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PII: S0167-4943(18)30035-9
DOI: https://doi.org/10.1016/j.archger.2018.02.016
Reference: AGG 3637

To appear in: *Archives of Gerontology and Geriatrics*

Received date: 20-9-2017
Revised date: 22-2-2018
Accepted date: 23-2-2018

Please cite this article as: Gusman, David Jonathan R., Mello-Neto, João M., Alves, Breno Edson S., Matheus, Herique R., Ervolino, Edilson, Theodoro, Letícia H., de Almeida, Juliano M., Periodontal disease severity in subjects with dementia: a systematic review and meta-analysis.Archives of Gerontology and Geriatrics https://doi.org/10.1016/j.archger.2018.02.016

"Periodontal disease severity in subjects with dementia: a systematic review and meta-analysis"

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Highlights

- Periodontal disease and dementia are common diseases in the older adults
- 14 articles meeting our inclusion criteria in the systematic review
- The meta-analysis was conducted with 4 articles
- Dementia patients seemed to present worsened periodontal conditions

ABSTRACT

Background and Objective: Despite clinical trials and reviews attempt to assess a possible relationship between dementia and periodontal disease, no meta-analysis has been performed and this issue remains undetermined. The aim of this study is to conduct a systematic review and meta-analysis to assess levels of periodontitis in subjects with dementia.

Methods: The search was conducted in Pubmed, Embase/MEDLINE. Two independent reviewers extracted data and assessed the risk bias (Newcastle–Ottawa scale). Meta-analyses were performed using the means of probing depth (PD) and clinical attachment loss (CAL) in patients with or without dementia. The mean difference were analyzed ($P \leq 0.05$).

Results: Fourteen studies were included in the systematic review. In the qualitative analysis, most studies reported higher prevalence of periodontal disease in dementia patients. The studies had low risk of bias and two meta-analyses were performed for each parameter, including or not a cross-sectional study. The meta-analyses including the cross-sectional study demonstrated significant association between dementia and periodontal disease (mean difference: PD = 1.41; CAL= 1.40, $P < 0.05$), however, it wasn't confirmed when the cross-sectional study was removed (1.25 mm, $P < 0.22$) and CAL (1.20 mm, $P < 0.22$).

Conclusion: Even the qualitative analysis have suggested worse periodontal conditions in dementia patients, due to different study types and the high heterogeneity among them, the meta-analysis does not support the association between dementia and severity of periodontal disease.

Key Words: Dementia, Meta-analysis, Periodontal disease, Systematic review

1. INTRODUCTION

Dementia is a progressive syndrome, leading to a deterioration of cognitive function that can affect memory, orientation, the ability to perform routine work, behavior, thinking, understanding, learning ability, and judgment.[1] More than 47 million people suffer from dementia worldwide and 7.7 million new individuals are diagnosed with dementia every year. Moreover, by 2050, cases of dementia are estimated to increase to almost 115 million, three times the current estimate.[2]

Dementia can be classified into different subtypes according to the associated brain pathologies, and the most common are Alzheimer's disease (AD), vascular dementia (VD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD).[3] In 2016, it is estimated that 700,000 Americans aged ≥ 65 years will die with Alzheimer's disease, and many of them will die because of the complications caused by Alzheimer's disease. These statistics underline the public health importance of identifying modifiable risk factors. Such data show that anything that contributes to the worsening of the patients' condition should be considered for treatment.

With the progression of severity in dementia, the ability of patients to perform self-care, including oral hygiene practice, deteriorates gradually,[3] increasing the amount of bacterial plaque and debris, and resulting in inflammation and gingival bleeding.[4] Persistence of gingival inflammation is determinant for the development of periodontitis[5,6,7] but may not consist an unquestionable statement to confirm progression of gingivitis to periodontitis.[7] The elements of host response and/or site-specificity shall be considered to explain long-term stability or progressive attachment loss in different sites in the same individual.[7]

Considering these aspects, it is speculated that patients with dementia could have poor oral hygiene habits and periodontal condition. Therefore, the aim of this study is to conduct a systematic review and meta-analysis to assess the severity of periodontal disease in subjects with dementia.

