lack of consensus regarding potential confounding variables. Such a challenge is not restricted to oral health, and examples can be drawn from the medical literature [25].

Therefore, concerns have been raised that confounding factors may affect the results obtained for the periodontitis-AD relationship, as well as their reproducibility across different studies. Accordingly, this study aims to systematically review the literature to evaluate whether individual observational studies exploring the relationship between periodontitis and AD considered confounding and their level of heterogeneity. Moreover, we examined data reporting and interpretation regarding the potential presence of confounding bias in individual studies.

Table 1
Strategies for database search.

Database	Search Strategy (June 2021) and Update (Until August 2022)
Main Databases	
Embase https://www.embase.com	('periodontal disease' OR 'peridontal disease' OR 'peridontal tissue disease' OR 'peridontium disease' OR 'periodontal atrophy' OR 'periodontal attachment loss' OR 'periodontal cyst' OR 'periodontal diseases' OR 'periodontal infection' OR 'periodontium disease' OR 'periodontopathy') AND ('alzheimer disease' OR 'alzeimer disease' OR 'alzeimers disease' OR 'alzheimer dementia' OR 'alzheimer sclerosis' OR 'alzheimer syndrome' OR 'alzheimers disease' OR 'neurologic disease' OR 'nervous disease' OR 'nervous system disease')
LILACS and BBO http://pesquisa.bvsalud.org/	**/pt** (((doenças periodontais) OR (periodontite) OR (periodontite agressiva) OR (periodontite crônica) OR (periodontite periapical)) AND ((doença de alzheimer) OR (mal de alzheimer) OR (alzheimer) OR (doenças do sistema nervoso))) AND (db:("LILACS" OR "BBO")) **/en** (((periodontal diseases) OR (periodontitis) OR (aggressive periodontitis) OR (chronic periodontitis) OR (periapical periodontitis)) AND ((alzheimer disease) OR (alzheimer) OR (nervous system diseases))) AND (db:("LILACS" OR "BBO"))
LIVIVO https://www.livivo.de/	**#1** ("Periodontal Diseases" OR "Periodontitis" OR "Periodontitides" OR "Chronic Periodontitis" OR "Adult Periodontitis" OR "Chronic Periodontitides" OR "Adult Periodontitides" OR "Aggressive Periodontitis" OR "Periodontal Disease" OR "Periodontal Infections") **#2** ("Alzheimer Disease" OR "Alzheimer's Disease" OR "Disease, Alzheimer" OR "Alzheimer Dementia" OR "Dementia, Alzheimer" OR "Alzheimer Type Dementia" OR "Dementia, Alzheimer Type" OR "Alzheimer-Type Dementia" OR "Dementia, Alzheimer-Type" OR "Alzheimer-Type Dementia (ATD)" OR "Dementia, Alzheimer-Type (ATD)" OR "Alzheimer Type Senile Dementia" OR "Senile Dementia, Alzheimer Type" OR "Alzheimer Sclerosis" OR "Sclerosis, Alzheimer" OR "Alzheimer Syndrome" OR "Acute Confusional Senile Dementia" OR "Cognitive Impairment" OR "Cognitive Decline" OR "Cognitive Loss" OR "Poor Cognitive Function" OR "Presenile Alzheimer Dementia*" OR "Presenile Dementia" OR "Dementia, Presenile" OR "Primary Senile Degenerative Dementia" OR "Senile Dementia" OR "Dementia, Senile" OR "Neurodegenerative Diseases" OR "Neurodegenerative Disorders" OR "Neurological Degenerative Diseases" OR "Neurological Degenerative Conditions" OR "Nervous System Degenerative Diseases") **#1** AND **#2**
MEDLINE (*via* PubMed) http://www.ncbi.nlm.nih.gov/pubmed	**#1** "Periodontal Diseases"[Mesh] OR "Periodontitis"[tw] OR "Periodontitides"[tw] OR "Chronic Periodontitis"[tw] OR "Adult Periodontitis"[tw] OR "Aggressive Periodontitis"[tw] OR "Periodontal Disease"[tw] OR "Periodontal Infections"[tw] #2 "Alzheimer Disease"[Mesh] OR "Alzheimer's Disease"[tw] OR "Disease, Alzheimer"[tw] OR "Alzheimer Dementia"[tw] OR "Dementia, Alzheimer"[tw] OR "Alzheimer Type Dementia"[tw] OR "Dementia, Alzheimer Type"[tw] OR "Alzheimer-Type Dementia"[tw] OR "Dementia, Alzheimer-Type"[tw] OR "Alzheimer-Type Dementia (ATD)"[tw] OR "Dementia, Alzheimer-Type (ATD)"[tw] OR "Alzheimer Type Senile Dementia"[tw] OR "Senile Dementia, Alzheimer Type"[tw] OR "Sclerosis, Alzheimer"[tw] OR "Alzheimer Syndrome"[tw] OR "Cognitive Impairment"[tw] OR "Cognitive Decline"[tw] OR "Cognitive Loss"[tw] OR "Poor Cognitive Function"[tw] OR "Presenile Alzheimer Dementia*"[tw] OR "Presenile Dementia"[tw] OR "Dementia, Presenile"[tw] OR "Senile Dementia"[tw] OR "Dementia, Senile"[tw] OR "Neurodegenerative Diseases"[Mesh] OR "Neurodegenerative Disorders"[tw] OR "Neurological Degenerative Diseases"[tw] OR "Neurological Degenerative Conditions"[tw] OR "Nervous System Degenerative Diseases"[tw] #1 AND #2
SciELO https://scielo.org/	**/pt** (("Doenças Periodontais" OR "Periodontite" OR "Periodontite Agressiva" OR "Periodontite Crônica" OR "Periodontite Periapical") AND ("Doença de Alzheimer" OR "Mal de Alzheimer" OR "Alzheimer" OR "Doenças do Sistema Nervoso")) **/en** (("Periodontal Diseases" OR "Periodontitis" OR "Aggressive Periodontitis" OR "Chronic Periodontitis" OR "Periapical Periodontitis") AND ("Alzheimer Disease" OR "Alzheimer" OR "Nervous System Diseases"))
Scopus http://www.scopus.com/	(TITLE-ABS-KEY (("Periodontal Diseases" OR "Periodontitis" OR "Periodontitides" OR "Chronic Periodontitis" OR "Adult Periodontitis" OR "Chronic Periodontitides" OR "Adult Periodontitides" OR "Aggressive Periodontitis" OR "Periodontal Disease" OR "Periodontal Infections")) AND TITLE-ABS-KEY (("Alzheimer Disease" OR "Alzheimer's Disease" OR "Disease, Alzheimer" OR "Alzheimer Dementia" OR "Dementia, Alzheimer" OR "Alzheimer Type Dementia" OR "Dementia, Alzheimer Type" OR "Alzheimer-Type Dementia" OR "Dementia, Alzheimer-Type" OR "Alzheimer-Type Dementia (ATD)" OR "Dementia, Alzheimer-Type (ATD)" OR "Alzheimer Type Senile Dementia" OR "Senile Dementia, Alzheimer Type" OR "Alzheimer Sclerosis" OR "Sclerosis, Alzheimer" OR "Alzheimer Syndrome" OR "Acute Confusional Senile Dementia" OR "Cognitive Impairment" OR "Cognitive Decline" OR "Cognitive Loss" OR "Poor Cognitive Function" OR "Presenile Alzheimer Dementia*" OR "Presenile Dementia" OR "Dementia, Presenile" OR "Primary Senile Degenerative Dementia" OR "Senile Dementia" OR "Dementia, Senile" OR "Neurodegenerative Diseases" OR "Neurodegenerative Disorders" OR "Neurological Degenerative Diseases" OR "Neurological Degenerative Conditions" OR "Nervous System Degenerative Diseases")))
Web of Science http://apps.webofknowledge.com/	**#1** TS=("Periodontal Diseases" OR "Periodontitis" OR "Periodontitides" OR "Chronic Periodontitis" OR "Adult Periodontitis" OR "Chronic Periodontitides" OR "Adult Periodontitides" OR "Aggressive Periodontitis" OR "Periodontal Disease" OR "Periodontal Infections") #2 TS=("Alzheimer Disease" OR "Alzheimer's Disease" OR "Disease, Alzheimer" OR "Alzheimer Dementia" OR "Dementia, Alzheimer" OR "Alzheimer Type Dementia" OR "Dementia, Alzheimer Type" OR "Alzheimer-Type Dementia" OR "Dementia, Alzheimer-Type" OR "Alzheimer-Type Dementia (ATD)" OR "Dementia, Alzheimer-Type (ATD)" OR "Alzheimer Type Senile Dementia" OR "Senile Dementia, Alzheimer Type" OR "Alzheimer Sclerosis" OR "Sclerosis, Alzheimer" OR "Alzheimer Syndrome" OR "Acute Confusional Senile Dementia" OR "Cognitive Impairment" OR "Cognitive Decline" OR "Cognitive Loss" OR "Poor Cognitive Function" OR "Presenile Alzheimer Dementia*" OR "Presenile Dementia" OR "Dementia, Presenile" OR "Primary Senile Degenerative Dementia" OR "Senile Dementia" OR "Dementia, Senile" OR "Neurodegenerative Diseases" OR "Neurodegenerative Disorders" OR "Neurological Degenerative Diseases" OR "Neurological Degenerative Conditions" OR "Nervous System Degenerative Diseases") #1 AND #2
Grey Literature	

