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REVIEW ARTICLE

Periodontal status in patients with Alzheimer's Disease: a scoping review

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ABSTRACT

Periodontitis is the most common condition of chronic periodontal infection and inflammation in the elderly population. Periodontal disease can cause local inflammation that contributes to higher risk of systemic inflammatory disease. Current research suggests a possible link between periodontal disease and neurodegenerative disease, such as Alzheimer's disease. The aim of the study is to provide a profile of the periodontal tissue status in people with Alzheimer's disease. This scoping review followed Joanna Briggs Institute (JBI) guideline, and the searching was conducted using PubMed, Cochrane, and EBSCOHost databases during February 6th – February 7th, 2021 with keywords of periodontal disease, periodontitis, periodontal inflammation, Alzheimer's disease and dementia. It also included MeSH terms of "periodontal disease" and "Alzheimer's disease" if available. Additionally, snowballing technique was used to include more articles. The identification and writing process for this article followed the PRISMA-ScR framework. There were 60 articles included in this study. This scoping review shows a profile of general characteristics including decreased oral hygiene and periodontal tissue status showed by high score of plaque and calculus, gingival inflammation, high percentage of Clinical Attachment Loss (CAL), Bleeding on Probing (BOP) along with deterioration of cognitive function. There was a decreasing level of periodontal health along with the decline in cognitive function experienced by AD participants. However, further research is needed to see the mechanism of this relationship.

Keywords: *Alzheimer's disease; dementia*; periodontitis; periodontal disease

INTRODUCTION

Periodontal disease is an inflammatory and destructive condition that affects periodontal tissue or the supporting tissues of the teeth, including the gingiva, alveolar bone, and supporting tissue of the surrounding teeth. The causes of periodontal disease are complex, but the primary cause is the presence of bacteria in dental plaque. Periodontitis triggers the body's immune reaction, which in turn can damage the soft and hard tissues around the teeth, movement of teeth, and the detachment or loss of some elements of the teeth.[1,2] Periodontitis is the most common chronic inflammation for older people, which contributes to higher level of endovascular inflammatory mediators. This condition could increase the risk of systemic inflammation. Therefore, periodontitis is indicated to have a role in neurodegenerative disease development, including Alzheimer's disease (AD).[3–5]

Acute and chronic systemic inflammation are characterized by the production of C-reactive protein (CRP) from the liver and pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) from macrophage. TNF-α plays a role in the immunity of the brain by activating the central immune system, including microglial cells. For the microglial cells that priorly have been activated by neurodegenerative change, the presence of acute systemic inflammation will cause excessive non-spesific immune response, which could produce cytotoxic inflammatory mediators leading to an acceleration of neurodegenerative process.[6]

AD is a chronic and progressive neurodegenerative disease which causes significant destruction on brain structure and function. AD is a multifactorial disease with unknown definite cause.[7] AD is the most common cause for dementia, where 80% of dementia cases are

resulted from AD.[8] The prevalence of AD is known to increase with age, supported by the majority of AD patients who are the elderly aged 65 years old or more.[9] The prevalence of AD is expected to be 2 times higher every 5 years after reaching the age of 65, and the risk of AD is expected to reach 50% after the age of 85.[10]

In Indonesia, dementia case is estimated to reach 1.894.000 cases in 2030. The main problem of neurodegenerative disease, such as AD, is the absence of effective treatment, and thus the prevention for the diseases is highly needed.[11] This study aims to provide a profile of periodontal tissue status in people with Alzheimer's disease dementia with the scoping review method.

MATERIALS AND METHODS

The study used scoping review method following the guidelines from *Joana Briggs Institute* (JBI).[12] The process of this study was guided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Review (PRISMA-ScR) which is a modified version for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13]

The framework used for this study was Population, Concept, Context (PCC) to determine criteria and research question. This framework is recommended by JBI to identify the main concept for the research question. The use of this framework also to avoid the overly specific topic and to include more criteria.[14] The Participant (P) of this study was: The Elderly population with Alzheimer's disease dementia; The Concept (C) was: Overview of periodontal disease on patients with Alzheimer's disease dementia; The Context (C) was: The mapping which included empiric articles and review articles.

Inclusion criteria for this scoping review are (1) Articles about periodontal disease on Alzheimer's dementia patients, (2) Articles with available and accessible abstract, (3) Studies that were performed on human as participants, (4) Articles written in English or Bahasa Indonesia, (5) Research articles with the following study designs: observational study (cohort study, cross-sectional study, case-control study), clinical study, clinical trial, controlled clinical trial, comparative study, pilot study and review article. The exclusion criteria are (1) articles that do not fit the inclusion criteria, (2) articles that cannot be accessed, (3) study on animal, and case report and case series.

The search of electronic articles was done using PubMed, Cochrane and EBSCOHost CINAHL with these following keywords: *Periodontal disease, periodontitis, periodontal inflammation, Alzheimer's disease* and *dementia.* The search also used MeSH terms of "periodontal disease" and "Alzheimer's disease" if available on the database mentioned. Furthermore, snowballing technique was used as the manual for searching relevant articles from the references of included articles. This searching process was performed from February 6th to February 7th, 2021.

All articles from three databases and additional articles from snowballing technique were imported to the reference manager (Mendeley). Its feature enabled article checking for any duplications, and the duplicated articles were then excluded from the study. After checking the duplicated articles, the first screening was done based on the inclusion criteria. Articles that were not suitable with the criteria were then excluded from the study. The second screening step was done by checking the relevance of the articles with the topic of the study. The irrelevant articles were then excluded, and thus resulting in the final articles that would be used for the study as presented on Figure 1.

Data were subsequently extracted by placing the data into excel spreadsheet table by including title of the article, publication year, author, research location, study design, assessment parameters, and result of the study. This process was done by reading the full-text of the article by including full-text articles to obtain data that were not available on the abstract. From the structured table, mapping and explanation for each category were added to provide information aligned with the research objective.