2. METHODS

This review is registered in the PROSPERO database (CRD42016053685), in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[8,9] The review also followed models proposed in the literature.[10,11]

2.1 Literature Search Strategy

Two independent reviewers (J.M.M.N., D.J.R.G.) conducted an electronic search on the PubMed/Medline and EMBASE databases for articles published in English within the last 20 years (January 1st 1997 to September 2st, 2017). The key words used were: periodontal disease, dementia, Alzheimer's disease, vascular dementia, and frontotemporal dementia. Specifically, the PubMed search terms were as follows: ((((Periodontal disease and dementia)) OR (Periodontal disease and Alzheimer's disease)) OR (Periodontal disease and vascular dementia)) OR (Periodontal disease and frontotemporal dementia).

On Embase/MEDLINE, the literature search terms were: periodontal AND ('disease'/exp OR disease) AND ((('dementia'/exp OR dementia OR alzheimers) AND ('disease'/exp OR disease) OR vascular) AND ('dementia'/exp OR dementia) OR frontotemporal) AND ('dementia'/exp OR dementia) AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [1997-2017]/py .

A further manual search was conducted of the reference lists of relevant review studies. We reviewed all potential abstracts and complete texts, and selected those that met the criteria detailed below. Disagreements between researchers were settled by consensus. Cohen's kappa coefficient was used to evaluate the disagreement between the researchers.

2.2 Focus Question

In accordance with the PICO framework,[12] we used the focus question "Is there an association between dementia and periodontal disease severity in older dementia adults?"

•Population: patients with dementia and without dementia, based on case definitions used in the publications

•Intervention: different periodontal indexes (PI: Plaque index; BOP: Bleeding on probing; GBI: Gingival bleeding index; PD: Probing depth; CAL: Clinical attachment loss; CPI: Community Periodontal index; CPITN: Community Index of Periodontal Treatment Needs)[13-25] (Table 1)

•Comparison: between the dementia and non-dementia group through the periodontal indexes presented

•Outcomes: Poorer results in the periodontal indexes in the dementia patients

2.3 Inclusion Criteria

Case-control, cross-sectional, longitudinal and cohort studies in humans with at least six patients that evaluated periodontal indexes in patients with dementia, with mild cognitive impairment, and without dementia.

2.4 Exclusion Criteria

Studies that did not evaluate periodontal indexes or evaluated only one periodontal index, without control groups, with only abstract available and those without access[26-45] (studies were considered without access after sending an e-mail to their corresponding authors) (Table 2).

2.5 Included in Meta-Analyses

We included studies that had, as variables, PD and CAL that used parametric data (means) in patients with and without dementia in a subsequent meta-analysis.[4,13,14,17]

2.6 Assessment of Bias Within Studies

The qualities of the studies selected for the meta-analysis were evaluated based on the Newcastle-Ottawa scale (NOS).[46,47] The scale has been shown to be reliable and valid.[48] Studies scoring five or more points were considered to be of high quality.[49]

2.7 Statistical Analysis

The Comprehensive Meta-Analysis Program (Review Manager 5.3, Cochrane Collaboration, Oxford, UK) was used for the meta-analysis. The meta-analysis was conducted including studies with similar comparisons and the same outcomes.

The fixed effects model was used when there was no statistically significant difference, and the random effects model was adopted when there was a statistically significant difference, which means a high index of heterogeneity among the trials. Heterogeneity was considered significant when $p<0.1$. Heterogeneity was assessed using a method in which the χ^2 and I^2 values were measured. The statistical value of I^2 was used to analyze variations in heterogeneity; values above 75% (0-100%) indicate relevant heterogeneity.[49-51] In cases with no appropriate data, the values were calculated.