(*continued on next page*)

Table 1 (*continued*)

Database	Search Strategy (June 2021) and Update (Until August 2022)
EASY https://easy.dans.knaw.nl/	(("Periodontal Disease") OR ("Alzheimer Disease"))
Google Scholar https://scholar.google.com.br/	("Periodontal Disease") AND ("Alzheimer Disease") filetype:pdf
OATD http://www.oatd.org/	(("Periodontal Diseases") AND ("Alzheimer Disease"))

2. Methodology

2.1. Protocol registration

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [26] was used to guide the reporting of the study protocol, which was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under number CRD42022293884.

The systematic review was carried out following the Joanna Briggs Institute (JBI) Manual [28] and the Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) guideline [29]. The reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [27].

2.2. Research question

A review question based on the **PECO** strategy guided the current study: "Is there an association between periodontitis and Alzheimer's disease in adults?", in which: **P** (population), **E** (exposure), **C** (comparison), and **O** (outcome).

- **P**opulation: adults;
- **E**xposure: periodontitis;
- **C**omparator: absence of periodontitis;
- **O**utcome: Alzheimer's disease;
- **S**tudy design: prospective or retrospective observational studies (cross-sectional, case-control, or cohort studies).

2.3. Eligibility criteria

2.3.1. Inclusion criteria

Studies that explored the association between periodontitis and Alzheimer's disease in adults were included. There were no restrictions on publication language or year. The definition of periodontitis applied by the authors in the primary studies was accepted in this review (clinical or self-reported definition).

2.3.2. Exclusion criteria

Exclusion criteria comprised studies that did not address Alzheimer's disease or did not specify the neurodegenerative disease or type of dementia studied. In addition, in studies with overlapping samples, we considered only the most recent study that provided more details of the methodology and results. Finally, articles describing non-original research were excluded.

2.4. Sources of information, search, and selection of studies

Electronic searches in Embase, Latin American and Caribbean Health Science Literature (LILACS), LIVIVO, MedLine (*via* PubMed), SciELO databases, Scopus, and Web of Science citation databases were performed. In order to partially capture the "grey literature", we used The EASY, Google Scholar, and Open Access Theses and Dissertations (OATD) databases in an attempt to minimize selection bias. We constantly updated the searches in all databases until August 2022. Table 1 shows more details of search strategies and databases.

The obtained results were exported to the EndNote Web™ software (Clarivate™ Analytics, Philadelphia, USA). Duplicates were automatically removed using the software function, followed by manual duplicate identification and removal. The remaining articles were exported to Rayyan QCRI (Qatar Computing Research Institute, Doha, Qatar) for study selection. The "grey literature" was analyzed manually using Microsoft Word™ 2010 (Microsoft™ Ltd., Washington, USA).

Prior to study selection, a calibration exercise was conducted with two reviewers involved in the process. For this exercise, the eligibility criteria were discussed and applied to a sample of 20% of the studies retrieved to determine inter-examiner agreement. The study selection started only after an adequate level of agreement (Kappa $\geq$0.81) was reached.

In the first phase, two reviewers (CMM and GHB) analyzed the titles and abstracts of the studies independently based on the eligibility criteria, and titles and abstracts not related to the topic were eliminated. In the subsequent phase, the full texts of the preliminary eligible studies were retrieved and appraised. Attempts to obtain full texts that were not found comprised a bibliographic request to the library database (COMUT) and an e-mail to the corresponding authors. Disagreements between the examiners were

explored and defined by a third examiner (LRP).

2.5. Data collection

Before data extraction, a calibration exercise was carried out to ensure consistency between the reviewers. The calibration exercise comprised joint data extraction from three eligible studies. Two reviewers (CMM and MTCV) extracted the data from the eligible studies, independently and blinded. Cases of disagreement about data extraction were solved by a third reviewer (GHB).

The following data were retrieved from the articles: study identification (author, year, country, location, and application of ethical criteria), sample characteristics (number of patients with and without Alzheimer's disease, distribution by sex and average age), collection and processing characteristics (Alzheimer's diagnostic method, cognitive assessment method, periodontal assessment method, and type of statistical analysis used), and main results (primary outcomes from each study, and number of Alzheimer's disease patients diagnosed with periodontal disease). In case of incomplete or insufficient data, the corresponding authors were contacted *via* e-mail up to three times at weekly intervals.

2.6. Risk of bias assessment

2.6.1. Evaluation of methodological quality

The studies were assessed for the risk of individual bias with the JBI Critical Appraisal Tools for use in the JBI Critical Appraisal Checklist for Analytical *Case-Control Studies* [30], *Cross-Sectional Studies* [30], and *Cohort Studies* [30] according to each study design. Two authors (CMM and MTCV) assessed each domain independently for the risk of bias, as recommended by the PRISMA statement [27].