RESULTS

The database searching, initially resulted in 335 articles, with 60 articles from PubMed, 256 articles from EBSCOHost CINAHL, and 19 articles from Cochrane. After duplicate removal, 299 articles remained and were screened afterwards based on inclusion criteria of the study, resulting in 259 articles for the next step. Subsequently, the process was continued by reviewing the full-text of each article to see their relevance with the topic under study, resulting in 58 articles to be included for this scoping review. Additionally, 2 articles were added using snowballing technique by reviewing the references from articles that were included before, resulting in a total of 60 articles included in this study as shown in Figure 1.

From the included articles (n=60), there were 32 empiric articles and 28 review articles which were grouped based on study design, year of publication, research location (regional) using United Nations Statistics Division,[15] assessment parameters and general overview regarding periodontal disease in Alzheimer disease patients, as can be seen in Table 1.

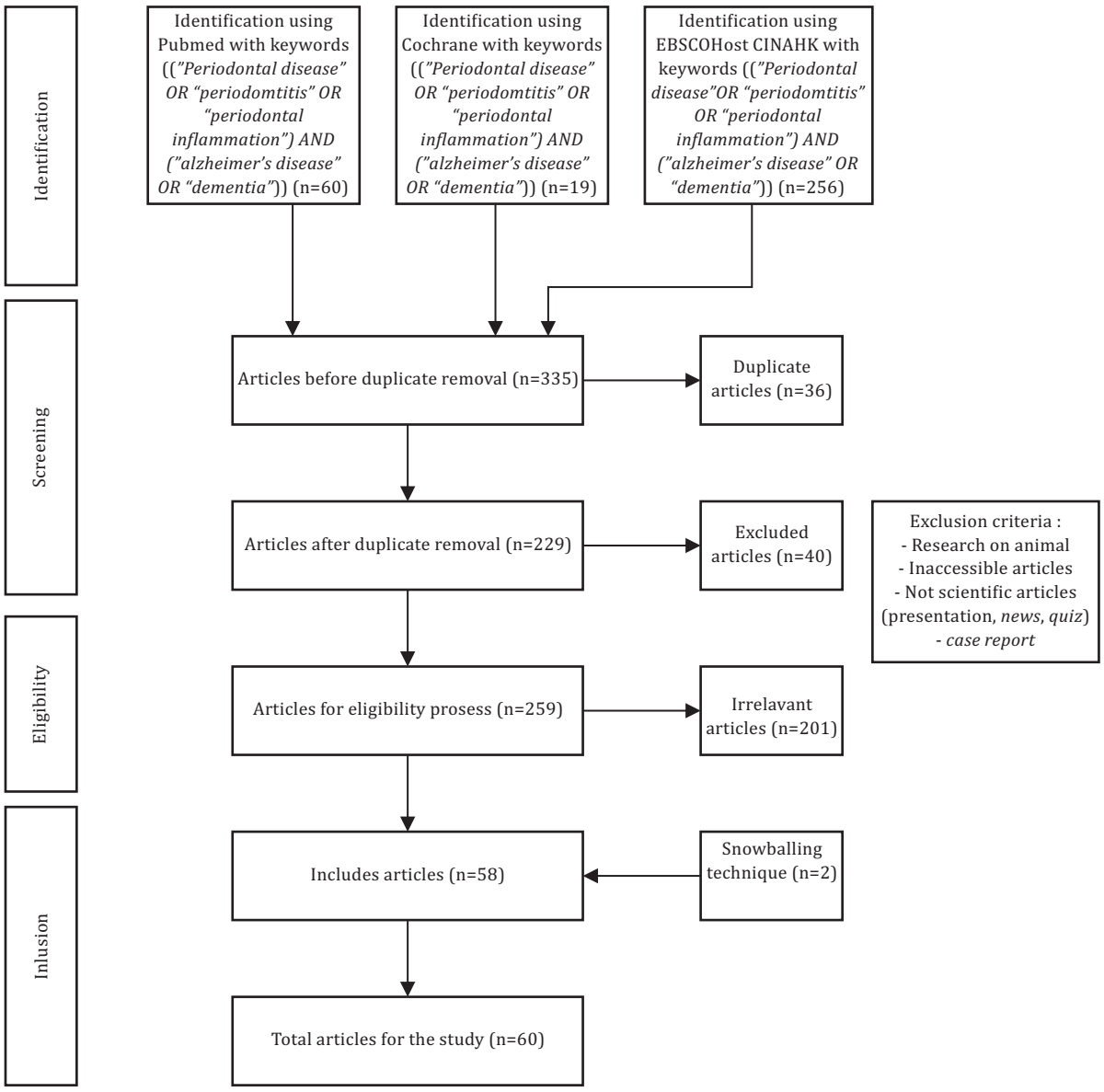

Figure 1. PRISMA-ScR Diagram Flow

Table 1. Mapping of included articles, consisting of empirical and structured review articles

Author (Year)	Title	Sample	Location	Study Design	Instrument / Diagnostic Criteria for Cognitive Status	Variable / Instrument for Periodontal Assessment	Other factors examined	Conclusion
Chalmers, et al.[16] (2003)	*Oral diseases and conditions in community-living older adults with and without dementia*	N=116 elderly with dementia, N= elderly without dementia (≤79 years old and ≥80 years old)	Australia	*Comparative study*	*Mini-Mental State Exam* (MMSE).	PI (Silness and Loe criteria)	oral hygiene, activities of daily index, demography, medical and medication, alcohol and cigarette consumption, chewing ability, difficulties faced by nurses	Participants with dementia have more experience of oral conditions and diseases than those without dementia.
Rejnefelt, et al.[17] (2006)	*Oral health status in individuals with dementia living in special facilities*	N=7 articles	Sweden	*Structured Review*	N.A	CAL, PPD, plaque and calculus	N.A	Individuals with dementia living in specialized facilities have more oral health problems than those without dementia.
Noble, et al.[18] (2009)	*Periodontitis is associated with cognitive impairment among older adults: Analysis of NHANES-III*	N=2.355, ≥ 60-year-old participants taking cognition measurements and P. gingivalis IgG	United States	*Cross-sectional*	*immediate and delayed logical verbal memory test from the East Boston Memory Test*	IgG P.gingivalis (ELISA units)	Medical history (CAD, CHF, stroke, DM, hypertension), medication history, socio-demography, health insurance, education level and smoking habits	A relationship between serological markers of periodontitis pathogens and low cognitive test results was found. Individuals with higher P gingivalis IgG level significantly have a greater chance of experiencing a decline in verbal memory and subtraction tests.