3. RESULTS

The electronic search on the databases identified 440 articles (Fig. 1 shows details of the research process and the study selection). After elimination of duplicates and analyses of the titles and abstracts according to the inclusion and exclusion criteria, we considered 34 articles as eligible; however, we had no access to the study by Bramanti et al.[45] which was excluded. Thus, 33 full texts were analyzed, and 19 were excluded based on the criteria (Table 2).

Finally, 14 articles were selected for systematic review[3,4,13-17,52-58](Table 3), with four of them being included in the meta-analyses[4,13,14,17] (Fig. 2a, b, c, d). The Kappa test statistic was 1.0 for the studies analyzed, indicating no disagreement between the reviewers.

3.1 Qualitative Review of Studies

Among the studies comparing the periodontal indexes between the dementia group and the non-dementia group, we found 1750 individuals with dementia (general mean age: 78.16) and 4816 without dementia (general mean age: 75.45). One study assessed only mild memory impairment,[52]

seven studies assessed dementia without distinguishing its type or degree of impairment,[13,15,16,53,55,57,58] one study divided their case groups according to types of dementia,[54] three studies evaluated only Alzheimer's disease,[3,14,56] one study evaluated mild cognitive impairment and dementia of any type or severity, together in the same group,[4] one study evaluated dementia severity[15], and one study had Alzheimer's disease and mild cognitive impairment in different case groups.[17]

In general, most of these studies showed that periodontal disease was more prevalent in patients with dementia (regardless of the type of dementia) than those without. The values for PI, BOP, PD and CAL indicated a larger prevalence of periodontal disease in the dementia group.[4,13,14,15,16,17] In addition, the severity of periodontal disease was found to worsen in accordance with the progression of Alzheimer's disease from mild to moderate and severe.[14,15] CPI and CPITN indicated greater need for periodontal treatment in dementia patients.[52,57]

Some studies evaluated by this systematic review[3,52,53] reported worsen periodontal indexes in initial periods of control and in late periods of dementia groups. Moderate periodontitis was shown to be more prevalent in the initial stages in the control group, while the severe stages of periodontitis were found to be more prevalent in the dementia group.[56]

Only three studies did not find a significant difference between periodontal disease and dementia[3,17,54] and Zenthofer et al[58] did not find a statistical difference in GBI between the groups.

3.2 Risk of Bias Assessment

All the studies included in this meta-analysis[4,13,14,17] are considered to be of high quality according to the NOS scores.[36]

3.3 Results of the meta-analysis

The meta-analyses were performed based on two different clinical parameters (PD and CAL), with (Fig. 2a, b) and without (Fig. 2c, d) cross-sectional study.[14] For Martande et al[14] and

Cestari et al,[17] the means needed to be calculated due to the division in their case groups (mild, moderate, and severe Alzheimer's disease, and Alzheimer's disease and mild cognitive impairment). The meta-analyses had high statistical and clinical heterogeneity (PD: both $I^2 = 98\%$; CAL: both $I^2 = 99\%$).

In a random effects analysis including the study by Martande et al,[14] the PD was significantly higher in the dementia group compared to the control group, regardless of the level of severity of dementia (1.41 mm, $P < 0.01$) (Fig. 2a). The CAL was also significantly higher in the group with dementia than in the control group, regardless of the level of severity of dementia (1.40 mm, $P < 0.01$) (Fig. 2b).

The meta-analyses without the cross-sectional study[14] showed no statistical difference in PD (1.25 mm, $P < 0.22$) (Fig. 2c) and CAL (1.20 mm, $P < 0.22$) (Fig. 2d) between the dementia and control group.

4. DISCUSSION

Impairment of cognitive capabilities and daily life activities predisposes dementia patients to poor oral health and poor oral hygiene.[54] Furthermore, as the world's population ages and dementia becomes more prevalent, it will possibly become a public health problem.[1] In response to the clinical needs of an aging population and the resultant growing incidence of dementia, this study was conducted to assess the severity of periodontal disease in subjects with dementia compared to non-dementia patients.