Each question could be answered as follows: "Yes" if the study did not report bias for the assessed domain; or "No" if bias was identified for the domain assessed in the question; or "Uncertain" in case of insufficient information to evaluate the question bias; or "Not Applicable" if the question did not fit in the study. Each study was categorized according to the rate of positive answers to the questions corresponding to the assessment tool. The risk of bias was classified as high when the study obtained 49% or less of "yes" responses, moderate when the study got 50%–69% of "yes" answers, and low when the study reached 70% or more of "yes" answers [31].

2.6.2. Evaluation of control statements for possible confounders and bias consideration

As reported by Hemkens et al. (2018) [32], the evaluation of control statements for possible confounders and risk of bias was carried out following two steps. The first step consisted in excluding eligible studies without multivariable analysis. Moreover, the second step was a critical appraisal of the remaining studies performed by two independent and blinded reviewers (CMM and MTCV). There was a third reviewer (WAV) to solve any disagreements, who was also blinded. Six previously established questions were used to assess each selected study to this critical appraisal regarding the Abstract, Discussion, and Conclusion sections.

2.6.3. Assessment of confounding factors

The assessment of confounding factors followed the methodology reported by Wallach et al. (2020) [25]. Two independent and blinded reviewers (CMM and MTCV) also carried out this assessment, as well as a third reviewer (GHB) resolved the conflicts. All selected studies from the previous evaluation ("Evaluation of control statements for possible confounders and bias consideration") were also analyzed for their Methodology and Result sections. This method aimed to identify potential confounders (variables considered in the selected studies) and confounding domains (groups of similar confounders). The variables were also classified as adjustment, stratification, or matching, depending on their use in each study.

Adjustment variables were those used in multivariable analysis. Variables used to make strata in sample selection were set as stratification variables. Lastly, variables used to match known characteristics between groups or participants were classified as matching variables.

2.7. Data synthesis

While a meta-analysis had been planned to evaluate whether the results from studies with and without properly addressing confounding would differ, the low number of studies precluded any formal quantitative synthesis of the available data. Hence, the data collected from the studies were organized in Microsoft Excel™ 2019 spreadsheets (Microsoft™ Ltd., Washington, USA) and described narratively (qualitative synthesis).

3. Results

3.1. Study selection

The electronic search identified 3255 results distributed into eight electronic databases, including the "grey literature". After removing the duplicates, 1986 results remained for the analysis. A careful reading of the titles and abstracts excluded 1840 results.

After reading the full texts, 131 records were excluded (Appendix 1), and 15 studies [33–47] were included in the qualitative analysis. After reading eligible studies' references and updating the search strategy in August 2022, three studies [48–50] were also

included in the qualitative synthesis. Fig. 1 displays details of the study selection process.

3.2. Study characteristics

The studies were published from 1992 to 2022 and conducted in nine different countries, with two studies in North America [33,34], eight in Europe [35,38,41–44,46,47], four in Asia [36,48–50], and four in South America [37,39,40,45]. Among the 18 eligible studies, only one was a retrospective cohort study [50]. The other studies were cross-sectional [35,36,40,42] and case-control [33,34,37–39,41,43–49]. Two studies [33,34] did not report the following ethical criteria in their execution, and only three studies [38,43,50] reported the use of the STROBE statement [51] as a reporting guide.

The sum of participants diagnosed with Alzheimer's in the eligible studies resulted in 1399 patients, and the sum of the control group (without a diagnosis of Alzheimer's) resulted in 1730 patients. The mean age of the sample with Alzheimer's disease ranged from 64 ± 9 to 84.8 ± 5.6 years, and the mean age of the control group ranged from 62.6 ± 7.1 to 81.4 ± 4.6. Female patients composed most of the sample for both groups. Regarding the direction of the association, ten studies investigated the periodontal status of AD patients [33–37,39–42,50], whereas eight studies explored whether periodontitis was associated with AD [38,43–49].

Among the diagnostic methods of Alzheimer's disease, the following organizations stood out: the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [33,34,36–39]; National Institute of Aging-Alzheimer's Association (NIA-AA) diagnostic guidelines [43,46,47]; Mini-Mental State Examination (MMSE) [40,41,49]; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [35,45,46]; Clinical Dementia Rating (CDR) score [42]; Alzheimer's Disease Assessment Scale (ADAS-cog) [44]; International Classification of Diseases [48] and Diagnostic and Statistical Manual of Mental Disorders (5th ed.) for major neurocognitive disorder or dementia [50].

Regarding the cognitive assessment method, the Mini-Mental State Examination (MMSE) was the most used among the eligible studies, being applied in 12 studies [33,34,36,37,39,43–49]. Other less used methods were: The Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III R) [35]; Neuropsychiatric Inventory Scale [38]; Global Deterioration Scale [38] and Clinical Dementia Rating [38,41,42,45]. Two studies [40,50] did not report how the cognitive assessment of the included patients was carried out.

Finally, different criteria were used to assess the individual's periodontal condition. Among these criteria, the following stood out: pocket probing depth (PPD); clinical attachment level (CAL); bleeding on probing (BOP); gingival recession; visible plaque index; the number of remaining teeth; the presence of dental calculus; degree of tooth mobility and furcation involvement. Some studies have

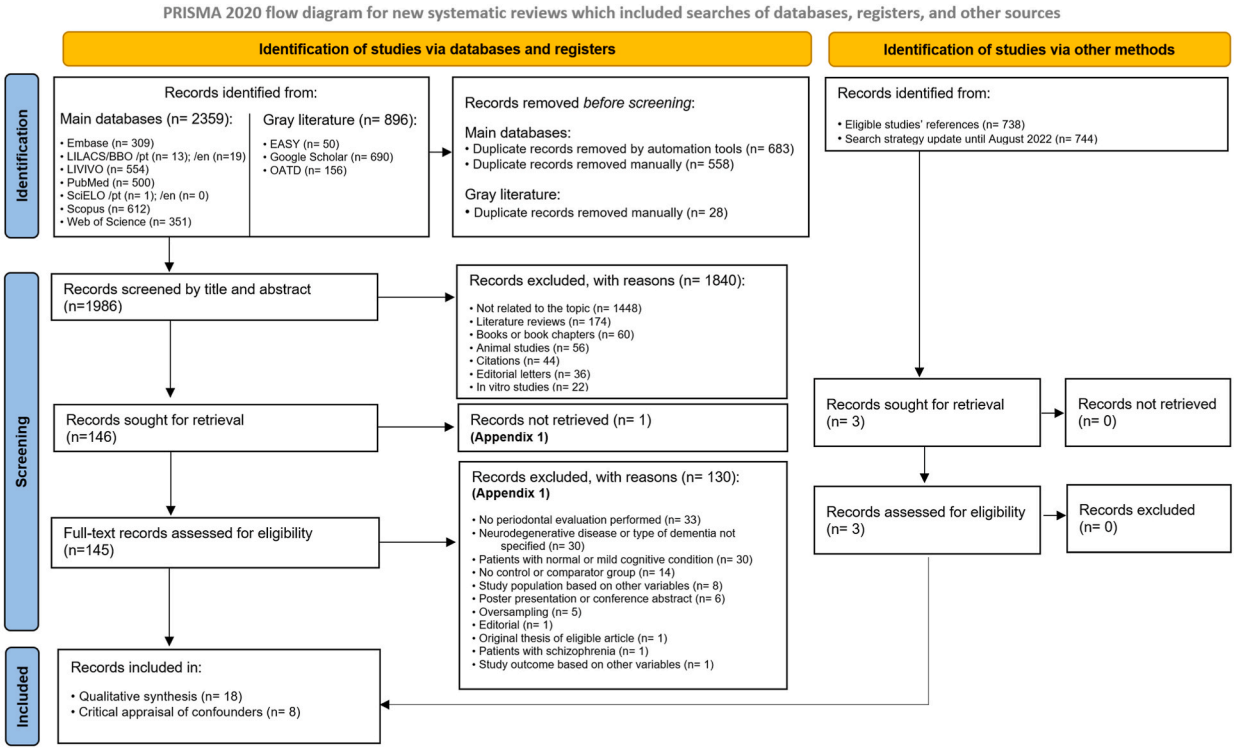

Fig. 1. Flowchart of the study selection process.