Hopcraft, et al.[19] (2012)	*Oral hygiene and periodontal disease in Victorian nursing homes*	N=275 (elderly in the <75-year-old category, 75-84 year-old category, and 85+ year-old category from 31 different nursing homes)	Australia	*Comparative study*	N.A	Turesky, Resesi, BOP, PD, calculus (*modified* CPI)	Socio-demography. dental and medical history, chronic medical conditions (Stroke, DM)	Those with dementia have worse oral hygiene than those without dementia.
Philip et al[20] (2012)	*Oral hygiene care status of elderly with dementia and in residential aged care facilities*	N=205 (elderly living in Residential aged care facilities with an average age of 85 years)	Australia	*Cross-sectional*	N.A	PI (O'Leary's plaque control index), *gingival redness*	ADLOH	Oral hygiene and gingival status are lower in those with dementia than those without dementia.
Rai, et al.[21] (2012)	*Possible relationship between periodontitis and dementia in a North Indian old age population: a pilot study*	N=55 patients with severe periodontitis (60-69 years old), N=20 patients with dementia (n=10 males, 10 females, aged 59-69 years) and N=32 healthy groups aged 58-69 years.	India	*Pilot study*	N.A	crevicular fluid, dental plaque, GI, remaining teeth, PD, CAL, BOP	Routine blood tests, age, education, occupation, smoking history, CAD, CHF and DM, edentulous status	After an adjustment for age, a significant difference was found between dementia and periodontitis compared to the normal group in gingival inflammation, dental plaque, BOP, and probing pocket depth.
Syjala, et al.[22] (2012)	*Dementia and oral health among subjects aged 75 years or older*	N=76 patient with dementia, N=278 patient without dementia from Geriatric multi-disciplinary strategy aged 75 or older.	Finland	*Cross-sectional*	DSM-IV, McKeith criteria , DSM-III-R	Remaining teeth, PD	Number of carious, presence of teeth, oral and denture hygiene; age, marital status, smoking history.	Patients with AD or other types of dementia have poor oral hygiene and oral disease (dental caries or periodontal infection) compared to those without dementia.

Chen, et al.[23] (2013)	*Oral health in nursing home residents with different cognitive statuses*	N=902 nursing home residents from a geriatric dental clinic community in Minnesota, aging 55 years old or older.	United States	*Cross-sectional*	Subjective assessment of memory, orientation and judgement.	calculus/ plaque/gingival bleeding subjectively.	Age, sex, medical and medication history, oral examination, subjective functionals (physical mobility, etc.)	Oral hygiene is related to cognitive function. > 40% of participants with dementia showed significantly higher plaque/calculus than the group without cognitive impairment.
Poole, et al.[24] (2013)	*Determining the Presence of Periodontopathic Virulence Factors in Short-Term Postmortem Alzheimer's Disease Brain Tiss*ue	N=10 brain tissue samples in patients with AD, N=10 age-related non-AD brain tissue that has the same or longer postmortem intervals.	England	*Experimental Study*	N.A	N.A	periodontal bacteria P. *gingivalis*, T. *denticola*, and T. *forsythia*; LPS and gingipains on P gingivalis culture.	LPS from periodontal bacteria can enter the brains of AD patients during the lifetime, meanwhile in the adjusted control group, at the same or longer postmortem interval, this was not found; this is the role of inflammation in AD pathology.
Farhad, et al.[25] (2014)	*The effect of chronic periodontitis on serum levels of tumor necrosis factor-alpha in Alzheimer disease*	N=80 (n=40 AD and chronic periodontitis, n=40 AD non-chronic periodontitis) aging from 40 to 70 years old.	Iran	*Case control study*	N.A	Clinical assessment, CAL	The measurement of the level of tumor necrosis factor-α with ELISA Kit.	The average TNF-a value in patients with AD and periodontitis was 3 times higher than in patients with only AD ($P < 0.001$).
Martade et al[26] (2014)	*Periodontal Health Condition in Patient with Alzheimer's disease*	N=58 individuals with AD N=60 normal individuals (aged 50-80 years old)	India	*Cross-sectional*	MMSE, NINCDS-ADRDA	PI, GI, PD, CAL, BOP	Age, sex, number of teeth, oral hygiene condition	Individuals with AD show a higher periodontal (PD, CAL, GI, PI and %BOP) damage.