Oral health plays a key role in the prevention of several diseases, especially in older adults,[4] making extremely important the knowledge concerning the periodontal conditions of dementia patients and how these conditions can affect people's daily lives. Patients with dementia typically have difficulties regarding plaque control, such as an opposition to oral care, and forgetting to brush their teeth, which increase the risk of developing periodontal disease.[29,55]

Chalmers et al[29] affirmed that these patients considerably worsen their buccal conditions in one year, possibly because of the progressive neurodegeneration in this period. Martande et al[14] also showed that the more severe the dementia, the more serious the involvement by periodontal disease.

Although the initial stages of periodontal disease were more prevalent in the control group in some studies, the severe periodontal disease was found to be more prevalent in the dementia group in several studies.[3,15,16,52,55,56] These findings suggest that periodontal disease and its progression may be associated with the presence and evolution of dementia; however, there is not yet enough data to prove this hypothesis.

The present study is the first meta-analysis to assess the magnitude of periodontal disease in non-dementia versus dementia patients. PD and CAL are important clinical parameters to indicate the presence of periodontitis. Our study showed that PD and CAL were significantly higher in the dementia group compared to the control group regardless of the severity level of dementia (PD = 1.41 mm, $P < 0.01$; Fig. 2a) (CAL = 1.40 mm, $P < 0.01$; Fig. 2b). However, is important to emphasize that in cross-sectional studies, it is not always possible to establish a causal link, since exposure and disease are evaluated at the same moment, increasing the risk of bias. Therefore, despite the significant increase of PD and CAL highlighted by the meta-analyses including the cross-sectional study, the meta-analyses without the cross-sectional study showed no association between dementia and periodontal disease severity (PD = 1.25 mm, $P < 0.22$; Fig 2c) (CAL = 1.20 mm, $P < 0.20$; Fig 2d). The same plausible tendency was reported by Pazos et al[59] and Wu et al.[60]

Other parameters such as CPI, PI, BOP, and CPITN were not statistically analyzed due to the inclusion criteria of the meta-analysis; however, all these clinical parameters were higher in the groups with some type of dementia compared to the control group.[4,13,52,53,55,56]

A limitation faced by the present study was the lack of details concerning the type of dementia and severity of AD. However, every type of dementia and AD showed worse results compared to the control groups. This finding suggests that patients with dementia need help in daily oral self-care and that, moreover, relatives, caregivers, and nurses in nursing homes and hospitals

should be informed and instructed to help meet this requirement.[54] Second, the methodological approaches used in the studies were different, and several different instruments, such as the Geriatric Depression Scale - short version (GDS), Mini-Mental State Examination (MMSE), Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), Diagnostic and Statistical Manual of Mental Disorders III (DSM-III), National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association - Alzheimer's Criteria (NINCDS-ADRDA Alzheimer's Criteria), Phototest, and medical history were used to determine dementia. There was also a large variation in sample size among the studies. These limitations may be responsible for the conflicting results among some studies, and the high statistical and clinical heterogeneity in both meta-analyses, both with (PD: I^2 = 98%; CAL: I^2 = 99%) and without the cross-sectional study (PD: I^2 = 98%; CAL: I^2 = 99%). The results presented by clinical trials shall be interpreted with caution, once statistically significant differences may not always represent clinical significance.

In summary, dementia patients might be less collaborative with oral hygiene and this can adversely affect their periodontal condition, though the association between dementia and the severity of periodontal disease remains unclear. Although worse periodontal conditions to be found in patients with dementia, the study of Chen et al. (2010)[53] affirmed that routine dental care carried by caregivers and dental professionals was capable to improve periodontal indices until reaching clinical outcomes similar to those without dementia, highlighting the reversibility of worse periodontal conditions and emphasizing the necessity of assisted dental care and professional assistance for dementia patients.

In conclusion, even the qualitative analysis have suggested worse periodontal conditions in dementia patients, due to different study types and the high heterogeneity among them, the meta-analysis does not support the association between dementia and severity of periodontal disease. Therefore, further research is needed to clarify this association.

