The Saudi Dental Journal (2023) **35**, 625–640

King Saud University

The Saudi Dental Journal

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REVIEW ARTICLE

Periodontal health status of people with dementia – A systematic review of case-control studies

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Received 4 January 2023; revised 9 June 2023; accepted 13 June 2023
Available online 19 June 2023

KEYWORDS

Periodontal Disease;
Dementia;
Alzhiemer's Disease;
Oral Health

Abstract *Background:* The number of older people increases globally, so is the risk of cognitive impairment. Periodontal diseases are common among older adults with significant tooth loss and periodontal problems. Thus, this review explored the periodontal disease conditions among individuals with and without dementia.

Methods: Available databases such as Medline/Pubmed, Web of Science, Scopus, Cochrane Library and Embase/OVID were used in the search. Case-control studies reporting on periodontal disease and dementia parameters were selected based on PICO (Population, Intervention, Comparison and Outcomes) framework. A Newcastle-Ottawa Scale (NOS) was used to assess the quality reporting of the studies and PRISMA guideline was used for screening.

Results: A total of ten studies were identified for analysis. Most studies reported higher plaque index score (PI), bleeding on probing (BoP), pocket depth (PD) and clinical attachment loss (CAL) among individuals diagnosed with dementia or Alzheimer's disease compared with clinically healthy controls or individual diagnosed without dementia. A higher prevalence of subjects with severe periodontal disease was also observed in individuals diagnosed with dementia/Alzheimer's disease. The quality of the studies was found to be moderate with lower comparability and ascertainment criteria scores.

Conclusion: This qualitative analysis has shown poor periodontal health and increased inflammatory mediators in case groups compared to the control groups. Thus, more quality studies and novel intervention are warranted to reduce the impact of periodontal health on dementia globally.

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https://doi.org/10.1016/j.sdentj.2023.06.004
1013-9052

Contents

1. Introduction

Dementias have been one of the main causes of disability and dependency among elderly globally (WHO 2017), and Alzheimer's disease (AD) ranked seventh in causing of death (WHO, 2021). Alzheimer's disease and vascular dementia contributed approximately 7.0% of all the causes of dementia. Dementia was stated to increase rapidly after 60 years old (Lin, Chang, and Caffrey 2020). In contrast, mild cognitive impairment (MCI) has been considered as a transitional state or an early phase which often appears prior to the actual occurrence of dementia (Kasper et al. 2020). Although the cognitive impairment is usually apparent, it does not interfere with a person daily activities (Gillis et al. 2019). However, they are more at risk of developing dementia.

Previously, studies have stated poor oral conditions among those with dementias, compared with clinically healthy subjects (Hamza, Asif, and Bokhari 2021; Mukherjee et al. 2020). Although there were no obvious differences in terms of the teeth with decayed, missing and filling cases, and the periodontal diseases, individuals with dementias were found to have poor oral conditions and higher cases of oral mucosa lesion or soft tissues compared to those without (Gao et al. 2020; Delwel et al. 2018). Recent evidence-based studies have shown that in addition to oral conditions being more severe in people with dementias, the brain function may be affected with an increased risks of developing dementia among those with poor oral conditions. Thus, the poor oral conditions may not only be the consequences of dementia but could also be the contributing factors in the onset or progression of dementias, where the associations with periodontal diseases are of particular significance (Kapellas et al. 2019).

Studies have also shown that periodontitis is related with dementia and a risk factor for the progression of AD (Kamer et al. 2020). This is due to the nature of the periodontal disease, whereby the chronic inflammation condition leads to the releases of inflammatory mediators locally and systemically (Hegde and Awan 2019). As a result, the serum cytokines levels increase for examples; Interleukin−6 (IL-6), IL-2, IL-β, Tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP). Besides, increases in the levels of acute phase proteins and, plasma antibody, total white blood cell count, coagulation factor and neutrophils have also been reported to be increased. These peripheral inflammation mediators may disturb the integrity of blood brain barrier and disrupt the brain function, which eventually result in impaired cognitive functions (Huang, Hussain, and Chang 2021). Hence, this systematic review was conducted to deliver insight into periodontal disease conditions among individuals diagnosed with dementia and those without, based on case-control studies.

2. Methods

2.1. Search strategy

Seven available electronic databases were used to search the related articles; Medline/PUBMED, Web of Science, Scopus, The Cochrane Library and Embase/OVID. The search conducted up to November 2021 was not limited to any date or type of dementia. The keywords used for the search were MESH terms used in previous reviews (Nadim et al. 2020; Gusman et al. 2018; Maldonado et al. 2018). The keywords were; periodontal disease or periodontitis or periodontal infection or chronic periodontal disease or chronic periodontitis, and dementia or Alzheimer's disease or vascular dementia or cognitive dysfunction or frontotemporal dementia. Additional keywords derived from the MESH terms were also added such as periodontal inflammation, periodontal pocket and Lewy Body Dementia. Selected studies which fulfilled the inclusion criteria were further read and analysed (Fig. 1).

2.2. Review questions

The review questions were defined using the PICO framework;

- Population: individuals with periodontal status.
- Intervention: Periodontal indices – Plaque index (PI), Bleeding on probing (BoP), Gingival Bleeding Index (GBI), Pocket depth or Periodontal pocket depth (PD or PPD), Clinical attachment loss (CAL) or attachment loss (AL), Community Periodontal Index or Community Index of Periodontal Treatment Needs (CPI or CPITN).
- Comparison: between individuals with any type of dementia and without.
- Outcome: results on the periodontal indices for individuals with dementia and those without.

2.3. Inclusion criteria

The inclusion criteria for the search were that papers reporting the outcomes of case-control studies must have evaluated the periodontal indices in both types of samples of individuals with