Zenthofer, et al.[27] (2014)	*Comparison of oral health among older people with and without dementia*	N=93 (n=60 females, n=33 males aging from 54 to 107 years old)	Germany	*Cohort Study*	MMSE	*plaque control record* (O'Leary), GB, CPITN	Sex, age, teeth status, chronic disease, drug consumption, denture hygiene.	Some hygiene aspects and oral hygiene are worse in independent elderly with dementia than those without dementia.
Gil-Montoya, et al. [28] (2015)	*Is Periodontitis a Risk Factor for Cognitive Impairment and Dementia? A Case-Control Study*	N=409 (n=180 with cognitive impairment, n=229 without cognitive impairment older than 50 years old)	Spain	*Case-control*	DSM-IV, NINDS-ADRDA, Spanish Society of Neurology Behavioral and Dementia Study Group, Phototest.	PI (Löe and Sillness index), number of teeth, CAL, PD, BOP.	Age, sex, education level, alcohol and tobacco consumption, hyperglycemia, and family, personal and drug history.	A moderate and statistically significant relationship was found between CAL and cognitive decline after adjustment for age, sex, education level, oral hygiene habits, and presence of hyperlipidemia.
Chu, et al[29] (2015)	*Oral health status of elderly chinese with dementia in Hong Kong*	N=59 (n=47 females, n=12 males aged 60 years or older)	Hong Kong	*Pilot study*	N.A	Periodontal status (CPI)	Tooth-brushing habits, difficulty in oral hygiene practice, salivary flow rate, mucosal status and dental status (DMFT).	No significant difference in caries condition or prevalence of advanced periodontal disease between Hong Kong Chinese elderly with dementia and without dementia.
Cestari, et al.[30] (2016)	*Oral Infections and Cytokine Levels in Patients with Alzheimer's Disease and Mild Cognitive Impairment Compared with Controls*	N=65 elderly (N=25 AD, N=19 MCI and N=21 controls with an age range of 56 to 92 years old)	Brazil	*Case-control study*	NINCDS-ADRDA	PI (O'Leary plaque index), GB, PPD, CAL, CEJ	Education level, age, sex, hypertension and DM, cytokines serum level (IL-6, IL-1B, and TNF-a)	Multivariate analysis showed that there was a relationship between IL-6 and TNF-a in AD or MCI patients with periodontal disease (p=0,023).

Gusman, et al.[31] (2016)	*Periodontal disease severity in subjects with dementia: A systematic review and meta-analysis*	N=14 article	Brazil	*Systematic review and meta-analysis*	MMSE, ICD, DSM-IV dan DSM-III, NINCDS-ADRDA, Phototest, Neurology and Behavioral and Dementia Study Group of the Spanish Neurology Society	PD, CAL, PI, BOP, GBI, CPITN, CPI	N.A	Although a quantitative analysis has shown a worse periodontal condition in patients with dementia, because of a difference in research types and a high heterogeneity level, the meta-analysis does not support the relationship.
Mark Ide, et al.[32] (2016)	*Periodontitis and Cognitive Decline in Alzheimer's disease*	N=60 (non-smoking, mild-moderate dementia, number of teeth of 10 or higher, without periodontal treatment in the last 6 months. Average age of 77.7 years)	England	*Cohort study*	NINCDS-ADRDA, ADAS-cog, sMMSE	Remaining teeth, Plaque scor, BOP	Age, sex, P Gingivalis. antibody	Participants with AD with low oral health periodontitis were associated with increased signs of cognitive decline during the 6-month follow-up period, which were independent at baseline.
Wu, et al.[33] (2016)	*Association Between Oral Health and Cognitive Status: A Systematic Review*	N=56 articles (40 cross sectional, 16 longitudinal)	United States	*Systematic Review*	MMSE, *determination of dementia*	N.A	N.A	The relationship between oral hygiene and cognitive status was still unclear. A further research on the relationship between oral hygiene and cognitive status is necessary.
Chen, et al.[34] (2017)	*Association between chronic periodontitis*	N=9.291 patients with CP diagnosis between	Taiwan	*Cohort study*	ICD-9-CM	ICD-9-CM	medical history (DM, hypertension, brain trauma,	Patients who had CP for 10 years were associated with a 1,707

	and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study	1997-2004, N=18.572 non-CP participants. Participants were 50 years old or older.					depression, stroke, hyperlipidemia) Socio-demography, diagnostic information,	times increased risk of developing AD.
Delwel, et al.[35] (2017)	*Oral health and orofacial pain in older people with dementia: a systematic review with focus on dental hard tissues*	N=37 articles	Netherland	*Systematic Review*	DSM-III/DSM-IV or ICD-10, MMSE, CDR NINDS-ADRDA, , DT/MRI, Abbreviated Mental Test (AMT)	N.A	N.A	Elderly with dementia had a worse oral condition, with a greater number of retained roots and more coronal and root caries than those without dementia.
Gil-Montoya et al[36] (2017)	*Oral hygiene in the Elderly with different degrees of cognitive impairment and dementia*	N=564, (n=27 MCI patients without dementia, n=80 patients with mild dementia, n=67 patients with moderate dementia, n=66 patients with severe dementia, n=324 control patients >50 years old)	Spain	*Case-control*	Neurology and Behavioral and Dementia Study Group of the Spanish Neurology Society, *DSM-IVR*, NINCDS-ADRDA, *Phototest.*	PI (Loe and Sillness Plaque Index*),* GB *(Ainamo and Bay bleeding index)*	Age, sex, education, alcohol and tobacco consumption, use of dentures.	Oral hygiene and health and periodontal tissue in participants with cognitive impairment were worse, and cognitively impaired patients have a higher risk for oral disease.
Gil-Montoya, et al.[37] (2017)	*Association Between Periodontitis and Amyloid β*	N=166 cases and N=122 controls recruited from a hospital with age	Spain	*Case-control*	DSM-IVR, Neurology and Behavioral and Dementia	PI (*Löe and Silness plaque index),* CAL, PD*, Bleeding*	Socio-demographic, medical data, alcohol and cigarettes history,	Aβ1-42 Plasma concentrates were higher in individuals with severe periodontitis.