Table 2
Summary of the main characteristics of the eligible studies.

Author, year (country of achievement)	Study type	Sample (n)	Sex (♀/♂)	Mean age ± SD	Alzheimer's diagnostic method	Cognitive assessment method	Periodontal assessment method
Ship, 1992 (United States)	Case-control	Case: 41 Control: 49	Case: 19/22 Control: 24/25	Case: 68.2 ± 9.3 Control: 64.1 ± 8.2	NINCDS-ADRDA	MMSE	CAL; Dental surfaces; Gingival bleeding; Gingival recession; PI Probing; Supra or subgingival calculus
Ship & Puckett, 1994 (United States)	Case-control	Case: 21 Control: 21	Case: 8/13 Control: 8/13	Case: 64 ± 9 Control: 65 ± 12	NINCDS-ADRDA	MMSE	CIL; Gingival bleeding; Gingival recession; PI; PPD; Supra or subgingival calculus; 6-tooth surfaces
Syrjälä et al., 2012 (Finland)	Cross-sectional	Case: 49 VaD: 16 Other: 11 Control: 278	Case: 41/8 VaD: 9/7 Other: 5/6 Control: 198/80	Case: 84.8 ± 5.6 VaD: 82.2 ± 4.7 Other: 85.3 ± 4.8 Control: 81.4 ± 4.6	DSM Fourth Edition	DSM Third Edition Revised	Oral hygiene; PPD
Martande et al., 2014 (India)	Cross-sectional	Case: 58 Control: 60	Case: 32/26 Control: 34/26	Case: 65.2 ± 7.3 Control: 64.5 ± 9.4	NINCDS-ADRDA	MMSE	BI; CIL; GI; PI; PPD
Rolim et al., 2014 (Brazil)	Case-control	Case: 29 Control: 30	Case: 16/13 Control: 22/8	Case: 75.2 ± 6.7 Control: 61.2 ± 11.2	NINCDS-ADRDA	MMSE	BoP; CIL; CPO; Distance from the cementoenamel junction; PI; PPD
Gil-Montoya et al., 2015 (Spain)	Case-control	Cog Imp: 180, with Case: 111 Control: 229	Cog Imp: 121/59 Case: nr Control: 128/101	Cog Imp: 77.0 ± 7.8 Case: nr Control: 78.5 ± 7.9	NINCDS-ADRDA	Neuropsychiatric Inventory Scale; Barthel Index; GDS; CDR	BI; CIL; PI; PPD; Tooth loss
Cestari et al., 2016 (Brazil)	Case control	Case: 25 MCI: 19 Control: 21	Case: 15/10 MCI: 13/6 Control: 14/7	Case: 77.7 ± 6.0 MCI: 73.1 ± 6.8 Control: 75.3 ± 5.8	NINCDS-ADRDA	MMSE	BoP; CIL; CPO; Distance from the cementoenamel junction; PI; PPD
Frota et al., 2016 (Brazil)	Cross-sectional	Case: 35 PD: 35 Control: 20	Case: nr PD: nr Control: 13/7	Case: 74.2 ± nr PD: 71.3 ± nr Control: 68.8 ± 5.5	MMSE	nr	Diagnosis of periodontitis; Edentulism with a history of periodontitis; PD
Aragón et al., 2018 (Spain)	Case-control	Case: 70 Control: 36	Case: 38/32 Control: 23/13	Case: 77.4 ± 10.6 Control: 62.6 ± 7.1	Severe MMSE; Mini-Cog Test; CDT; Functional Assessment Staging of Alzheimer's Disease	CDR GDS	BG; CPI; CPO; Dental calculus; PPD
D'Alessandro et al., 2018 (Italy)	Cross-sectional	Case: 120 Control: 103	Case: 83/37 Control: 60/43	Case: nr Control: nr	CDR score	CDR	CPI; CPO; Dental calculus; GI; Gingival bleeding; PPD

(*continued on next page*)

Table 2 (*continued*)

Author, year (country of achievement)	Study type	Sample (n)	Sex (♀/♂)	Mean age ± SD	Alzheimer's diagnostic method	Cognitive assessment method	Periodontal assessment method
Holmer et al., 2018 (Sweden)	Case-control	Case: 52 MCI: 51 SCD: 51 Control: 76	Case: 28/24 MCI: 25/26 SCD: 18/33 Control: 43/33	Case: 71 ± 6 MCI: 69 ± 7 SCD: 62 ± 6 Control: 69 ± 6	NIA-AA diagnostic guidelines	MMSE/Montreal Cognitive Assessment; CDT; Blood tests; Brain imaging; Electroencephalography; Lumbar puncture with cerebrospinal fluid analysis	Furcation Involvement; Oral hygiene; PPD; Suppuration on probing; Tooth mobility
Maurer et al., 2018 (Germany)	Case-control	Case: 20 Control: 20	Case: 5/15 Control: 5/15	Case: nr Control: nr	Alzheimer's Disease Assessment Scale	MMSE	BI; PPD; Tooth mobility
Araújo et al., 2020 (Brazil)	Case-control	Case: 50 Control: 52	Case: 31/19 Control: 41/11	Case: 72.6 ± 1.1 Control: 69.8 ± 1.0	DSM	CDR; MMSE	AAP/EFP: BoP; CAL; Dental calculus; PI; PPD;
Panzarella et al., 2020 (Italy)	Case-control	Case: 20 MCI: 20 Control: 20	Case: 12/8 MCI: 9/11 Control: 12/8	Case: 83.5 ± 7.7 MCI: 78.0 ± 9.5 Control: 78.8 ± 8.1	DSM Fourth Edition Translated; NIA-AA diagnostic guidelines	MMSE	CPI; CPO; Dental Calculus; Gingival bleeding; PPD
Guo et al., 2021 (China)	Case-control	Case: 26 Control: 26	Case: 16/10 Control: 17/9	Case: 71.96 ± 7.9 Control: 70.04 ± 6.44	According to the International Classification of Diseases	MMSE	AAP/EFP: BoP; CAL; Dental calculus; PPD
Holmer et al., 2021 (Sweden)	Case-control	Case: 46 MCI: 40 SCD: 46 Control: 63	Case: 23/23 MCI: 19/21 SCD: 25/21 Control: 35/28	Case: 71 ± 6 MCI: 69 ± 7 SCD: 61 ± 6 Control: 69 ± 6	NIA-AA diagnostic guidelines	MMSE; CDT	Attachment loss on radiography; BoP; PPD; Subgingival microbiota samples
Fu et al., 2022 (China)	Case-control	Case: 20 Control: 20	Case: 13/7 Control: 13/7	Case: 74.7 ± 1.75 Control: 73.0 ± 1.71	CDR; MMSE	MMSE	AAP/EFP: CAL; Gingival recession; PI; PPD; Remaining teeth
Ma et al., 2022 (China)	Cohort	Case: 606 Control: 606	Case: 333/273 Control: 340/266	Case: nr Control: nr	DSM Fifth Edition	nr	AAP/EFP: BoP; CAL; PPD