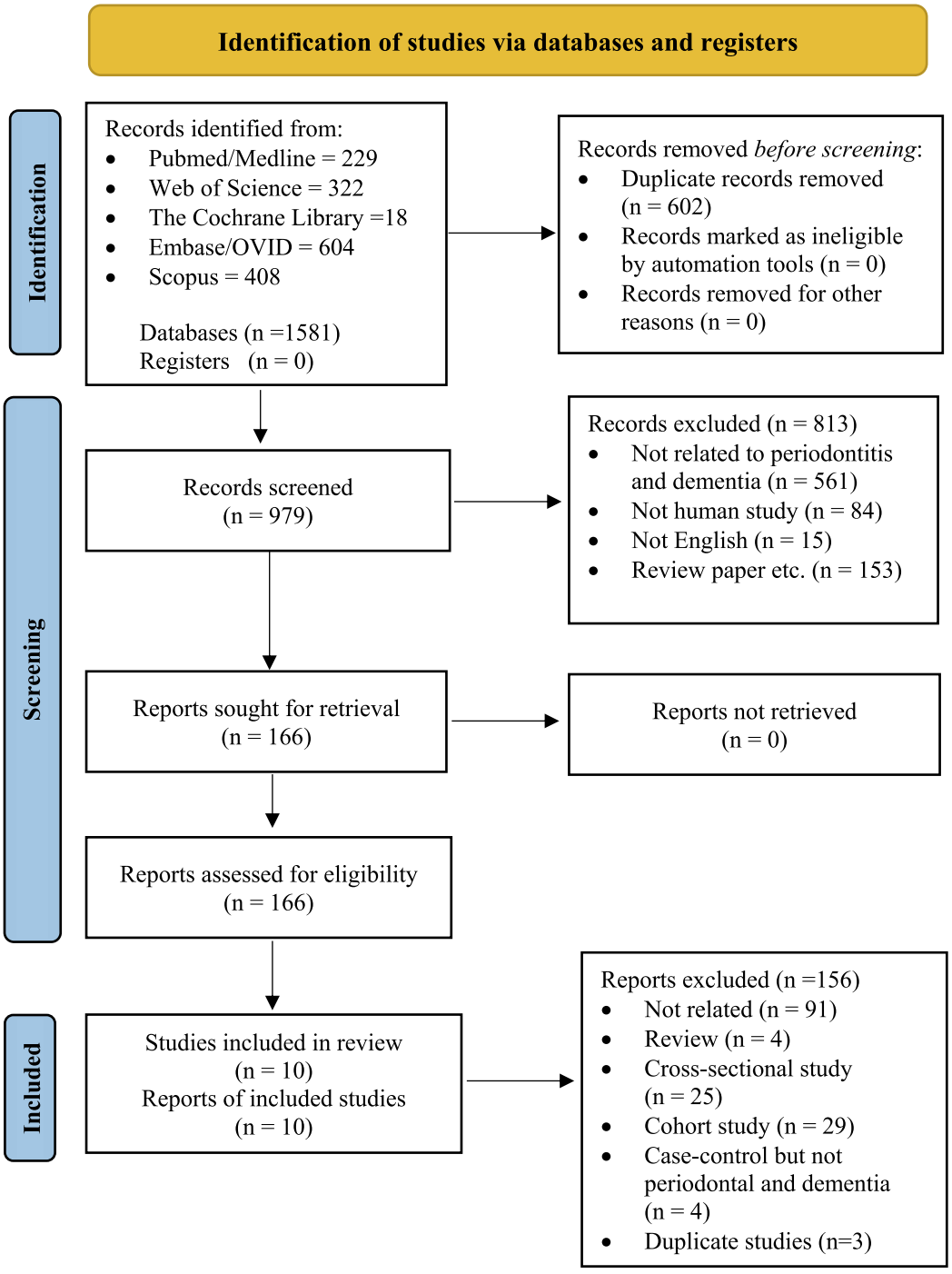

Fig. 1 Flow chart illustrating the selection process of the systematic review.

Table 1 Details of the studies - case study/comparative study.

Author & year	Title and Country of study	Study setting	Sample frame (Inclusion & Exclusion criteria)	Sample size and mean age	Instruments	Study Outcome(s)	Duration of study	Findings
Aragon F. et al. 2018	Oral Health in alzheimer's disease: a muliticentre case-control study Spain	Alzheimer Centres	**Inclusion**- Alzheimer disease (AD) based on McKhann et al. dementia criteria **Exclusion** - unable to collobrate in saliva test Control - healthy - no neurological disease *among patient's caregivers and friends	**Recruited**:106- AD (n = 70; 77.4 ± 10.6yrs) - Control (n = 36; 62.6 ± 7.1yrs)	Oral assessment (WHO 1987) i) Clinical - DMFT/DMFS- Periodontal (Community Periodontal Index – CPI) - Prosthetic status (fixed, removable)- Oral pathology (excessive wear, cheilitis, xerostomia, TMJ) - Saliva flow - Microbiology assay ii) Interview on oral health care (brushing frequency, visit to dentist and used of other oral aids) Cognitive decline & Dementiai) Clinical Dementia Rating (CDR-is the overall degree of dementia) - values from 0 to 3 (the higher score indicate greater degree of dementia) ii) Global Deterioration Scale (GDS-is a complete characterization of the decline stages) : values from 0 to 7 (the higher score indicate greater degree of dementia) Neurological conditions-Severe Mini-Mental State Exam (SMMSE), Mini-Cog Test, Clock Draw Test, Functional Assessment Staging of Alzheimer's Disease (FAST)	**Primary Outcome**- to compare oral helath status (DMFT/DMFS, CPI, prosthetic status, oral mucosa, saliva,microbiology assay) in case-control study	March 2012-July 2013	AD (n = 70) and Control (n = 36) **CPI scores** CPI = 0 (mean ± SD) (P < 0.001) AD = 0.1 ± 0.4 Control = 1.4 ± 2.1 CPI = 1 (mean ± SD) (P < 0.001) AD = 0.0 ± 0.3 Control = 1.0 ± 1.4 CPI = 2 (mean ± SD) (P = 0.29) AD = 1.1 ± 1.8 Control = 1.4 ± 1.8 CPI = 3 (mean ± SD) (P = 0.012) AD = 0.6 ± 1.1 Control = 1.3 ± 1.7 CPI = 4 (mean ± SD) (P = 0.54) AD = 0.5 ± 1.2 Control = 0.4 ± 0.8 *CPI = 1; bleeding on probing Regression analysis (n = 120) CPI = 0 (SE:-0.42, 95%CI: -(0.3–0.9), P < 0.001) CPI = 1 (SE:-0.44, 95%CI: -(0.2;-0.7), P < 0.001) *The number of sextants coded CPI = 0 and CPI = 1 decreased as a result of AD
Bramanti et al. 2015	Clinical evaluation of the oral health status I vascular-type dementia patients Italy	Institution Centre	**Inclusion** - Vascular Dementia (VD) **Exclusion** - edentulous Control - healthy *not mentioned	**Recruited**:168- Case -VD (n = 86; 82.7 ± 6.2yrs) - Control (n = 82; 80.2 ± 7.4yrs)	Oral assessment - DMFT- Periodontal (Plaque index;scale 0 to 3, BoP. PPD) - Oral mucosa and removal prosthetic status Cognitive decline & Dementia - VD diagnosed by medical specialist -imaging and clinical assessment - Cognitive and functional decline using MMSE Scores 26–30 – normal cognitive condition Scores 21–25 – mild dementia Scores11-20 – moderate dementia Scores 10 and less – severe dementia	**Primary Outcome** - to evaluate the oral health status in patients with vascular dementia (VD).	Jan 2014 – June 2014	VD (n = 86) and Control (n = 82) **PPD** (< 4mm; n,%) (P < 0.05) VD = 8; 9.3% Control = 69; 84.15% **PPD** (> 4mm; n, %) (P < 0.05) VD = 78; 90.7% Control = 13; 15.85% **PI** (%)Scores 0 (P > 0.05) VD = 1; 1.16% Control = 7; 8.54% Scores 1 (P > 0.05) VD = 12; 13.95% Control = 30; 36.58% Scores 2 (P > 0.05) VD = 32; 37.21% Control = 35; 42.68% Scores 3 (P < 0.05) VD = 41; 47.68%

Table 1 (*continued*)