	Peptide in Elderly People with and without Cognitive Impairment	categories of <75 years, 75-85 years and >85 years.			Study Group of the Spanish Neurology Society, NINCDS-ADRDA, Phototest	*index (Ainamo & Bay)*	dental prostheses, oral hygiene, dentist visits; AB plasma with ELISA kits.	AB1-42 serum and AB1-40 serum concentrates were associated with cognitive decline, where periodontitis probably has a role as a modifying-effect.
Lee, et al.[38] (2017)	*Periodontal disease Associated with Higher Risk of Dementia: Population-Based Cohort Study in Taiwan*	N=182.747, aged ≥45 years recently diagnosed with PD in Taiwan National Health Insurance Research Database	Taiwan	*Cohort study*	ICD-9-CM	ICD-9-CM	Age, sex, socio-economic status, place of residence, comorbid factors (hypertension, DM, hyperlipidemia)	Participants with more severe PD or patients that did not receive periodontal treatment had a higher risk of developing dementia than those who received prophylaxis.
Lee, et al.[39] (2017)	*Periodontitis as a Modifiable Risk Factor for Dementia: A Nati onwide Population-Based Cohort Study*	N=3.028 aged ≥65 years with periodontitis, N=3.028 as a control group from National Health Insurance Research Database in Taiwan	Taiwan	*Cohort study*	ICD-9-CM	ICD-9-CM	Medical history (Hypertension, DM, cardiovascular disease, CHF, atrial fibrillation, stroke)	Participants with periodontitis had a significantly higher risk in the progress of dementia compared with the controls.
Leira, et al.[40] (2017)	*Is Periodontal disease Associated with Alzheimer's disease? A Systematic Review with Meta-Analysis*	N=5 articles (n=2 cross sectional, n=2 case control, n=1 cohort study)	Spain	*Systematic Review and Meta-Analysis*	NINCDS-ADRDA, MMSE, DSM-IV	PI, GB, PPD, CAL, GI, gingival recession	N.A	In this research, a significant relationship between Periodontal disease and AD was found.

Tonsekar, et al.[41] (2017)	*Periodontal disease, tooth loss and dementia: Is there a link? A systematic review*	N=16 articles	United States	*Systematic Review*	MMSE, Delayed Word Recall (DWR), Digit Symbol, DSM-III, Substitution Test (DSST), DSM-IV	Plaque, calculus, BOP, PD, CPI, GCF,	N.A	This research did not come up with any conclusion, and thus a Randomized Clinical trials research is necessary.
Holmer, et al.[42] (2018)	*Association between periodontitis and risk of Alzheimer's disease, mild cognitive impairment and subjective cognitive decline: A case–control study*	N=153 cases from the Karolinska memory Clinic, grouped AD, MCI and SCD with an age range of 50-80 years old.	Sweden	*Case-control*	MMSE atau Montreal Cognitive Assessment (MoCA),	*Plaque Control Record modified*, PPD, BoP, suppuration, tooth mobility, furcation involvement	Private information, medical history, and oral health (smoking, oral mucosa, number of teeth, implant, denture, caries)	The relationship between an increase in the number of deep periodontal pockets occurred in all groups of patients compared to the control group.
Laugisch, et al[43] (2018)	*Periodontal Pathogens and Associated Intrathecal Antibodies in Early Stages of Alzheimer's disease*	N=20 patients with AD, N=20 patients with other dementia (DEM-nonAD) with an age range of 30-70 years old.	Germany	*Pilot study*	NIAA, MMSE.	Remaining teeth, PD, CAL, BOP, Subgingival biofilm, GCF	neuropsychological battery of tests, sex, age	Local production of antibodies in CSF samples against P. gingivalis and other periodontal pathogens may occur in dementia patients, but no relationship was found with AD.
Maldonado, et al. [44] (2018)	*Clinical periodontal variables in patients with and without*	N=7 articles (n=5 articles used for meta-analysis)	Switzerland	*Systematic Review and Meta-analysis*	NINCDS-ADRDA, MMSE	PPD, BOP, GBI, CAL, PI	N.A	Dementia patients showed significantly worse clinical periodontal conditions. Further epidemiological study

	dementia—a systematic review and meta-analysis							with many participants is necessary.
Choi, et al.[45] (2019)	*Association of Chronic Periodontitis on Alzheimer's disease or Vascular Dementia*	N= 262.349 (n= 216.005 without CP, n= 46.344 with CP aged ≥40 years)	South Korea	*Cohort study*	ICD-10	ICD-10	Medical (DM, stroke Hypertension, etc), cigarette and alcohol, medication history, body measurements, social, demographic, physical activity.	Patients with chronic periodontitis tend to have a higher risk of dementia and AD, but they also tended to be at increased risk for VD. Patients with CP had a 6% higher risk of dementia.
Iwasaki, et al.[46] (2019)	*Periodontitis, periodontal inflammation, and mild cognitive impairment: A 5-year cohort study*	N=179 individuals (N=62 males, N=117 females) with an average age of 80,1 years.	Japan	*Cohort study*	MMSE, DSM- IV.	Remaining teeth, PPD, gingival recession, BOP, CAL, Periodontal Inflamed Surface Area (PISA).	Medical and drug (hypertension, DM), physical status, activity of daily living (ADL), cigarette and alcohol consumption, socio-demography, hearing.	Severe periodontitis and periodontal inflammation were associated with MCI incident in elderly women and men aged ≥75 years.
Lauritano, et al.[47] (2019)	*Aging and oral care: An observational study of a characteristics and prevalence of oral diseases in an Italian cohort*	N=39 Individuals aged 79-99 years recruited from 2 institutions.	Italy	*Cross sectional*	*Clinical Dementia Rating Scale (CDR)*	Remaining teeth, periodontal pocket, BOP, plaque and calculus, bone crest	Medical history (hypertension, DM, dyslipidemia, anemia, etc), oral mucosa, and cooperative level.	The poor degree of oral hygiene status tends to decrease as the degree of dementia increases. This shows a linear relationship between the two quantitative variables.
Sung, et al[48] (2019)	*Association between periodontitis*	N=4.663 individuals with an age range of 20 to 59 years	United States	*Cross-sectional*	Neurobehavioral Evaluation System 2 (NES2):	Criteria of Periodontitis by Eke, Page,	Age, sex, race, physical activity, blood pressure,	There were statistically significant differences for SDST and SDLT