Case - related to Alzheimer Disease; VaD - vascular dementia; Other - other types of dementia not specified; Cog Imp - cognitive impairment not specified; MCI - mild cognitive impairment; PD - Parkinson's disease; SCD - subjective cognitive decline; NINCDS-ADRDA - National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; DSM - Diagnostic and Statistical Manual of Mental Disorders; MMSE - Mini-Mental State Examination; CDT - Clock Drawing Test; CDR - Clinical Dementia Rating; NIA-AA - National Institute of Aging-Alzheimer's Association; GDS - Global Deterioration Scale; PI - Plaque Index; CAL - Clinical Attachment Loss; PPD - Probing Pocket Depth; CIL - Clinical Insertion Level; GI - Gingival Index; CPO - Decay-missing-filled index; BoP - Bleeding on Probing; BI - Bleeding Index; CPI - Community Periodontal Index; nr - not reported by the study.

reported the use of scientifically established criteria such as the Community Periodontal Index (CPI) [41,42,46]; O'Leary Plaque Index [37,39], while four used the 2017 AAP/EFP classification criteria [45,48–50]. Table 2 presents the main characteristics of each eligible study.

3.3. Individual results of the studies

Among the studies that presented numerical data through measures of effect [35,43,45,50], an association was found between

Table 3
Main quantitative results and outcomes of eligible studies.

Author, year	Measure and adjusted effect size (95% confidence interval)	Concern about the results	Statistical analysis	Main findings
Ship, 1992	nr	–	Student's t-test (normal distribution); Mann-Whitney U procedure (non-parametric values); Fisher's chi-square and two-way exact tests (prevalence data); Correlation analyses (level of dementia between groups - MMSE score); One-way ANOVA tests (Alzheimer's diagnosis and oral findings).	The management of Alzheimer's patients requires attention to hygiene and oral care (brushing, flossing, use of chlorhexidine spray, collaboration with family and friends, and frequent visits to the dentist), use of fluoride (fluoride toothpaste, fluoride water, and topical application of fluoride gel), and resolution of salivary problems such as xerostomia from psychoactive drugs (prescription of fluoride supplements, sugar-free candy and chewing gum, and artificial saliva).
Ship & Puckett, 1994	nr	–	Student's t-test (normal distribution); Mann-Whitney U procedure (non-parametric values); Fisher's chi-square and two-way exact tests (prevalence data); Correlation analyses (level of dementia between groups and over time - MMSE score).	The gingival health of subjects with Alzheimer's was considerably worse than that of control subjects and worsened with increasing severity of dementia. In contrast to the gingival findings, the periodontal results did not demonstrate significant differences between individuals with Alzheimer's and controls. The six-tooth surface index used in this study provided an accurate indication of gingival health but may underestimate the progression of periodontal disease.
Syrjälä et al., 2012	Probing depth: RR 1.4 (0.9–2.1)	The confidence interval includes the null value (lack of statistical significance).	Risk estimates, relative risks (RR), odds ratios (OR) and 95% confidence intervals (CI) were estimated using Poisson's multivariate regression models and logistic regression models, respectively.	The results showed that patients with Alzheimer's disease were more likely to have decayed teeth, teeth with deep periodontal pockets, and poor oral hygiene and dentures, compared to healthy people.
Martande et al., 2014	nr	–	Unpaired *t*-test (compare demographic characteristics and different clinical parameters between 2 groups); Single factor analysis of variance (examine the differences between the 4 groups for different parameters).	All periodontal parameters evaluated were higher in subjects with Alzheimer's than in healthy subjects. The periodontal health status of diseased individuals has deteriorated with disease progression and is closely related to their cognitive function.
Rolim et al., 2014	nr	–	Shapiro-Wilk test and Q-Q plot for the distribution of quantitative variables; ANOVA, MANOVA and Pearson's correlation coefficient for variables with normal distribution; Non-parametric chi square test was also performed.	The prevalence of gingivitis and periodontal disease was higher in the group of patients with Alzheimer's. Periodontal infections were more common in patients with mild Alzheimer's than in healthy individuals.
Gil-Montoya et al., 2015	Attachment loss: OR 2.31 (1.15–4.66)	The lower limit of the confidence interval is close to the null value.	After descriptive and comparative analyses of the study variables, multiple logistic regression analysis was applied.	Periodontitis was associated with cognitive impairment after controlling for confounding factors such as age, sex, and educational level.
Cestari et al., 2016	nr		Shapiro-Wilk test and Q-Q plot for the distribution of quantitative variables; ANOVA, MANOVA and Pearson's correlation coefficient for variables with normal distribution; Non-parametric chi square test was also performed.	Alzheimer's patients had elevated serum levels of IL-6 and patients with periodontitis had elevated serum levels of TNF-alpha. There was an association between IL-6 and TNF-alpha in patients with Alzheimer's and periodontitis.
Frota et al., 2016	nr	–	The results were analyzed using Fisher's exact test.	Elderly people with Alzheimer's Disease and Parkinson's Disease have poor oral health, as well as those without neurodegenerative diseases. As for the oral examination in the Alzheimer's group, it was observed that 54.2% had periodontal disease, and this was the most frequent oral manifestation in this group.
Aragón et al., 2018	nr	–	The differences between groups were analyzed using the unpaired Student's *t*-test for quantitative variables or chi-square tests for categorical variables. Spearman's correlation coefficients were calculated to assess the linear relationship between Alzheimer's and	Alzheimer's patients exhibited, compared to the control group, fewer teeth, fewer periodontally healthy sextants, and poorer oral health. After taking into account the influence of age, Alzheimer's patients had worse oral health (caries and periodontal disease).