Author & year	Title and Country of study	Study setting	Sample frame (Inclusion & Exclusion criteria)	Sample size and mean age	Instruments	Study Outcome(s)	Duration of study	Findings
								Control = 10; 12.2% **BI** (%) (P < 0.05) VD = 76; 88.37% Control = 32; 39.02%
Cestari J. A.F. 2016	Oral infections and cytokines levels in patients with Alzheimer's Disease and mild cognitive impairment compared with controls Brazil	Geriatric Clinic of a hospital	**Inclusion**- AD and MCI (mild-cognitive impairment) **Exclusion** - other neurodegenerative / neurological conditions, cerebral, facial or cervical tumors Control - healthy - without dementia *among patients who had followed in the same clinic	**Recruited**:65 - AD (n = 25; 77.68 ± 6.03yrs) - MCI (n = 19; 73.11 ± 6.79yrs - Control (n = 21; 75.33 ± 5.75yrs	Oral assessment -DMFT - oral mucosa, tongue and orofacial pain- Periodontal (plaque index - PI based on O'Leary plaque index, bleeding index - BI, periodontal pocket depth - PPD, clinical attachment loss - CAL and cemento-enamel junction distance - CEJ distance)*based on AAP Cytokines-serum level of cytokines (IL-6, IL-1β and TNF-α) -using multiplex panel (MILLIPLEX map High Sensitivity Human Cytokine Panel) Dementia-AD and MCI based on the National Institute of Neurological for Communicative Disorders and stroke (Alzheimer's Disease and Related Disorders Associations) (NINCDS-ADRDA)	**Primary Outcome** - to investigate the prevalence of oral infections and serum levels of IL-6 and TNF-α in patients with AD, MCI and non-demented elderly	Not mentioned	AD (n = 25), MCI (n = 19) and Control (n = 21) **PPD** (mean ± SD) (P = 0.766) AD = 2.82 ± 1.68 MCI = 3.05 ± 1.61 Control = 2.63 ± 3.25 **CAL** (mean ± SD) (P = 0.851) AD = 4.15 ± 3.90 MCI = 4.32 ± 3.12 Control = 3.92 ± 1.44 **PI** (%; mean ± SD) (P = 0.357) AD = 71.87 ± 26.58 MCI = 67.69 ± 28.41 Control = 58.47 ± 26.52 **BI** (%; mean ± SD) (P = 0.247) AD = 46.00 ± 33.32 MCI = 44.61 ± 34.26 Control = 29.17 ± 26.58 **IL-1β** (mean; units) No figure **IL-6** (mean ± SD; units) (P = 0.029) AD = 4.5 ± 2.5 MCI = 2.0 ± 2.0 Control = no figure **TNF-α** (mean ± SD; units) AD = 32.0 ± 19.0 MCI = 28.0 ± 11.0 Control = 18.5 ± 6.0
Chu C.H. et al. 2015 (Pilot)	Oral health status of elderly Chinese with dementia in Hong Kong Hong Kong	Alzheimer and Dementia Day-care Centres (case) and dental hospital (control)	**Inclusion** - Diagnosed with dementia - ≥ 60 yrs - no significant systemic disease **Exclusion** - require antibiotic prophylaxis for dental treatment Control - no systemic disease - without dementia *among registered list of dental patients in dental hospital who are not receiving dental treatment	**Recruited**:118 - Dementia (n = 59) (mild level of late-onset Alzheimer's disease) (79.8 ± 7.4 yrs) - Control (n = 59; no age mentioned)	Oral assessment (WHO 1997) - DMFT -Periodontal; CPI = 0 (no bleeding no probing) CPI = 1 (bleeding after probing) CPI = 2 (calculus is present) CPI = 3 (periodontal pocket of 4 to 5 mm) CPI = 4 (periodontal pocket ≥ 6 mm) Sialometric test; unstimulated salivary flow rate only Questionnaire - toothbrushing habits, use of dental aids and oral hygiene practices	**Primary Outcome** -to compare toothbrushing habits, unstimulated salivary flow and oral health status with and without dementia	March 2010	Dementia (n = 47) and Control (n = 50) (for CPI only) **CPI scores;** n (%) CPI = 0 Dementia = 0 (0) Control = 1 (2) CPI = 1 Dementia = 5 (11) Control = 7 (14) CPI = 2 Dementia = 5 (11) Control = 5 (10) CPI = 3 Dementia = 24 (51) Control = 26 (52)

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Table 1 (*continued*)

Author & year	Title and Country of study	Study setting	Sample frame (Inclusion & Exclusion criteria)	Sample size and mean age	Instruments	Study Outcome(s)	Duration of study	Findings
								CPI = 4 Dementia = 13 (27) Control = 12 (22) *CPI 3 and 4; P = 0.64
de Souza R.T. et al. 2014	Oral infections and orofacial pain in Alzheimer's Disease: a case-control study Brazil	Department of Neurology, School of Medicine of the University	**Inclusion** - met AD criteria with Mini-Mental Status Exam -MMSE scores 18 to 26 **Exclusion** - had any neurodegenerative / neurological conditions or tumours- diagnosed of moderate to severe AD by the MMSE (< 18 scores) Control - without AD *among patient's relative and family members	**Recruited**:59 - Case (n = 29; 75.17 ± 6.7yrs) - Control (n = 30; 61.17 ± 11.2yrs; without AD)	Oral assessment - DMFT- Periodontal (PI based on O'Leary's plaque, GBI, PPD-distance from the bottom of the pocket to the gingival margin, ref. value of > 3 mm, CAL-sum of PPD and CEJ, CEJ distance-distance from the gingival margin to the CEJ)	**Primary Outcome** - to evaluate the oral status (oral infections, periodontal disease), mandibular functions and orofacial pain in patients with mild AD verses healthy subjects.	Aug 2007 and July 2008	Case (n = 29) and Control (n = 30) **Gingivitis;** (n; %) (P < 0.001) Case = 9 (31%) Control = 3 (10%) **Moderate Periodontal Disease (PD);** (n; %) (P = 0.002) Case = 2 (6.9%) Control = 3 (10%) **Severe PD;** (n; %) Case = 6 (20.7%) Control = 2 (6.7%) *no description on PD
Gil-Montoya J.A. et al. 2015.	Is periodontitis a risk factor for cognitive impairment and dementia? A case-control study Spain	Neurology Department in Hospitals (case) and primary health care centre (control)	**Inclusion** - Dentate patient - > 50yrs old - diagnosed of MCI or dementia - > 30 points of phototest score **Exclusion** - Depressive, schizophrenia or personality disorder - Acute or chronic disease - Consumption of drug abuse - Had a periodontal treatment in the previous 6 months Control -without cognitive impairment * non-dental patients visiting primary health care center	**Recruited**:409 - Case (n = 180; 77.0 ± 7.8yrs) (MCI = 21; mid/moderate dementia = 123; severe dementia = 36) - Control (n = 229; 78.5 ± 7.9yrs; without cognitive impairment)	Oral assessment - Teeth present- Periodontal (PI based on Loe and Silness, attachment loss – AL; sum of PD with distance between the CEJ and gingival margin, probing depth -PD;distance from the gingival margin to the base of the periodontal pocket and BI based on Ainamo and Bay; - *at least 3 sites on at least two teeth per sextant when less than 12 teeth) - Degree of periodontitis disease based on % of sites for AL > 3 mm) 0% = absent 0% –32% = mild 33%-66% = moderate 675–100% = severe Dementia -Diagnostic and Statistical Manual of Mental Disorders-IV from National Institute of Neurological AD - NINCDS-ADRDA MCI -Spanish Society of Neurology Behavioural and Dementia Study Group Phototest – a brief cognitive impairment/dementia test used for the control group	**Primary Outcome** - to determine whether clinical periodontitis is associated with the diagnosis of cognitive impairment/dementia after controlling for known risk factors (age, sec and education level)	Jan 2011 and Dec 2012	Case (n = 180) and Control (n = 229) **PI scores** (mean ± SD) (P < 0.001) Case = 2.37 ± 0.65 Control = 1.55 ± 0.89 **BI scores** (%; mean ± SD) (P < 0.001) Case = 63.0 ± 31.1 Control = 50.6 ± 34.2 **PD** (mean ± SD) (P < 0.001) Case = 3.0 ± 0.7 Control = 2.6 ± 1.5 **AL** (mean ± SD) (P = 0.06) Case = 4.9 ± 1.6 Control = 4.5 ± 1.8 **AL** (> 3mm-% mean ± SD) (P = 0.002) Case = 75.0 ± 28.8 Control = 65.3 ± 35.2 **AL** (> 3mm-%) (P < 0.001) Case Mild = 18 (10.0) Moderate = 39 (21.7) Severe = 123 (68.3) Control Mild = 56 (24.5) Moderate = 47 (20.5) Severe = 126 (55.0)
Holmer et al.2018	Association between periodontitis and risk of Alzheimer's disease, mild cognitive impairment and subjective	Memory Clinic at University hospital	**Inclusion** – 50 to 80 years old- newly diagnosed with AD, MCI or	**Recruited**:230 - Case (n = 154; median	Oral assessment - Number of teeth - Prostheses, caries, restorations	**Primary Outcome** - to investigate the claimed association between marginal periodontitis (PD), AD and	October 2013 to April 2017	Case (n = 154) and Control (n = 76) **PI scores** (% of site)