	and cognitive impairment: Analysis of national health and nutrition examination survey (NHANES) III	who have received periodontal examination and cognition tests.			SRTT (simple reaction time test), SDST (symbol digit substitution test) dan SDLT (serial digit learning test).	Wei, Thornton-Evans, dan Genco (2012)	cigarette consumption, medical condition (congestive heart failure and stroke)	between the 3 groups of subjects with normal, moderate, and severe periodontitis. Although there was an increase in the score for SRTT in subjects with moderate and severe periodontitis, there was no significant difference between the two groups.
Tiisanoja, et al.[49] (2019)	*Oral diseases and inflammatory burden and Alzheimer's disease among subjects aged 75 years or older*	N=170 individuals aged 75 years or older	Finland	*Cross-sectional study*	DSM-IV, McKeith et al, MMSE.	Periodontal pocket	Number of dental caries, oral mucosa, diabetes, education, hypertension, CHD, and stroke.	Dental caries, periodontal disease, stomatitis, and inflammatory burden are associated with dementia and AD.
Beydoun, et al. [50] (2020)	*Helicobacter pylori, periodontal pathogens, and their interactive association with incident all-cause and Alzheimer's disease dementia in a large national survey*	N= ≤1431 participants from phase 1 the National Health and Nutrition Survey III (1988–1991) aged ≥65 years..	United States	*Cross-sectional*	ICD-9	CAL, PD, periodontal pathogen	H. pylori antibodies, age, sex, race, socio-economic status, lifestyle (diet), tooth status, nutrition biomarker.	Periodontal pathogen titers, factors, and clusters selected interact largely and synergistically with Hp sero-positivity to alter the risk of AD and all-cause dementia.
Beydoun, et al.[51] (2020)	*Clinical and Bacterial Markers of Periodontitis*	N=4.465 (aged ≥45 years, gone through phase 1 and 2 of	United States	*Cohort Study*	ICD-9, ICD-10	Attachment loss (AL), PPD	IgG serum titers, demographic, socio-economic, lifestyle	The positive relationship between periodontal disease and periodontal

	and Their Association with Incident All-Cause and Alzheimer's disease Dementia in a Large National Survey	P. gingivalis and CMS-Medicare)					and health factors, diet quality, and nutrition.	pathogens with various dementia outcomes reflects previous results with cognitive outcomes.
Demmer, et al.[52] (2020)	*Periodontal disease and incident dementia: The Atherosclerosis Risk in Communities Study (ARIC)*	N=8.275 (periodontal examination at the fourth visit and dementia was declared) with an age range of 45-64 years.)	United States	*Atherosclerosis Risk in Communities Study (ARIC)*	NIAA, DSM-IV, National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences	AL, PD, BOP, *periodontal profile class* (PCC)	Socio-demographic, smoking history, oral hygiene and access to health facilities, blood examination, BMI, blood pressure, medical history (DM, heart failure, CHD, stroke, incident stroke)	Periodontal disease was associated with an increased incidence of dementia and MCI in both white and black community participants in the ARIC study. The possible association between periodontal disease and vascular dementia is indirect, with the cardiometabolic disease as the causal mediator.
Gil-Montoya, et al.[53] (2020)	*Systemic inflammatory impact of periodontitis on cognitive impairment*	N=171 case groups, N=131 control groups with an age group of those <75 years, 75-85 years and >85 years.	Spain	*Case-control*	Neurology and Behavioral and Dementia Study Group of the Spanish Neurology Society, DSM-IVR, NINCDS-ADRDA	Remaining teeth, PI (Löe and Silness plaque index), CAL, probing depth dan BI (Ainamo & Bay)	Sex, age, smoking history, Cytokines and chemokine examination, education level	11 of 29 inflammation biomarkers were associated with the decline in cognition in patients with severe periodontitis and in 5 patients with mild periodontitis.
Kamer, et al.[54] (2020)	*Periodontal disease as a possible cause*	N=27 (n=14 longitudinal study, n=6 case-	United States, Spain	*Structured review*	ICD-10, ICD-9, MMSE, ADAS-Cog, Clock	ICD-10, ICD-9-CM, PISA, PD, alveolar bone	Socio-demographic, habits (cigarette and alcohol	Periodontitis may cause systemic inflammation, damage

	for Alzheimer's disease	control, n=7 cross sectional)			Drawing Test, DSM-III, NINCDS-ADRDA	loss, gingival recession, CPI,	consumption), medical condition.	the blood-brain barrier, neuroinflammation, neurodegeneration and cognitive decline.
Lee, et al.[55] (2020)	*Risk of dementia in patients with periodontitis and related protective factors: A nationwide retrospective cohort study*	N=56.018 patients aged ≥50 years, experienced periodontitis in 2000-2008 from Taiwan's National Health Insurance Database	Taiwan	*Cohort study*	ICD-9-CM	ICD-9-CM	Medical history (hypertension, DM, stroke, hyperlipidemia, etc.), mental disorder. drug vaccine history. socio-demographic.	Periodontitis is a risk factor of dementia. Patients with periodontitis have an increased risk for dementia.
Nadim, et al.[56] (2020)	*Influence of periodontal disease on risk of dementia: a systematic literature review and a meta-analysis*	N=12 articles (n=5 cohort, n=7 case-control)	England, China, Australia	*Systematic Review and Meta-Analysis*	NINCDS-ADRDA, ICD-9-M	PPD, CAL, BOP, ICD-9-M, AAP	N.A	Periodontal diseases may increase the risk of dementia incidence.
Sansores-España, et al.[57] (2021)	*Periodontitis and Alzheimer´s disease*	N=25 articles	Mexico, Chile	*Literature Review*	N.A	N.A	N.A	There is no sufficient evidence to decide the relationship between 2 pathologies, thus a further study is necessary.