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Table 3 (*continued*)

Author, year	Measure and adjusted effect size (95% confidence interval)	Concern about the results	Statistical analysis	Main findings
			several oral health related clinical variables	
D'Alessandro et al., 2018	nr	–	T-test for independent samples and the Spearman's correlation test were used to evaluate all variables.	Patients with Alzheimer's disease have a poor oral health status that progressively declines as the severity of the disease worsens. Patients had significantly higher rates of gingival bleeding, dental calculus, probing depth and gingival index compared to the control group.
Holmer et al., 2018	Probing depth: OR 15.12 (5.93–38.58) Attachment loss: OR 5.99 (1.02–35.13)	The confidence intervals are wide and reflect great variability in the study.	Intergroup differences were analyzed with a chi-squared test or Fisher's exact test for categorical variables; Logistic regression models adjusted for potential confounders.	The case group was associated with generalized marginal alveolar bone loss and increased number of deep periodontal pockets. Therefore, the results suggest that marginal periodontitis is associated with early cognitive impairment and Alzheimer's, but without evidence of causality.
Maurer et al., 2018	nr	–	nr	Three bacterial strains were found most prominently in patients with inflamed periodontitis: *Aggregatiobacter actinomycetemcomitans*, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*. These germs were also found in the molars of Alzheimer's patients.
Araújo et al., 2020	Probing depth: OR 6.23 (1.59–24.38) Attachment loss: OR 5.68 (1.73–18.57) Periodontal disease: OR 11.08 (3.99–30.75)	The confidence intervals are wide and reflect great variability in the study.	Significance of differences between groups was sought by the chi-square, Student's t, or the Mann-Whitney test; association between the periodontal variables with the variable group was tested in binary logistic regression models; Logistic Regression Models were used to test the association of oral findings, demographics, and groups.	Individuals with Alzheimer's had fewer teeth and greater clinical attachment loss than controls. Patients had a higher percentage of sites with plaque, calculus and bleeding on probing than controls. Periodontitis was a variable associated with Alzheimer's.
Panzarella et al., 2020	nr	–	Data with normal distribution were assessed using the Shapiro-Wilk test and analyzed with the *t*-test or one-way ANOVA; non-parametric tests; Dunn's post-hoc test (test pairwise multiple comparisons); Chi-square and Fisher's exact tests (test marginal associations between qualitative variables).	Current research suggests that Alzheimer's is associated with chronic periodontitis, which is able to determine tooth loss due to the pathogenicity of *Fusobacterium nucleatum*. These data still need to be confirmed in large population cohorts.
Guo et al., 2021	nr	–	Student's *t*-test, Welch's *t*-test and the Mann–Whitney *U* test were used to determine the significance of continuous data. Chi- squared test and Fisher's exact test were selected to calculate the difference in the categorical variable data.	The microbiome community of oral microbes was altered in Alzheimer's patients and the periodontal microbiome was sensitive to changes in cognition. In addition, *V. parvula* and *P. gingivalis* have been associated with Alzheimer's.
Holmer et al., 2021	nr	–	Intergroup differences were analyzed with a chi-squared test or Fisher's exact test for categorical variables; Logistic regression models adjusted for potential confounders.	Alzheimer's patients had high levels of *Slackia exigua* and Lachnospiraceae, which were associated with periodontal disease (deep periodontal pockets). In individuals with different degrees of cognitive deficit, the subgingival microbiota showed changes in relation to healthy individuals.
Fu et al., 2022	nr	–	The demographic and clinical data of the study population were analyzed by Student's *t*-test, Chi-Square test, Binary Logistic Regression.	The data showed that periodontal destruction was positively correlated with the severity of Alzheimer's Disease. Serological findings imply that Alzheimer's is a disease related to inflammation and *P. gingivalis* infection. The results of the present study suggested that periodontal infection and the oral microbiome are associated with Alzheimer's.

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Table 3 (*continued*)

Author, year	Measure and adjusted effect size (95% confidence interval)	Concern about the results	Statistical analysis	Main findings
Ma et al., 2022	Periodontal disease: HR 1.67 (1.24–2.23)	The lower limit of the confidence interval is close to the null value.	The comparison of the dementia and nondementia groups was made with the absolute standardized difference; Kaplan-Meier analysis was used to calculate the cumulative incidence of chronic periodontitis; and the log-rank test was used to test the significant difference between the groups.	Dementia and Alzheimer's were associated with an increased risk of periodontal disease that was age-dependent and independent of systemic confounders.

RR - Relative Risk; OR - *Odds Ratio*; HR - *Hazard Ratio*; nr - not related on the study.

Alzheimer's and periodontal disease. The relative risk (RR) was used as a measure of effect in two studies [35,50], and the odds ratio was used in two other studies [43,45]. Table 3 shows details of the outcomes of each eligible study.

In the study by Syrjälä et al. (2012), individuals with AD had a 40% higher risk of having periodontal pockets (RR 1.4; 95% CI 0.9; 2.1) without reaching statistical significance [35]. On a similar note, Ma et al. (2022) also found a 50% higher risk of periodontitis (PPD ≥5 mm in at least four teeth with each ≥1 site, CAL ≥5 mm on the same site, and BOP), among individuals with AD (RR 1.7; 95% CI 1.2; 2.2) [50]. Even though most studies did not provide an effect/association measure, such as risk or odds ratio, all studies evaluating the periodontal status among individuals with AD revealed that those individuals had poorer periodontal health than their counterparts.

For the studies evaluating periodontitis as a risk indicator for AD, Holmer et al. (2018) observed a 15-fold (OR 15.1; 95%CI 5.9; 38.6) higher chance of AD among individuals with teeth with PPD ≥6 mm and six times higher among those with CAL (OR 6.0; 95%CI 1.0; 35.1), both of which with wide confidence intervals, thus, representing great variability [43]. Similar estimates were noted by Araújo et al. (2020), who found an OR of 11.1 (95%CI 4.0; 30.7), with a broad confidence interval, for AD among periodontitis patients (presence of two or more interproximal sites with PPD ≥5 mm and CAL ≥5 mm, not on the same tooth, with BOP) [45]. Gil-Montoya et al. (2015) also found increased odds of AD among individuals with CAL (OR 2.3; 95%CI 1.1; 4.7) [38]. Results from these studies are imprecise, given the lack of a positive association, wide confidence intervals, and confidence intervals whose lower limit is close to the null value.

All studies, even those without effect/association measure estimates, indicated a positive association between periodontitis and AD.

Table 4
Risk of bias assessment by Joanna Briggs Institute Critical Appraisal Tools using the JBI Critical Appraisal Checklist for Case-Control Studies (Moola et al., 2020), Cross-Sectional Studies (Moola et al., 2020), and Cohort Studies (Moola et al., 2020).

Author, year	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Q.9	Q.10	Q.11	% yes/risk
Case-control studies												
Ship, 1992	✓	✓	✓	✓	✓	✓	✓	✓	U	–	*	80%/Low
Ship & Puckett, 1994	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	*	90%/Low
Rolim et al., 2014a	–	–	✓	✓	✓	U	✓	✓	✓	–	*	60%/Moderate
Gil-Montoya et al., 2015	–	–	✓	✓	✓	✓	✓	✓	✓	✓	*	80%/Low
Cestari et al., 2016	✓	✓	✓	✓	✓	✓	✓	✓	U	✓	*	90%/Low
Aragón et al., 2018	–	–	U	✓	✓	✓	✓	✓	✓	✓	*	70%/Low
Holmer et al., 2018	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	100%/Low
Maurer et al., 2018	✓	U	U	U	✓	U	✓	✓	U	–	*	40%/High
Araújo et al., 2020	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	*	90%/Low
Panzarella et al., 2020	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	100%/Low
Guo et al., 2021	✓	–	✓	U	✓	✓	–	✓	U	–	*	50%/Moderate
Holmer et al., 2021	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	100%/Low
Fu et al., 2022	✓	✓	✓	–	✓	✓	✓	✓	✓	–	*	80%/Low
Cross-sectional studies												
Syrjälä et al., 2012	U	✓	✓	✓	✓	✓	✓	✓	*	*	*	87,5%/Low
Martande et al., 2014	✓	✓	✓	✓	–	–	✓	–	*	*	*	62,5%/Moderate
Frota et al., 2016	U	✓	U	U	✓	–	U	–	*	*	*	25%/High
D'Alessandro et al., 2018	✓	✓	U	✓	U	–	✓	–	*	*	*	50%/Moderate
Cohort study												
Ma et al., 2022	✓	✓	✓	✓	✓	✓	✓	✓	U	U	✓	81,2%/Low

√ - yes; – - no; U - unclear; NA - not applicable; * - not related to the study.