Table 1 (*continued*)

Author & year	Title and Country of study	Study setting	Sample frame (Inclusion & Exclusion criteria)	Sample size and mean age	Instruments	Study Outcome(s)	Duration of study	Findings
	cognitive decline: a case-control study Sweden		SCD (Subjective Cognitive Decline) –no memory loss or sought medical attention - >28 MMSE scores, pass CDT - for control group **Exclusion** -epilepsy - meningioma/brain tumour - liver, kidney or lung dysfunction -endocrine disease - severe bleeding disorders - stroke - CVD disease - psychiatric disease - chronic inflammation - on medications Control - not experience memory loss or treatment - MMSE scores > 28 and pass CDT *among the residents in the municipal.	age = 70yrs) (AD = 52, MCI = 51, SCD = 51) - Control (n = 76; median age = 67)	- Oral mucosa,- Periodontal (oral hygiene- PI based on O'Leary-4 surfaces, PPD-6 sites, BoP-6 sites, suppuration, tooth mobility and furcation, marginal alveolar bone loss – MABL, periapical index) MABL –no/mild = loss of supporting bone < 1/3 of the root length -local = loss of supporting bone tissue ≥ 1/3 of the root length in < 30% of the teeth - general = loss of supporting bone tissues ≥ 1/3 of the root length in ≥ 30% of the teeth) Dementia- Neurological and psychiatric assessment, MMSE, Montreal Cognitive Assessment (MoCA). Clock drawing test (CDT), blood test, brain imaging (MRI/CT), electroencephalography (EEG), lumbar puncture (CSF) , neuropsychological assessment - other criteria were also used (AD-McKhann et al,2011; MCI- Winblad; SCD – pre-SCD criteria)	cognitive impairments **Secondary Outcome** - to investigate the association among other common biofilm-induced dental diseases and cognitive impairment		CaseAll (n = 154; P = 0.527 with control) 0–19 = 19 (12.4) 20–50 = 96 (62.8) ≥51 = 38 (24.8) AD (n = 52) 0–19 = 3 (5.8) 20–50 = 35 (67.3) ≥51 = 14 (26.9) MCI (n = 51) 0–19 = 5 (10.0) 20–50 = 29 (58.0) ≥51 = 16 (32.0) Control (n = 76; P = 0.527 with all) 0–19 = 6 (7.9) 20–50 = 48 (63.2) ≥51 = 22 (29.0) **BoP scores** (% of site) CaseAll (n = 154; P = 0.001 with control) 0–24 = 79 (51.6) 25–49 = 60 (39.2) 50–100 = 14 (9.2) AD (n = 52) 0–24 = 39 (59.6) 25–49 = 16 (30.8) 50–100 = 5 (9.6) MCI (n = 51) 0–24 = 20 (40.0) 25–49 = 26 (52.0) 50–100 = 4 (8.0) Control (n = 76; P = 0.001 with all) 0–24 = 59 (77.6) 25–49 = 14 (18.4) 50–100 = 3 (4.0) **PPD 4–5 mm** (%) CaseAll (n = 154; P = 0.000 with control) 0 = 3 (3.3) 1–8 = 58 (37.9) ≥9 = 90 (58.8) AD (n = 52) 0 = 2 (3.9) 1–8 = 20 (38.5) ≥9 = 30 (57.7) MCI (n = 51) 0 = 2 (4.0) 1–8 = 15 (30.0) ≥9 = 33 (66.0) Control (n = 76; P = 0.000 with all) 0 = 13 (17.1) 1–8 = 45 (59.2)

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Table 1 (*continued*)

Author & year	Title and Country of study	Study setting	Sample frame (Inclusion & Exclusion criteria)	Sample size and mean age	Instruments	Study Outcome(s)	Duration of study	Findings
								≥9 = 18 (23.7) **PPD ≥ 6 mm** (%) CaseAll (n = 154; P = 0.000 with control) 0 = 67 (43.8) ≥6 = 86 (56.2) AD (n = 52) 0 = 15 (28.9) ≥6 = 37 (71.2) MCI (n = 51) 0 = 26 (52.0) ≥6 = 24 (48.0) Control (n = 76; P = 0.000 with all) 0 = 63 (82.9) ≥6 = 13 (17.1) **MABL** (%) CaseAll (n = 154; P = 0.156 with control) No or mild = 88 (57.5) Localized = 51 (33.3) Generalized = 14 (9.2) AD (n = 52) No or mild = 27 (51.9) Localized = 17 (32.7) Generalized = 8 (15.4) MCI (n = 51) No or mild = 29 (58.0) Localized = 19 (38.0) Generalized = 2 (4.0) Control (n = 76; P = 0.156 with all) No or mild = 50 (65.8) Localized = 24 (31.6) Generalized = 2 (2.6)
Lopez-Jornet P. et al. 2021	Oral health status in older people with dementia: a case-control study Spain	Elderly home centres	**Inclusion** - age 65yrs an older - diagnosed with dementia **Exclusion** - on or had chemotherapy or radiotherapy - serious personality disorders - schizophrenia - drug abuse Control - without dementia or CI impairment, - no neurodegenerative disease - MMSE ≥ 28 *among the patients with the same sociocultural levels	**Recruited**:152 - Case (n = 69; mean age = 76.54 ± 5.65yrs) - Control (n = 83; mean age = 74.82 ± 8.17yrs)	Oral assessment (WHO 1997) - number of teeth - periodontal (PI based on O'Leary, BI, PPD-from gingval margin to the base of the periodontal pocket and halitosis) Dementia- Global Deterioration Scale-(GDS) GDS1 = normal individual GDS2 = very mild cognitive impairment (CI)/benign senile memory loss GDS3 = mild CI/incipent dementia GDS4 = moderate CI/mild dementia GDS5 = moderately severe CI/moderate dementia GDS6 = severe CI/moderately severe dementia GDS7 = very severe CI/severe dementia	**Primary Outcome** - to assess the impact of dementia upon oral health	Not mentioned	Case (n = 69) and Control (n = 83) **BI scores** (%; mean ± SD) (P < 0.001) Case = 70.97 ± 14.48 Control = 54.72 ± 19.57 **Pocket Depth** (mean ± SD) (P = 0.004) Case = 3.05 ± 0.99 Control = 2.57 ± 0.98 **PI** (%; mean ± SD) (P < 0.001) Case = 57.75 ± 12.66 Control = 44.85 ± 16.84 *Higher bleeding index increased the risk of dementia (OR:1.16, CI 95%:1.09–1.24, p-value: < 0.001)

Table 1 (*continued*)