*Academy of Periodontology classification (AAP), Activities of Daily Living Oral Health (ADLOH), Alzheimer's disease Assessment Scale (ADAS-cog), Bleeding on Probing (BOP), Clinical attachment loss (CAL)/attachment loss (AL), Chronic Periodontitis (CP), Community Periodontal Index (CPI), Congestive heart failure (CHF), Coronary artery disease (CAD), Diabetes Melitus (DM), Diagnostic and Statistical Manual of Mental Disorders (DSM), gingival crevicular fluid (GCF), Gingival Bleeding index (GBI), Gingival Index (GI), International Classification of Diseases(ICD), Mini-Mental State Examination (MMSE), N.A (Not Available, National Institute of Aging-Alzheimer's Association (NIAA), National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA), Plaque Index (PI), Probing depth (PD)/Probing pocket depth (PPD), standardized Mini-Mental State Examination (sMMSE)

The mapping shows that almost all empiric articles (n=30 from 32) agree that there was a poor oral health in patients with AD, including low degrees of oral hygiene as indicated by higher score of plaque and calculus. The elderly with dementia had worse oral hygiene than elderly without dementia. More than 40% of participants with dementia showed gingival inflammation with plaque and calculus that were significantly higher than the group without cognitive impairment, which revealed that oral hygiene was associated with cognitive function.[19,23]

Bad oral hygiene was also shown by the presence of gingival inflammation. Oral hygiene tends to decrease as the severity of dementia increases. This showed a linear relationship between two quantitative variables, namely the degree of oral hygiene and the severity of dementia.[23,47] Gil-Montoya, et al (2015), who studied the risk factors for periodontitis with cognitive impairment and dementia, found that there was a moderate and significant relationship between CAL and cognitive decline after adjustment for age, gender, education level, oral hygiene habits, and the presence of hyperlipidemia.[28]

The association between oral infections and cytokine as parameters of inflammation was demonstrated in a study by Cestari, et al. (2016). The results showed an increase of IL-6 and TNF-α in AD and MCI patients compared to controls. Multivariate analysis proved that there was an association between IL-6 and TNF-α in AD or MCI patients with periodontal disease (p=0.023). The increase in these cytokines was in line with the decline in the cognitive status experienced by the participants.[30] However, different opinions were found in the articles of Chu, et al. (2015)[29] where the authors revealed that there was no significant difference in caries experience or prevalence of periodontal disease in the elderly Hong Kong Chinese with and without dementia. In addition, Laugisch, et al. (2018)[43] also revealed that local production of P. gingivalis antibodies in CSF and periodontal pathogens was not associated with AD.

Several structured review articles showed that there was a relationship between the condition of the oral tissues, particularly the periodontal tissues with cognitive function in patients with AD. The level of oral health and periodontal tissue was found lower in people with dementia, indicated by periodontal clinical variables such as BOP, CAL, PI, PD, and GBI.[17,35,40,44]

The diagnostic criteria/instruments used to examine the cognition status and diagnosis of AD in the research subjects of the article were quite diverse. There were 21 types of diagnostic criteria or instruments used to examine cognitive status, but the most widely used are the NINCDS-ADRDA diagnostic criteria,[22,28,36,37,46,49,53] Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),[34,38,39,50,51,55] and The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).[34,38,39,50,51,55] As for instrument, the most widely used was the Mini-Mental State Examination (MMSE).[16,26,27,42,43,46,49] Lower MMSE score indicated more severe cognitive problems, as showed in the study of Martande, et al (2014) which stated that the MMSE score in the AD group was 14.2 ± 8.4 and 28.5 ± 1.2 in the non-AD group.[26]

In addition to those aforementioned, are other diagnostic criteria/instruments included the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),[22,28,36,37,46,49,53] International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM),[34,38,39,50,51,55] The International Classification of Diseases, Tenth Revision (ICD-10),[45,51] Neurology and Behavioral and Dementia Study Group of the Spanish Neurology Society,[36,37,53] National Institute of Aging-Alzheimer's Association workgroups (NIAA)[43,52] and the criteria of McKeith et al.[22,49] Other instruments used were the standardized Mini-Mental State Examination (sMMSE),[32] Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog),[32] Clinical Dementia Rating Scale (CDR),[47] Phototest,[28,36,37] Montreal Cognitive Assessment (MoCA),[42] clock drawing test (CDT),[42] Neurobehavioral Evaluation

System 2 (NES2),[48] immediate and delayed logical verbal memory test from the East Boston Memory Test,[18] and subjective test for memory, orientation and judgment.[23]

From the mapping on Table 1, there were 26 variables/instruments for examining periodontal status used by empirical articles. The examination can be done by assessing Periodontal Depth (PD),[19,21,22,26,28,30,37,42,43,46,47,49–53] Gil-Montoya (2015)[28] stated that the depth of periodontal probing in the cognitive impairment group was deeper than that of the control group, namely 3.0 ± 0.7 for the cognitive impairment group and 2.6 ± 1.5 for the control group. The next most widely used variable were Plaque Index (PI),[16,19–21,23,26–28,30,32,36,37,42,47,53] the average plaque scores on the case group with MCI/ dementia was higher than the control group's based on the research by Gil-Montoya, et al. (2015).[28] Percentage Bleeding on Probing (BO P)[19,21,26,28,32,42,43,46,47,52] increases along with the following worsening AD conditions: the elderly without AD vs MCI vs moderate AD and severe AD, namely (29.17 ± 5.43 vs. 37.09 ± 5.24 vs. 55.44 ± 7 vs. 67 ± 12.36);[26] and more severe CAL[21,25,26,28,30,37,43,46,50–53] detected in AD patients. Martande, et al. (2014) stated that AD individuals showed higher score of periodontal damage (PD, CAL, GI, PI and %BOP) than control individuals.[26]

Few other variables/instruments used by the inclusion articles were Gingival Bleeding Index (GBI),[23,27,30,36,37,53] Calculus Index (CI),[19,23,47] gingival recession,[19,46] furcation involvement,[42] and involvement of bone crest,[47] periodontal pathogens,[50] Gingival Crevicular Fluid (GCF),[21,43] and subgingival biofilm.[43] For establishing the diagnosis, it can be seen that the included studies used the diagnostic criteria of ICD-9,[34,38,39,55] ICD-10,[45] Criteria of Periodontitis by Eke, Page, Wei, Thornton-Evans, and Genco (2012)[48] and used periodontal status instruments such as the periodontal profile class (PCC),[52] the community periodontal index (CPI)[29] and the community periodontal index of treatment needs (CPITN).[27]

DISCUSSION

According to the accomplished mapping on Table 1, characteristic of the articles can be seen from the study designs, years of publication, and research locations used by both the empirical and review articles. For empirical articles, there were 31 observational study and one experimental study on the post-mortem brain tissue of AD and Non-AD patients. From these results, it is recommended to conduct experimental research on animals to support the hypotheses on the relationship between periodontal disease and AD dementia. The review articles can be classified into publications about systematic review and meta-analyses articles, which can continuously be updated with the increasing empirical studies. For the years of publication, it can be concluded that both types of articles, empirical and review, gained a significant number of publications from 2011 through 2020, indicating an increased interest in this topic among researchers.