3.4. Risk of individual bias in the studies

3.4.1. Methodological quality of the eligible studies

Detailed methodological information of eligible studies is shown in Table 4.

Only three case-control studies [43,46,47] met all the criteria from the checklist. For the case-control studies [33,34,37–39,41,43–49], the main biases were found in Q.1 and Q.2: three studies [37,38,41] and five studies [37,38,41,44,48], respectively, did not present adequate group matching to ensure comparability; Q.4: three studies [44,48,49] did not use standard measurements for the exposure compared to the majority of studies; Q.9: four studies [33,39,44,48] did not present clear follow-up time description; and Q.10: seven studies [33,34,37,44,45,48,49] lacked multivariate regression analysis.

For the cross-sectional studies [35,36,40,42], three studies [36,40,42] did not meet Q.6 and Q.8 because they did not perform strategies to deal with confounding factors and lacked multivariate regression analysis.

The cohort study [50] did not meet Q.9 and Q.10 due to not presenting a clear follow-up description.

3.4.2. Evaluation of control statements for possible confounders and bias consideration

All 18 eligible studies were analyzed, and ten studies [33,34,36,37,40,42,44,45,48,49] were excluded for mentioning only bivariate analysis or not reporting approaches to deal with confounding (e.g., multivariable, stratification). After this, eight studies [35,38,39,41,43,46,47,50] were included in the evaluation of control statements for possible confounders and bias consideration. Only one study [39] did not mention the term "confounding". Five studies [35,39,41,47,50] did not mention the term "bias". Only three studies [35,43,50] mentioned non-adjusted variables, and only one [50] reported them as not measured. One study [39] had no mention of confounding factors affecting their results, and another study [46] mentioned them possibly being affected. All eight studies stated the need for caution in interpreting their results. Only three studies [39,47,50] did not include limitations in their Conclusion section. The results of this evaluation of control statements for confounders and bias consideration are presented in Table 5.

3.4.3. Assessment of confounding factors

In the studies included in this analysis, 214 variables were identified. They were classified into six domains: (1) oral health-related; (2) sociodemographic and socioeconomic; (3) neurocognitive; (4) comorbidities; (5) lifestyle and habits; and (6) biochemical and genetic markers. The domain with more variables was the oral health-related domain, with 83 different variables. The most frequent variables were "age" and "sex" from the sociodemographic and socioeconomic domain, and they were present in all studies. Some variables had similar meanings, so they were set together in standardized terms for a better analysis. The confounding domains identified in each eligible study are presented in Table 6 and described in Appendix 2.

Only one study [50] used stratification variables, which were "age", "cardiovascular disease", "chronic obstructive pulmonary disease", "diabetes", "hyperlipidemia", "hypertension", "sex", "stroke", and "traumatic brain injury". Four studies used matching

Table 5
Evaluation of control statements for possible confounders and bias consideration.

Section	Question	Possible answers with explanation	N (%)
Abstract and Discussion	Is the term "confounding" mentioned in Abstract or Discussion?	Specific: if authors used the exact term "confounding".	8 (100%)
		Alluded: if authors used a similar term or phrase.	0
		No: if the authors used neither the exact nor similar term.	0
	Is the term "bias" used in Abstract or Discussion?	Yes: if authors used the term "bias".	3 (37,5%)
		No: if authors did not use this term.	5 (62,5%)
	Is any specific mention about non-adjusted variables in Abstract or Discussion?	Yes: if there was specific mention about non-adjusted variables with no reasons presented.	2 (25%)
		Not measured: if there was specific mention about non-adjusted variable not being measured.	0
		Other reasons: if there was specific mention about non-adjust variables and with plausible reasons for not adjusting them.	0
		No reasons: if there was specific mention about non-adjusted variables and with implausible reasons for not adjusting them.	0
		No: if there was no mention about any non-adjusted variable.	6 (75%)
	Is there any mention about confounders affecting results in Abstract or Discussion?	Likely: if authors used terms such as "likely" or convincing statements that confounders were not controlled.	6 (75%)
		Possibly: if authors used terms such as "possibly" or unsure statements that confounders were or were not controlled.	2 (25%)
		Unlikely: if authors used terms such as "unlikely" or convincing statements that confounders were controlled.	0
		No mention: if there was no mention about this possibility.	0
	Is there any statement about the need for caution in interpretating the results?	Yes: if there was explicit mention about the need for caution in interpretating the results obtained in the study.	8 (100%)
		No mention: if there was no mention about this need for caution.	0
Conclusion	Does Conclusion include any limitation about confounders?	Yes: if there was a mention of this limitation.	6 (75%)
		No: if there was no mention of this limitation.	2 (25%)

Table 6
Confounding domains identified in selected studies.

Author, year	Confounding domains					
	Oral health-related	Sociodemographic and socioeconomic	Neurocognitive	Comorbidities	Lifestyle and habits	Biochemical and genetic markers
Syrjälä et al., 2012	x	x	x	–	x	–
Gil-Montoya et al., 2015	x	x	x	x	x	–
Aragón et al., 2018	x	x	x	–	–	–
Holmer et al., 2018	x	x	x	x	x	–
Araújo et al., 2020	–	x	–	–	–	–
Panzarella et al., 2020	x	x	x	x	x	x
Holmer et al., 2021	x	x	x	x	x	–
Ma et al., 2022	x	x	x	x	–	–

x - identified in the study; – - not identified in the study.

variables: “age” [39,43,47,50], “diabetes” [39], “education” [39], “hypertension” [39], “propensity score” [50], and “sex” [39,43,47]. Fig. 2 shows the count graph of adjustment variables per domain.

4. Discussion

This study aimed to explore whether individual observational studies exploring the relationship between periodontitis and AD considered confounding and their level of heterogeneity. Furthermore, we examined data reporting and interpretation regarding the potential presence of confounding bias in individual studies. Our analysis suggests that confounding is neglected in more than 50% of the articles examining the relationship between periodontitis and AD. Among those studies accounting for confounding, there is a substantial variation in how adjustment approaches are defined, operationalized, and discussed across these studies. Additionally, while most authors mention the term “confounding” in their Abstract and Discussion, 62% do not mention the term bias in these respective sections. Moreover, the same proportion of studies does not state non-adjusted variables, whereas approximately 40% of the studies do not include any limitations about confounders in their conclusions. Interestingly, all studies reported the need for caution in interpreting the results, and 75% mentioned the possibility of confounders affecting their results. Only one study performed sensitivity analyses for unmeasured confounding to explore the potential role of unmeasured confounders in their findings [43]. Caution should also be applied when interpreting the results from the individual studies, as most of the evidence originates from cross-sectional and case-control studies in the presence of issues related to wide confidence intervals and inclusion and proximity of those with the null value.