Financial Support:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that there are no conflicts of interest

Acknowledgements

None

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LEGENDS

Figure 1. PRISMA flow diagram of search processes and results. Fourteen articles met the inclusion criteria and were thus selected for inclusion in the systematic review. Four articles were included in the meta-analysis.

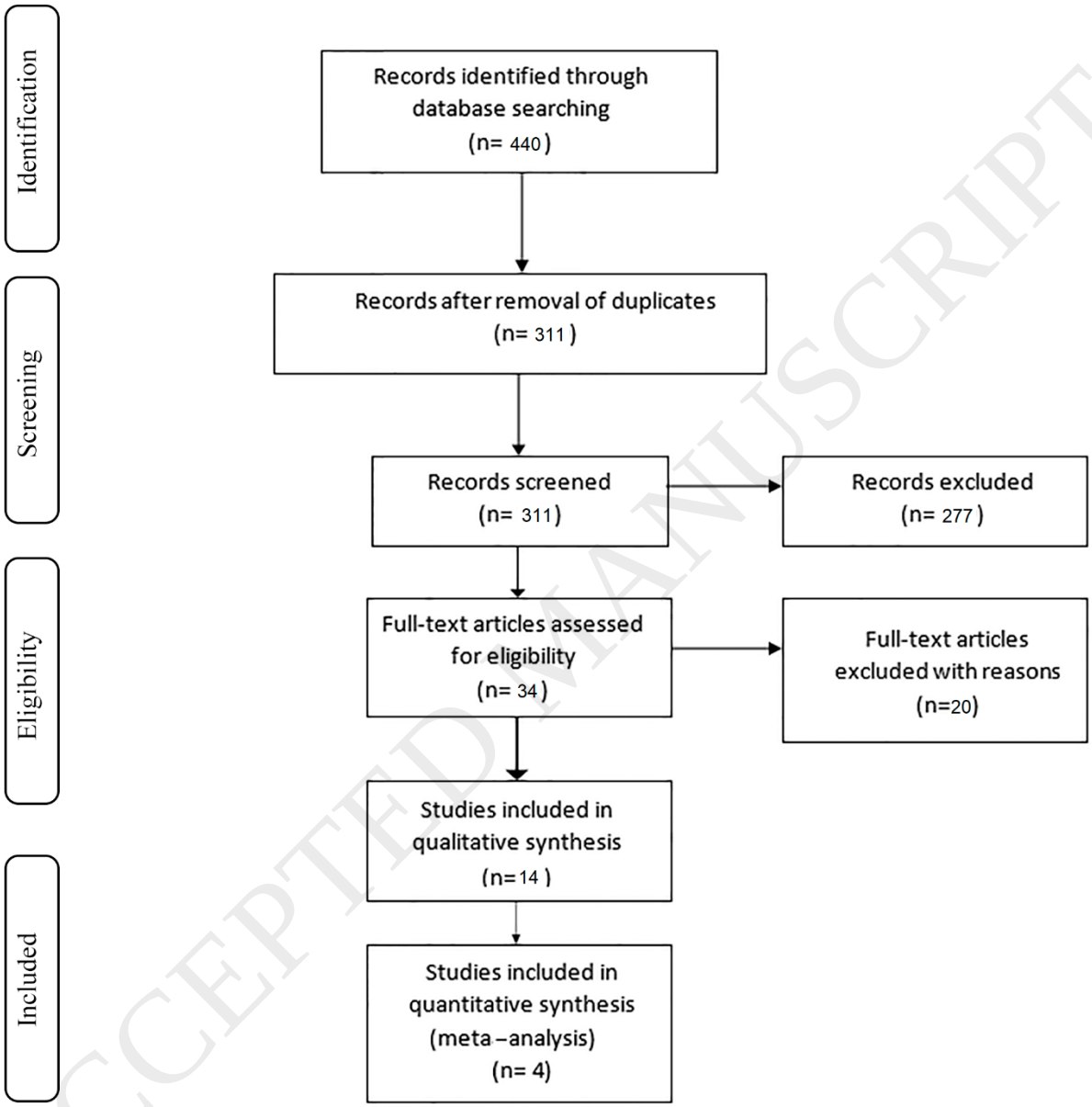

Figure 2. Forest plot of random effects meta-analysis with (**a, b**) and without (**c, d**) the cross-sectional study evaluating: **a)** the difference in probing depth (PD) level between dementia patients and non-dementia patients. Statistical and clinical heterogeneity (I^2: 98%) and mean difference (1.41 mm, P < 0.01); **b)** the difference in clinical attachment loss (CAL) between dementia patients and non-dementia patients. Statistical and clinical heterogeneity (I^2: 99%) and mean difference (1.40 mm, P < 0.01).**c)** the difference in probing depth (PD) level between dementia patients and non-dementia patients. Statistical and clinical heterogeneity (I^2: 98%) and mean difference (1.25 mm, P < 0.22); **d)** the difference in clinical attachment loss (CAL) between dementia patients and non-dementia patients. Statistical and clinical heterogeneity (I^2: 99%) and mean difference (1.20 mm, P < 0.20).