NINCDS-ADRDA diagnostic criteria is the most widely used criteria for included articles. The use of NINCDS-ADRDA is supported by the considerably high accuracy (ratio of the number of pathologically confirmed cases of AD to the number of clinically diagnosed AD cases), which is 65%-92%.[58] NINCDS-ADRDA is a type of diagnostic criteria commonly used for clinical research and clinical trials.[59] In addition, the most commonly used instrument for included articles is MMSE,[16,26,27,42,43,46,49] a paper-based short cognitive test widely used for clinical and research purposes. MMSE is used to see cognitive function decline and impairment. The maximum score for MMSE is 30, consisting of 11 inspection items,[60] while the cut point of MMSE to describe the normal cognitive function condition is usually set at 24.[61] MMSE is commonly used as a cognitive status examination instrument in many studies for a rapid implementation process and is available in various languages. It is also well-accepted among medical personnel and researchers,[62] facilitating researchers during the process of measuring the cognitive status of the elderly. However, the difficulty

of the MMSE lies in detecting early dementia. MoCA becomes a consideration for another cognitive screening tool. MoCA was developed for assessing cognitive status on patients with mild cognitive impairment (MCI) and is usually used in patients who have normal range for MMSE score. MoCA is a simple instrument, since it can be registered within 10 minutes. MoCA is a stand-alone cognitive assessment tool with superior sensitivity and it also fits for a single page, and thus MoCA is suitable for study setting as well.[63]

Variables/instruments for examining the status of periodontal tissues used in the articles studied are very diverse. There are 26 types of variables/instruments used in the empirical articles. Each variable used in the study has its advantages and disadvantages. However, it is also necessary to consider the condition of the participants when choosing the type of examination variable to be used. The use of the same variable will make it easier to compare the examination results from one study to another. One of indexes that can be used for the examination of periodontal status on the elderly is the Community periodontal index of treatment needs (CPITN)[27] as a periodontal index consisting of pocket depth, calculus, and bleeding response. The advantages of this index is based on the fact thatit is easy to use, it has been widely used around the world,[64] fast, and reproducible,[65,66] and thus, this index can be an option for research conducted on the elderly participants who experience cognitive decline. In addition to CPITN, the Community periodontal index (CPI), which is a modified version of CPITN, is also applicable. The difference between the two indexes is the elimination of recommendations or references to maintenance needs.[67]

From the mapping, there are several articles that conducted assessment on other variables, such as caries and saliva flow, as in the study conducted by Chu, et al. (2015).[29] It was revealed that the average value of unstimulated saliva flow rate was 0.30 ± 0.17 (ml/min) for the dementia elderly group and 0.41 ± 0.28 (ml/min) for the healthy elderly group. For caries, the average DMFT score was 22.3 ± 8.2 (dementia group) vs 21.5 ± 8.2 (control group). Based on these findings, research on other oral diseases in patients with cognitive decline may be applicable for future studies. Moreover, other variables such as socio-demographic data including age, gender, level of education; smoking and alcohol consumption; medical history and drug consumption in participants need to be assessed, since these variables are risk factors of AD.

Age is a risk factor for the development of AD.[7,68] It is mentioned that aging can increase the prevalence of AD, indicated by the fact that the majority of AD patients are the elderly populations aged 65 years or older.[9] The study shows that the incidence increases from an average of 1 : 1000 in the population aged 60-64 years, to 70 : 1000 in the population aged 90 years or older.[69] Neuronal death shows mitochondrial damage and dysfunction, both of which are related to neurodegenerative diseases and normal aging process.[70] AD may also occur in the younger population under 65 years old known as Early Onset Alzheimer's Disease (EOAD). The difference between EOAD and Late Onset Alzheimer's Disease (LOAD) in the elderly lies in the speed of the disease progression, and the presence of metabolic perfusion and deficits in the temporal and parietal lobes. Additionally, when viewed from its clinical signs, EOAD shows a higher prevalence for language disorders and other signs besides memory impairment on its early stages.[71]

Nadim, et al (2020) suggested that there was a significant influence of periodontal disease on the increased incidence of dementia.[56] This opinion is linear with study conducted by Ganesh, et al (2017),[72] which revealed that periodontal pathogens and their products and inflammatory mediators can enter the blood vessels. This condition can cause systemic effects and/or contribute to systemic diseases and accelerate the neurodegeneration process.[6] However, further research is still needed to find out the causal relationship for preventing the occurrence of cognitive disorders such as AD dementia.

Research on this topic has been conducted in high-populated countries such as India and the

United States, and has also been conducted in Japan, which has the highest life expectancy rate in the world.[73] However, there has been no research conducted in Indonesia which is demographically densely populated, and thus having the increasing projected prevalence of dementia every year with cases estimated at 1,894,000 by 2030.[11] This ground underpins the necessity to conduct similar research in Indonesia and it is recommended to use a case-control type of design with case incidents or retrospective cohort design to obtain more evidence regarding the relationships of both to support the hypotheses proposed by previous studies.

This study used a scoping review to map and provide a general profile of periodontal disease in participants with AD dementia through qualitative analysis. Subsequent systematic review is recommended using quantitative analysis, by conducting a critical appraisal in its process such as in Rapid Review or Systematic Review and Meta-Analysis to show the relationship between the two in the form of quantitative analysis.

CONCLUSION

The periodontal health condition decreases along with the decline of cognitive status experienced by AD participants. However, further research is needed to see the mechanism of this relationship.

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