While all studies adjusted their results for sociodemographic variables (e.g., sex, age, and socioeconomic status), not all studies accounted for relevant conditions in the association between periodontitis and AD, such as smoking. While smoking is a crucial confounder in this association, three studies did not consider smoking formerly in their analyses (even though one used comorbidities as proxies), and the remaining performed poor adjustment for smoking (e.g., dichotomous or categorical variable). Hujoel and co-workers [52], using data from the National Health and Nutrition Survey I Epidemiologic Follow-up Study (NHEFS), have demonstrated

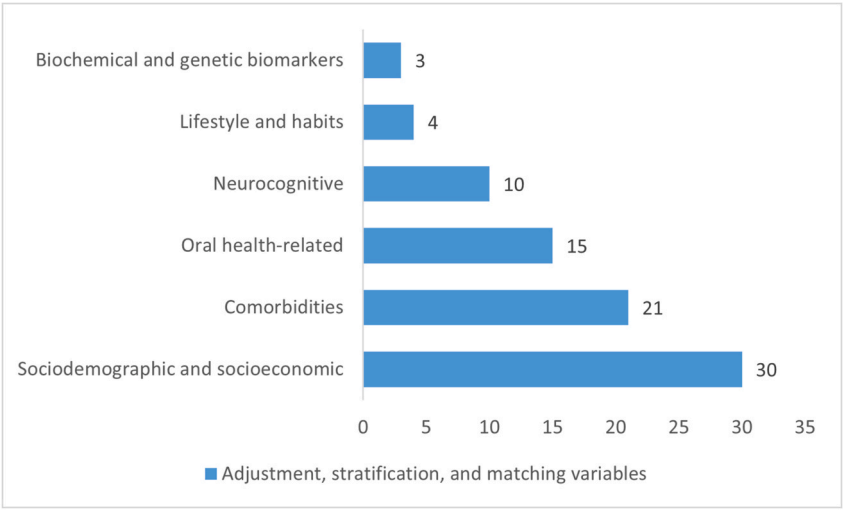

Fig. 2. The most common higher-level confounder domains considered in observational studies on periodontitis and Alzheimer’s disease.

that the poorer the control for smoking, the higher the chance periodontitis will reproduce the direction and strength by which smoking is associated with the explored systemic condition. Hence, it is not possible to rule that the lack or poor level of adjustment for smoking might have influenced the results toward a positive association, as in the phenomenon reported by Hujoel and colleagues [52].

Controlling for confounders can only be performed if the information on confounders is adequately obtained. The more inaccurate the data, the larger the residual confounding due to the impossibility of correctly adjusting the model. In the case of socioeconomic status and smoking, both influence health outcomes on multiple levels, which makes it challenging to obtain an accurate measure. The accumulation of the effects of the confounder along the life course may have an even stronger influence on the final estimates. Therefore, information about known confounders shall be collected more accurately as possible to minimize the bias introduced for data on the confounders we are unaware of, also called unknown confounders.

We also observed that despite using similar confounders, studies rarely measured these variables similarly. Let us examine the example of body mass index (BMI). Despite the existence of standard categories for BMI in the literature, two different cut-off levels were used in our small sample, not to mention the use of BMI as a continuous variable. Previous studies have discussed the difficulties in determining how categorical or continuous variables should be accounted for in the analytical models and potential issues that may arise [53,54]. On that note, it appears that inadequate adjustment for continuous variables with a non-linear but instead J- or U-shaped relation with the outcome, like BMI, may lead to substantial residual confounding [55].

Another aspect that merits attention relates to the variability in the adjustment variables. Even though it is not possible to discard that authors could not measure all potential confounders, it is more likely to speculate that such a diversity stems from the approaches used for confounding selection. While the available evidence should guide confounders' selection, dental researchers still rely on statistical significance to select potential confounders. Such an approach may be problematic as it does not consider the relationship between variables, and adjustment for variables in the causal pathway may lead to other sources of bias, including collider bias and over-adjustment. Thus, researchers should base their adjustment strategy on the best available evidence and use tools like directed acyclic graphs to conceptualize their thinking and communicate it to readers and peers. The careful study of exposure, outcome, and confounders also reduced the probability of interaction among confounders, which may increase the residual confounding multiplicatively [56].

Although most authors mentioned the concept of confounding, very few have explicitly used the term "bias" in their Abstract or Discussion. In addition, all authors ask for caution in interpreting their results; however, approximately 40% of them do not mention any limitations about confounders in their conclusions, and 60% do not state non-adjusted variables. Even though these findings are higher than those observed in the medical field, there is a need for more transparent reporting, in addition to discussions about the selection of confounders and residual and unmeasured confounding.

As a secondary finding, we observed that two studies did not mention any ethical considerations, whereas only three studies reported the use of the STROBE statement for their report. Interestingly, the two articles that did not report any ethical aspects of their research were published in the early 90s, when these ethical issues were not in the spotlight. With the implementation of the Declaration of Helsinki, reporting ethical aspects became mandatory in scientific journals. More recently, research guidelines have been developed not only to comply with ethical aspects but also to enhance the completeness and transparency of biomedical publications at the expense of wasted research resources, publication inaccuracy, or misleading findings with implications on healthcare decisions [57].

Our study has several potential limitations that need to be highlighted. Firstly, our sample included only 18 studies, of which eight had data on confounding. Despite our strategy to capture the most studies on this topic, some articles might have been missed, thus, precluding the generalization of our findings to all studies examining the association between periodontitis and AD. Secondly, we did not examine whether improvements in reporting practices (with the use of guidelines and their implementation by journals) has affected our results. Given our small sample size, it is not possible to perform such an accurate analysis at this stage. Additionally, the different populations might have deselected some potential confounders prior to the study (e.g., adjusting for age in a birth cohort study). It is possible that variables beyond age, such as sex, were used to restrict the enrolment of participants with a potential confounder. Fourthly, different criteria and classifications have been used to assess periodontitis and AD, and some heterogeneity in our results could be attributed to the different disease definitions.

Although all studies suggest an association between periodontitis and AD, irrespective of the direction, caution should be applied when interpreting these results. Additionally, the existing variation in the selection and operationalization of confounders might have affected this positive association. Our results indicate that while all authors ask for caution when interpreting their results, they do not mention or discuss potential bias due to confounding. Further longitudinal studies with proper assessment of periodontitis and AD and handling of confounders are required to elucidate this matter.

5. Conclusions

After identifying and analyzing potential confounders and confounding domains, caution must be taken to properly interpret the association between periodontitis and Alzheimer's disease. Although there is an association, no causality or specific roles can be addressed to any of them yet due to the observational design of the studies.

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Author contribution statement

Gustavo G. Nascimento and Luiz Renato Paranhos: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Fábio R M Leite: Conceived and designed the experiments; Analyzed and interpreted the data. Caio Melo Mesquita, Maria Tereza Campos Vidigal, Guilherme Henrique Borges: Performed the experiments; Analyzed and interpreted the data.

Data availability statement

Data associated with this study has been deposited at Systematic Review - all data originated from published articles.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15402.

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