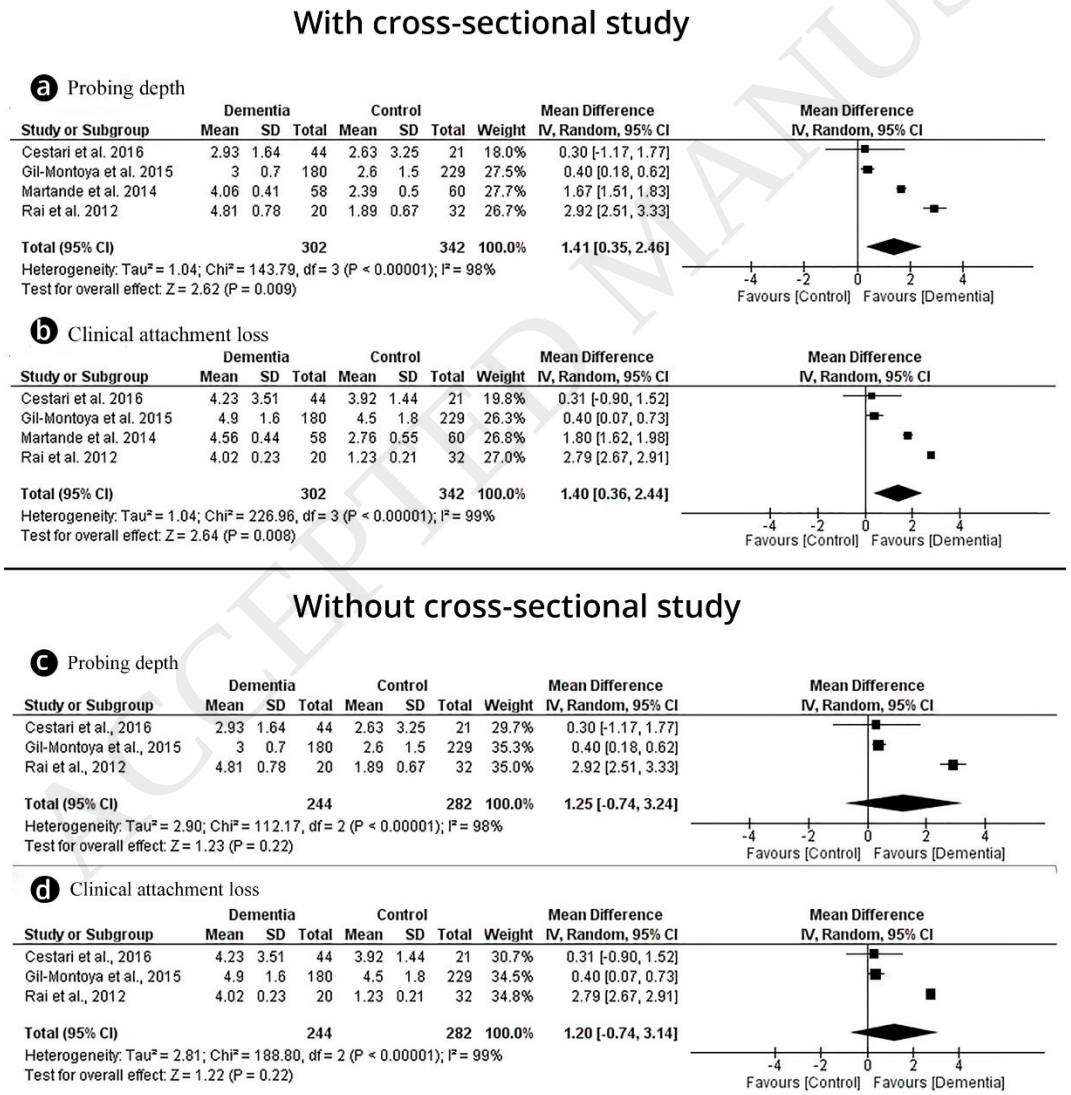

Table 1. Periodontal indexes evaluated in the intervention criteria.

Plaque index (PI)	Mean[13,14,15,16] or percentage[17] of bacterial plaque in the cervical region of the teeth.
Bleeding on probing (BOP)	Presence or absence of bleeding after insertion of periodontal probe within the sulcus or pocket.[18]
Gingival bleeding index (GBI)	Presence or absence of bleeding after gentle probing of the orifice or the gingival crevice.[19,20]
Probing depth (PD)	Distance from the gingival margin to the base of the sulcus or pocket.[21]
Clinical attachment loss (CAL)	Distance from the cemento-enamel junction to the base of the sulcus or pocket. [22]
Community index of periodontal treatment needs (CPITN)	CPITN assesses the presence or absence of gingival bleeding on probing, supra or subgingival calculus and periodontal pockets by using a 0.5 mm ball tip WHO probe. Ten index teeth are examined, resulting in six scores determining the individual's treatment needs.[23,24] Score 0: health periodontal conditions Score 1: gingival bleedings Score 2: calculus and bleeding Score 3: shallow periodontal pockets (4 to 5 millimeters) Score 4: deep periodontal pockets (6 millimeters or more) Score X: When only one or no teeth are present in a sextant