Author & year	Title and Country of study	Study setting	Sample frame (Inclusion & Exclusion criteria)	Sample size and mean age	Instruments	Study Outcome(s)	Duration of study	Findings
Rai B. et al. 2012 (pilot)	Possible relationship between periodontitis and dementia in a North India old age population: a pilot study Belgium	University clinic	**Inclusion** - no details but according to the group Control - healthy *not mentioned the population	**Recruited:**107 - Case1; dementia patients (n = 20; mean age = 44.69 ± 13.68yrs) - Case2; periodontitis with CAL ≥ 6 mm (n = 55; mean age = 45.45 ± 14.25yrs) - Control; no CAL or not > 5 mm (n = 32; mean age = 44.12 ± 12.45yrs)	Oral assessment- Periodontal (PI – 2 surfaces;B&L, GI, PPD-6 sites, CAL- 6 sites from CEJ, BoP) Inflammatory mediator- GCF sampling from the four most inflamed sites in each quadrant. For matrix metalloproteinase (MMP) -9 and MMP-9. - used ELISA - Peripheral blood samples for MMP-8, MMP-9, IGF-I, free IGF-I and TNF-alpha -used ELISA Dementia assessment was not mentioned	**Primary Outcome** - to establish a possible relationship of inflammatory mediators between periodontitis and dementia	Not mentioned	**Dental plaque** (mean ± SD) (P = 0.05) *Case1 (Dementia) = 0.38 ± 0.15*Case2 (Periodontitis) = 0.23 ± 0.13* Control = 0.11 ± 0.09 **Gingival inflammation** (mean ± SD)-was not described (P = 0.05)*Case1 (Dementia) = 0.98 ± 0.38*Case2 (Periodontitis) = 0.68 ± 0.34* Control = 0.44 ± 0.28 **BoP** (%; mean ± SD) (P = 0.05) *Case1 (Dementia) = 89.12 ± 15.6*Case2 (Periodontitis) = 44.12 ± 10.56* Control = 21.84 ± 10.86 **Probing depth** (mm; mean ± SD) (P = 0.05)Case1 (Dementia) = 4.81 ± 0.78*Case2 (Periodontitis) = 2.85 ± 0.67* Control = 1.89 ± 0.67 **Clinical attachment level** (mm; mean ± SD) (P = 0.05)Case1 (Dementia) = 4.02 ± 0.23*Case2 (Periodontitis) = 2.34 ± 0.36* Control = 1.23 ± 0.21 **MMP-8 GCF** (mean ± SD) (P = 0.01)Case1 (Dementia) = 25.78 ± 6.89*Case2 (Periodontitis) = 18.12 ± 5.65* Control = 9.09 ± 4.13 **MMP-9 GCF** (mean ± SD) (P = 0.01) Case1 (Dementia) = 29.78 ± 15.56*Case2 (Periodontitis) = 19.67 ± 8.12* Control = 14.67 ± 12.13 **MMP-8 serum U/ml** (mean ± SD) (P = 0.01)Case1 (Dementia) = 1.56 ± 0.78*Case2 (Periodontitis) = 0.89 ± 0.61* Control = 0.63 ± 0.21 **MMP-9 serum U/ml** (mean ± SD) (P = 0.01)Case1 (Dementia) = 3.24 ± 0.68* Case2 (Periodontitis) = 2.17 ± 0.64* Control = 1.66 ± 0.64 **TNF-α pg/ml** (mean ± SD) (P = 0.01) Case1 (Dementia) = 4.36 ± 1.29*Case2 (Periodontitis) = 3.49 ± 1.15* Control = 2.12 ± 1.12 **IGF-I ng/ml** (mean ± SD) (P = 0.01) Case1

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Table 1 (*continued*)

Author & year	Title and Country of study	Study setting	Sample frame (Inclusion & Exclusion criteria)	Sample size and mean age	Instruments	Study Outcome(s)	Duration of study	Findings
								(Dementia) = 145.42 ± 47.45*Case2 (Periodontitis) = 196.45 ± 46.78* Control = 246.03 ± 69.45 **IGF-I ng/ml** (mean ± SD) (P = 0.01) Case1 (Dementia) = 121.13 ± 36.74*Case2 (Periodontitis) = 126.42 ± 35.86* Control = 134.12 ± 35.42 * with control
Ship J.A. 1992	Oral health of patients with Alzhiemer's disease USA	Clinic center of National Institute of Health	**Inclusion** - healthy and was diagnosed with AD **Exclusion** - other medical, neurological or psychiatric conditions Control - not taking any medication for systemic disease - not being treated for other disorder -MMSE > 28 (mean = 29.4 ± 0.7) *among community dwelling individuals	**Recruited**:90 - Case (n = 41; mean age = 68.2 ± 9.3yrs) - Control (n = 49; mean age = 64.1 ± 8.2yrs)	Oral assessment - number of teeth, DMFT-Periodontal (perio assessed on 6 surface & 6 teeth based on Ramfjord for dental plaque, gingival bleeding and calculus, pockets, attachment loss, recession & oral mucosa) AD - NINCDS-ADRDA criteria, CTscan, diagnostic radiograph, MRI, PET and neuropsychological and medical tests) Cognitive impairment- MMSE (for severity of cognitive impairment)	**Primary Outcome** - to investigate the oral conditions in unmedicated essentially healthy patients with AD	Not mentioned	Case (n = 41) and Control (n = 49) **Plaque** (%; mean ± SD) (P < 0.05) Case = 70.0 ± 2.0 Control = 45.0 ± 4.0 **Gingival bleeding** (%; mean ± SD) (P < 0.05) Case = 35.0 ± 2.0 Control = 27.0 ± 3.0 **Recession** (mm; mean ± SD) (P > 0.05) Case = 0.85 ± 0.10 Control = 1.30 ± 0.20 **Pockets** (mm; mean ± SD) (P > 0.05) Case = 2.50 ± 0.05 Control = 2.65 ± 0.05 **Attachment loss mm;** (mean ± SD) (P > 0.05) Case = 2.10 ± 0.1 Control = 2.70 ± 0.2

AD - Alzheimer disease; DMFT/DMFS – Decay, missing, filled, teeth/surfaces; CPI – Community Periodontal index; TMJ – temporal mandibular joint; CDR – Clinical Dementia Rating; GDS – Global Deterioration Scale; MMSE – Mini-Mental State Exam; MoCA – Montreal Cognitive Assessment; FAST – Functional Assessment Staging of Alzheimer's Disease; VD – Vascular Dementia; PPD – Periodontal Pocket Depth; MCI – Mild-Cognitive Impairment; SCD – Subjective Cognitive Decline; CDT – Clock Drawing Test; GDS – Global Deterioration Scale; BI – Bleeding Index; GBI- Gingival Bleeding Index; BoP – Bleeding on Probing; PI – Plaque Index; GI – Gingival Index; B- Buccal; L – Lingual; CEJ – Cemento-enamel junction; AL – Attachment Loss; MABL – Marginal alveolar bone loss; CAL – Clinical Attachment Loss; IL – Interleukin; TNF – Tumor Necrosis Factor; NINCDS-ADRDA - National Institute of Neurological for Communicative Disorders and stroke (Alzheimer's Disease and Related Disorders Associations); MILLIPLEX - map High Sensitivity Human Cytokine Panel); CVD – Cardiovascular Disease; MRI – Magnetic Resonance Imaging; CT – Computerized tomography; EEG – Electroencephalography; CSF – Cerebrospinal fluid; MMP – Metalloproteinase.

and without dementia. Studies that did not have explicit differentiation between the case and control groups were excluded. Besides, only studies that were in English and which reported the periodontal indices in the search criteria were included in the study.

2.4. Information retrieved

Study profiles such as the names of authors, countries of study, study settings and sample frames were retrieved. The studies' methods such as the number of participants and instruments used were also retrieved from the paper. The study's findings related to the objectives were extracted and tabulated. Table 1 summarizes the ten papers.

2.5. Assessment of studies' quality

The evaluation of the studies' quality was based on the Newcastle-Ottawa Scale (NOS). The total NOS scores indicated the study quality (Peterson et al. 2011). The NOS has three categories with a maximum score of nine. The three categories are; i) selection (maximum of four scores), ii) comparability (maximum of two scores), and iii) outcome (maximum of three scores). A total score of seven and higher indicates that the study is of good quality. The scores of five to six indicate that the study is fair in quality, and the scores less than 5 indicate that the study is of poor quality (McPheeters et al. 2012).

3. Results

A total of 1581 studies were retrieved out of which 602 duplicated studies were removed, and 979 were screened. Eight hundred thirteen studies were excluded, because of non-fulfilment to the inclusion criteria such as not being related to periodontitis and dementia, not human or clinical study, not in English language, a review, poster or other forms of presentations (which were not considered in this review). A total of one hundred sixty-six of potential studies papers were retrieved and screened. Ninety-one papers were further excluded because the periodontal conditions and dementia were not measured and four of them were review papers. Fifty-four papers were excluded for not being case-control studies; 25 were cross-sectional studies and 29 were cohort studies. Four case-control studies were not included; three papers had not related to periodontal parameters and dementia (Yang et al. 2021; Holmer et al. 2021; Franciotti et al. 2021); oral microbiome were compared between those diagnose with cognitive dysfunction and without (Yang et al. 2021; Holmer et al. 2021), broader neurogenerative disease were group together such as multiple sclerosis (Franciotti et al., 2021) and one did not have a dementia group (Shin et al. 2016). Four of the studies were found to be from the same authors (Gil-Montoya et al. 2015; Gil-Montoya, Sánchez-Lara, et al. 2017; Gil-Montoya, Barrios, et al. 2017; Gil Montoya et al. 2020). Most of the authors, the setting, the inclusion criteria, the characteristic of the participants and the assessment were all the same with slightly different in the style of reporting. Therefore, only the earliest study was considered for this review (Gil-Montoya et al. 2015). Hence, only a total of 10 studies were included for the final qualitative analysis. The screening and selection process of the study flow is summarised in Fig. 1.

3.1. Qualitative analysis of the studies

Among the 10 selected studies, only six stated a case-control study in their title (de Souza Rolim et al. 2014; Gil-Montoya et al. 2015; Holmer et al. 2018; Lopez-Jornet et al. 2021; Aragón et al. 2018; Bramanti et al. 2015). Four of the studies were conducted between the years 2010 and 2015 (Aragón et al. 2018; Chu et al. 2015; Gil-Montoya et al. 2015; Bramanti et al. 2015), one study between 2007 and 2008 (de Souza Rolim et al. 2014), one study had a longer duration of completion which was from 2013 to 2017 (Holmer et al. 2018), and the rest of the studies did not explicitly state the study duration (Cestari et al. 2016; Lopez-Jornet et al. 2021; Rai, Kaur, and Anand 2012; Ship 1992). Three studies were conducted in Spain (Aragón et al. 2018; Gil-Montoya et al. 2015; Lopez-Jornet et al. 2021), two studies were conducted in Brazil (Cestari et al. 2016; de Souza Rolim et al. 2014), one in Italy (Bramanti et al. 2015), one in Hong Kong (Chu et al. 2015), one in Belgium (Rai, Kaur, and Anand 2012) and one in USA (Ship 1992). Four of the study case group were from health centres (Aragón et al. 2018; Chu et al. 2015; Lopez-Jornet et al. 2021; Ship 1992; Bramanti et al. 2015), three were from clinics or departments of the hospital (Cestari et al. 2016; Gil-Montoya et al. 2015; Holmer et al. 2018) and two from clinics or departments in the university (de Souza Rolim et al. 2014; Rai, Kaur, and Anand 2012).

In total, there were 1504 subjects involved in the studies, 807 in the case groups and 697 in the control groups. The sample size of the cases ranged from 20 to 213 for dementia, 25 to 70 for Alzheimer's disease and 82 to 86 for Vascular dementia. The control group sample size ranged from 21 to 229. Most of the studies in the case group had the mean age of the subjects ranging from a minimum of 68.2 years old to a maximum age of 82.7, while in the control group had a minimum age of 62.6 years old and a maximum age of 80.2. One study used a median for the subjects' age (case = 70 years old and control = 67 years old) (Holmer et al. 2018), and one study had a younger population of the subjects (approximately 44 to 45 years old) (Rai, Kaur, and Anand 2012).

The cases were divided into subjects diagnosed with dementia, Alzheimer's disease, vascular dementia, Mild Cognitive Impairment (MCI) or subjective cognitive decline (SCD). Six studies distinctly divided the subjects into case and control groups; Alzheimer's disease and control groups (Aragón et al. 2018; de Souza Rolim et al. 2014; Ship 1992), Vascular dementia and control group (Bramanti et al. 2015) and dementia and control groups (Chu et al. 2015; Lopez-Jornet et al. 2021). Two studies have three distinct groups; Alzheimer's disease, MCI and control groups (Cestari et al. 2016), and dementia, MCI and control groups (Gil-Montoya et al. 2015). One study has four groups, namely Alzheimer's disease, MCI, SCD and the control groups (Holmer et al. 2018). One study has three groups, but one case group is not specific to the dementia category, rather it is a group with subjects having periodontitis disease (Rai, Kaur, and Anand 2012).

3.2. Quality of the studies

Four studies had NOS scores of seven and more (Cestari et al. 2016; de Souza Rolim et al. 2014; Holmer et al. 2018; Ship 1992), five studies had NOS scores of six (Aragón et al.

2018; Gil-Montoya et al. 2015; Lopez-Jornet et al. 2021; Rai, Kaur, and Anand 2012; Bramanti et al. 2015), and one study had a score of five (Chu et al. 2015) Table 2. Two studies had the control population within the same community (Cestari et al. 2016; Lopez-Jornet et al. 2021), and two studies did not describe the control population (Rai, Kaur, and Anand 2012; Bramanti et al. 2015). Regarding the comparability between the cases and controls, three studies did not describe the matching criteria of the control group (Aragón et al. 2018; Ship 1992; Rai, Kaur, and Anand 2012). One study matched the age range between the case and control groups (Gil-Montoya et al. 2015). Two out of the ten studies were based on existing medical records only for the ascertainment of exposure (Chu et al. 2015; Lopez-Jornet et al. 2021). All studies had the same methods of oral assessment between the case and control groups. Five studies had different cognitive assessment methods for the case and control groups (Aragón et al. 2018; Chu et al. 2015; Gil-Montoya et al. 2015; Holmer et al. 2018; Bramanti et al. 2015). For the non-response rate, most studies had the same response rate for both groups, except one study which had no description for the case group (Chu et al. 2015).