Community periodontal index (CPI)	CPI is a modified version of CPITN by inclusion of measurement of 'Loss of attachment' and elimination of 'Treatment needs'. The periodontal status is assessed with a 0.5 mm ball tip WHO probe taking into consideration 10 teeth in the oral cavity. The scores are: Score 0: health periodontal conditions Score 1: gingival bleedings Score 2: calculus and bleeding Score 3: shallow periodontal pockets (4 to 5 millimeters) Score 4: deep periodontal pockets (6 millimeters or more) [24,25]

Table 2. List of excluded studies according to the exclusion criteria and access availability

No control groups	Zenthöfer et al. 2016[26]; Sochocka et al. 2017[27], Lee et al. 2017[28]
Evaluates only plaque index (PI)	Chalmers et al. 2003[29], Hatipoglu et al. 2011[30]
Didn't evaluate the clinical parameters of periodontal disease	Kim et al. 2007[31], Kamer et al. 2009[32], Noble et al. 2012[33], Sparks Stein et al. 2012[34], Noble et al. 2014[35], Luo et al. 2015[36], Stewart et al. 2015[37], Lee et al. 2016[38], Fereshtehnejad et al. 2017[39], Chen et al. 2017[40], Takeuchi et al. 2017[41]
Only abstract available (Congress Presentation)	Noble et al. 2017[42], Sochocka et al. 2017[43], Singh 2016[44]
No access	Bramanti et al. 2015[45]

Table 3. Characteristics of the studies included in the systematic review and risk of bias of the studies included in the meta-analysis.