3.3. Instruments for assessment

3.3.1. Dementia

Three of the studies used the National Institute of Neurological for Communicative Disorders and stroke - Alzheimer's Disease and Related Disorders Associations criteria (NINCDS-ADRDA) (Cestari et al. 2016; Gil-Montoya et al. 2015; Ship 1992) and two studies used McKhann *et al*. 2011 criteria to diagnose Alzheimer's disease (Aragón et al. 2018; Holmer et al. 2018). For dementia, one study used the Diagnostic and Statistical Manual of Mental Disorder-IV (Gil-Montoya et al. 2015). Four studies did not specifically state the assessment used for dementia (Chu et al. 2015; Lopez-Jornet et al. 2021; Rai, Kaur, and Anand 2012) or Alzheimer's disease (de Souza Rolim et al. 2014). Mini-Mental State Exam (MMSE) was used in studies for MCI assessments (Holmer et al. 2018) and vascular dementia (Bramanti et al. 2015). One study used the Spanish Society of Neurology Behavioural and Dementia Study Group criteria for MCI (Gil-Montoya et al. 2015).

3.3.2. Periodontal disease

Seven studies measured the dental plaque using plaque index (PI); four were based on O'Leary plaque assessment (Cestari et al. 2016; de Souza Rolim et al. 2014; Holmer et al. 2018; Lopez-Jornet et al. 2021), two studies were based on Loe & Silness plaque index criteria (Gil-Montoya et al. 2015; Bramanti et al. 2015), and one did not specify the criteria used to measure the dental plaque (Rai, Kaur, and Anand 2012). Six studies measured the gingival bleeding using the term either bleeding index (BI) or BoP; three studies were based on Ainamo & Bay 1975 criteria (de Souza Rolim et al. 2014; Gil-Montoya et al. 2015; Bramanti et al. 2015), one study based on the American Academy of Periodontology 2000 (Cestari et al. 2016), one study based on the National Institute of Dental Research, US (Ship 1992) and three studies did not specify the criteria used to measure the gingival bleeding (Holmer et al. 2018; Lopez-Jornet et al. 2021; Rai, Kaur, and Anand 2012). One study has an outcome on the gingival inflammation but with no description of the gingival index criteria (Rai, Kaur, and Anand 2012). PD was measured in seven studies; six sites measurement were used on each tooth for two studies (Holmer et al. 2018; Rai, Kaur, and Anand 2012), a minimum of three sites measurements were used in one study, for the number of teeth less than 12 (Gil-Montoya et al. 2015) and four studies did not specify the measurement type used (Cestari et al. 2016; de Souza Rolim et al. 2014; Ship 1992; Bramanti et al. 2015). Five studies measured the AL (Gil-Montoya et al. 2015) or CAL (Cestari et al. 2016; de Souza Rolim et al. 2014; Rai, Kaur, and Anand 2012) or AL (Ship 1992). Community Periodontal Index (CPI) was based on WHO criteria in 1987 (Aragón et al. 2018) and 1997 (Chu et al. 2015). Periodontal disease severity was measured in one study (de Souza Rolim et al. 2014) and bone loss was based on MABL, also in one study (Holmer et al. 2018).

3.3.3. Synthesis of periodontal results

3.3.3.1. Dental plaque. Five out of seven studies showed a significant difference in the dental plaque scores between the case and control groups (Gil-Montoya et al. 2015; Lopez-Jornet et al. 2021; Rai, Kaur, and Anand 2012; Ship 1992; Bramanti et al. 2015). Higher plaque scores were observed in the case group (mean; min: 0.38 ± 0.15 to max: 2.37 ± 0.65; % = 58%) compared with the control group (mean; min: 0.11 ± 0.09 to max: 1.55 ± 0.89; % = 45%). Bramanti *et al*. (Bramanti et al. 2015) showed a significantly higher percentage of subjects with PI scores of 3 in the case group (48%) than the control group (12%). Two studies did not show a significant difference (Cestari et al. 2016; Holmer et al. 2018), although Alzheimer's disease patients had higher plaque scores compared with the MCI and control groups (AD = 71.87 ± 26.58, MCI = 67.69 ± 28.41, control = 58.47 ± 26.58) (Cestari et al. 2016). Meanwhile, Holmer *et al*. (Holmer et al. 2018) showed a higher percentage of sites with plaque (≥51 %), in the control group (29%) compared with the case group (24.8%), but with no significant difference between the groups. Four studies measured mean of percentage of sites with plaque (Cestari et al. 2016; Holmer et al. 2018; Ship 1992; Lopez-Jornet et al. 2021) and the other studies used PI scores (Gil-Montoya et al. 2015; Rai, Kaur, and Anand 2012; Bramanti et al. 2015).

3.3.3.2. Gingival bleeding. Most studies revealed significant differences in measures of gingival bleeding, indicative of inflammation, between the case and control groups. The case group has a higher percentage of bleeding scores in five of the studies (mean between35.0 ± 2.0 to 89.12 ± 15.6), compared with the control group (mean between 21.8 ± 10.9 to 54.7 ± 19.6) (Gil-Montoya et al. 2015; Holmer et al. 2018; Lopez-Jornet et al. 2021; Rai, Kaur, and Anand 2012; Ship 1992). Bramanti *et al*. (Bramanti et al. 2015) showed significantly higher bleeding scores in vascular dementia group (88%) than the control group (39%). A study by Cestari et al. (Cestari et al. 2016) found a higher percentage of bleeding scores in AD and MCI (mean: AD = 46.00 ± 33.32, MCI = 44.61 ± 34.26) among the case groups compared with the control group (mean: 29.17 ± 26.58). However, there was no significant difference between the groups.

3.3.3.3. Periodontal pocketing. Seven studies reported on periodontal pocket depth with four of them showing a significant difference between the case and control groups. Three studies had deeper mean PD in the case group (mean; min: 3.0 ± 7.0 mm to max: 4.81 ± 0.48 mm) compared with the control group (mean; min: 1.89 ± 0.67 mm to max: 2.57 ± 0.98 m m) (Gil-Montoya et al. 2015; Lopez-Jornet et al. 2021; Rai, Kaur, and Anand 2012). In the study by Holmer *et al.* (Holmer et al. 2018), significant differences were observed between the case and control group; case: 56.2% of subjects had one or more sites with ≥ 6 m pocketing and 58.8% had ≥ 9 sites with PD of 4 to 5 mm and control: 17.1% of subjects had one or more sites with ≥ 6 m pocketing and 23,7% had ≥ 9 sites with PD of 4 to 5 mm. Bramanti *et al.* (Bramanti et al. 2015) also showed a significant difference between the case and control group with higher percentage of subjects in the case group (90.7%) had PD > 4 mm compared with the control group (15.8%). Two studies did not show a significant difference between the case and control groups (Cestari et al. 2016; Ship 1992).

3.3.3.4. Clinical attachment loss (CAL). Four out of six studies reported a significant difference in the CAL between the case and control groups (Gil-Montoya et al. 2015; Holmer et al. 2018; Rai, Kaur, and Anand 2012; Ship 1992). The CAL in the case group and the control group ranged from 4.02 ± 0.23 mm to 4.9 ± 1.6 mm and1.23 ± 0.21 mm to 4.5 ± 1.8 mm respectively (Gil-Montoya et al. 2015; Rai, Kaur, and Anand 2012). Meanwhile two other studies found higher percentages for CAL > 3 mm for case group (79.5% and

Table 2 Studies quality based on Newcastle-Ottawa Scales (NOS) assessment.

Criteria and Authors	Aragon et al. 2018	Bramanti et al. 2015	Cestari at al. 2016	Chu et al. 2015	De Souza et al. 2014	Gil-Montoya et al. 2015	Holmer et al. 2018	Lopez-Jornet et al. 2021	Rai et al. 2010	Ship et al. 1992
1 Is the case definition adequate?										
yes, with independent validation*	*	*	*	*	*	*	*	*	*	*
yes, e.g. record linkage or based on self-reports										
no description										
2 Representativeness of the cases										
consecutive or obviously representative series of cases *	*	*	*	*	*	*	*	*	*	*
potential for selection biases or not stated										
3 Selection of Controls										
community controls *	*	*		*	*	*	*			*
hospital controls										
no description										
4 Definition of Controls										
no history of disease (endpoint)*	*	*	*	*	*	*	*	*	*	*
no description of source										
5 Comparability of cases and controls on the basis of the design or analysis										
study controls for_____(Select the most important factor.) *			*	*	*		*	*		
study controls for any additional factor (These criteria could be modified to indicate specific control for a second important factor)*										
6 Ascertainment of exposure										
secure record (eg surgical records) *	*	*	*		*	*	*		*	*
structured interview where blind to case/control status *										
interview not blinded to case/control status										
written self-report or medical record only										
no description										
7 Same method of ascertainment for cases and controls										
yes *			*		*			*	*	*
no										
8 Non-Response rate										
same rate for both groups *	*	*	*		*	*	*	*	*	*
non respondents described										
rate different and no designation										
Total score	6/9	6/9	7/9	5/9	8/9	6/9	7/9	6/9	6/9	7/9

84.2%) compared with the control group (62% and 49%) (Gil-Montoya, Barrios, et al. 2017; Gil Montoya et al. 2020). Cestari *et al*. (Cestari et al. 2016), showed a higher mean of CAL in AD (4.15 ± 3.90 mm) and MIC (4.32 ± 3.12 mm) for the case group than the control group (3.92 ± 1.44 mm), but with no significant difference ($P > 0.05$). There was also no significant difference between the case and control groups in Ship *et al*.'s study, with the latter having a higher CAL (case: 2.10 ± 0.1 mm, control: 2.70 ± 0.2 mm).

3.3.3.5. Community periodontal index (CPI). Only two studies measured periodontal index using CPI (Aragón et al. 2018; Chu et al. 2015). There were significant differences between the case and control groups in mean scores of CPI 1 ($P < 0.001$) and CPI 3 ($P < 0.05$). However, the scores were higher in the control group than in the case group (Aragón et al. 2018). No significant difference was found between the case and control groups for CPI 3 and 4 (78% and 74%; $P > 0.05$) (Chu et al. 2015).

3.3.3.6. Periodontal disease. Only one study measured periodontal disease based on its severity; mild, moderate and severe (de Souza Rolim et al. 2014). There was a significant difference between the case and control groups, with a higher percentage of subjects in the case group having more severe conditions of periodontal disease (min: 20.7%, max: 78.1%) compared to the control group (min: 6.7%, max: 48.9%).

3.3.3.7. Marginal alveolar bone loss (MABL). Only one study used the alveolar bone loss to assess the periodontal condition (Holmer et al. 2018). There was no significant difference between the case and control groups ($P > 0.05$). A higher percentage of subjects had localized and generalized bone loss in the case group (33% and 9%, respectively) compared with the control group (32% and 3%, respectively). No MABL or mild MABL was found higher in percentage in the control group compared to the case group (control group; 65% and case group; 57%).

3.4. Inflammatory mediators

Two studies reported the serum levels of cytokines (Cestari et al. 2016; Rai, Kaur, and Anand 2012). Both studies used venous blood samples to evaluate the cytokines serum levels. The high level of IL-6 was reported in subjects with lower cognitive tests, while a high level of TNF-α was associated with poorer periodontal conditions ($P < 0.05$) (Cestari et al. 2016). Total white blood cells, neutrophils, thrombocytes, CRP, Matrix metalloproteinase (MM-8, MM-9) and TNF-α were found to be significantly higher among those diagnosed with dementia and periodontitis, compared to healthy control individuals (Rai, Kaur, and Anand 2012). Meanwhile the insulin-like growth factor (IGF-1) was found to be significantly lower among dementia and periodontal subjects compared to healthy control individuals ($P = 0.01$).

4. Discussion

The periodontal disease and poor oral health increased with the severity of dementia (Sukhumanphaibun and Sangouam 2020; Patcharawan Srisilapanan and Jai-Ua 2013). This review based on case-control studies showed poorer periodontal conditions among individuals diagnosed with dementia compared with healthy individuals, despite limited associations reported between periodontal condition and dementia from the studies. Among the studies, only three performed regression analysis on the association between dementia and periodontal condition exposure (Holmer et al. 2018), where it was found that PPD of ≥ 6 mm was more likely to be associated with AD. A higher percentage of AL was significantly associated with approximately three times more likely among individuals diagnosed with cognitive impairment, and with dementia (Gil-Montoya et al. 2015). A study by Lopex-Jornet et al. (2021) stated that, the higher bleeding index was one time more likely to increase the risk of dementia (Lopez-Jornet et al. 2021). Hence, these studies showed the significant association between periodontal conditions and cognitive impairment. A systematic review concluded that a 50% of reduction of the periodontal cases will reduce the number of patients with dementia (Nadim et al. 2020). This provides a good indication that preventing or minimising the periodontal condition could reduce the number of people diagnosed with dementias globally.

Despite the lack of association reported in the case-control study, longitudinal studies have showed significant results. A ten-year follow-up study in Taiwan reported that subjects with intensive periodontal treatment and dental prophylaxis were at lower risk of developing dementia than those with PD but did not have periodontal treatment and had their teeth extracted (Lee et al. 2017). Another ten-year follow-up study also reported the same finding with higher risks of developing dementia and Alzheimer's disease among subjects with chronic periodontitis compared to those who did not have this diagnosis (Choi et al. 2019). The findings were associated with the pathogenesis of periodontal and dementia inflammatory conditions. Past studies have support the possibility of periodontal inflammation affecting cognitive abilities (Kamer et al. 2012; Sochocka et al. 2017).

Studies revealed that periodontal conditions were higher among those diagnosed with dementia compared with the clinically healthy controls. Despite the fact that people with dementias may have a more limited ability to manage their oral hygiene, measures for periodontal disease severity showed higher scores among the case groups compared with the control groups. The MABL was also reported to be more in the case group compared to the control group. The level of the inflammatory mediators were found to increase in individuals diagnose with dementia and periodontal diseases compared to those diagnosed without dementia and periodontal disease. Hence, the roles of the peripheral inflammatory mediators could be proposed as one of the probable risk factors for cognitive impairment. However, more quality studies should be conducted to confirm these findings.

A few limitations had to be considered. First, the studies were found to be varied in terms of instruments used to identify dementia. Some studies were based on previously existing medical records, while others had a *de novo* assessment of the disease state. A review reported that MOCA is one of the most common and preferable tool for MCI screening, while Addenbrooke's Cognitive Examination (ACE) is a preferable tool for dementia screening (Abd Razak et al. 2019), although no review paper had been reported on the most recommended tool to diagnose dementia. Second, the outcomes of

periodontal conditions were varied in terms of the units, measurements, or indices used. Third, the populations of the samples were varied in terms of the age, sampling and assessments. Overall, this review revealed that the published case-control studies were relatively heterogenic, mainly related to the instruments used to assess dementia and periodontal diseases.

5. Conclusion

Although periodontitis is suggested as one of the risk factors for dementia and Alzheimer's disease, the association remains unclear and the studies summarised here have high heterogeneity. Thus, more well-designed, better quality and highly evidence-based studies for the aforementioned relationship should be conducted to reduce the impact of dementia globally.

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.

Acknowledgment

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' statements

N. Ab Malik, contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript. A. W. G, Walls, contributed to conception, data acquisition and interpretation, and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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