Author	Country and type of study	Periodontal diagnosis and dementia diagnosis respectively	Amount sample and mean age	Periodontal measure or percentages	Main outcomes	Selected for meta-analysis	Risk of bias (NOS)
Okamoto et al. 2010 [52]	Japan Cross-sectional	- CPI (Code 0, healthy; code 1, bleeding on probing; code 2, calculus present in the periodontal pocket; code 3, periodontal pocket 4–5 mm deep; and code 4, periodontal pocket at least 6 mm deep) - GDS and MMSE	Control group Without mild memory impairment (MMI) (n= 2960) Mean age: 71 Group 1 Mild memory impairment (n= 101) Mean age: 74	CPI Code 0, 1 or 2 Control= 26.3% Mild memory impairment: 18.7% Code 3 Control: 38.3% Mild memory impairment: 32.7% Code 4 Control: 22.2% Mild memory impairment: 24.8%	A lower prevalence of "code 0 or 1 or 2" were found in the MMI group than in the control group; therefore, it was considered that periodontal disease is associated with MMI	No	-
Chen et al., 2010[53]	Retrospect ive longitudi n al United States of America	- Percentage of calculus, plaque, and gingival bleeding index - International Classification of Diseases and medical history (diagnosis of AD, other types of dementia, or chronic brain syndrome recorded were consided having dementia)	Control group Without Dementia (n=372) Mean age: 73.8 Group 1 With Dementia (n=119) Mean age: 81.5	Calculus, plaque and gingival bleeding index % None Control: 1.2% Dementia: 0.9% Mild to moderate Control: 85.5% Dementia:67.9% High Control:: 13.3% Dementia: 31.3%	Oral health remains poor in older adults with dementia. More than 30% of participants with dementia presented with heavy calculus, dental plaque, or gingival bleeding index	No	
Syrjälä et al. 2012[54]	Cross-sectional Finland	- Mean of teeth with periodontal pockets +4 mm and percentage of poor oral hygiene - DSM-IV and DSM-IIIR	Control group Without dementia (n= 278) Mean age: 81.4 Group 1 Alzheimer's disease (n = 49) Mean age: 84.8 Group 2 Vascular dementia (n= 16) Mean age: 82.2	Periodontal pockets +4 mm (mean ± SD) Control: 2.9 (SD: 3.8) Alzheimer's disease: 2.8 (SD: 3.3) Vascular dementia: 2.8 (SD: 3.8) Other types of dementia: 1.7 (SD: 1.5) Poor oral hygiene % Control: 36.6% Alzheimer's disease: 77.8% Vascular dementia: 60.0% Other types of dementia: 66.7%.	No difference between the groups were found	No	-

			Group 3 Other types of dementia (n= 11) Mean age: 85.3				
Rai et al. 2012[13]	Case-control, pilot study India	- Means of PI, BOP, PD and CAL - Not Cited	Control group Healthy (n= 32) Age range: 58-69 Group 1 Dementia (n= 20) Age range: 59-69	PI: Control: 0.11 (SD: 0.09) Dementia: 0.38 (SD: 0.15) BOP: Control: 21.84% (SD: 10.86) Dementia: 89.12 %(SD: 15.6) PD: Control: 1.89 (SD: 0.67) Dementia: 4.81 (SD: 0.78) CAL: Control: 1.23 (SD: 0.21) Dementia: 4.02 (SD: 0.23)	Individuals with Alzheimer's disease and with other types of dementia had an increase of all periodontal measures compared with healthy group.	Yes	Low risk of bias
Chen et al. 2013[55]	Cross-sectional United States of America	- Percentage of calculus, plaque index and gingival bleeding index - Administering part of the MMSE; (ii) asking the caregiver about the cognitive status; (iii) verbal communication; and (iv) repeat and/or demonstrate clinical instructions	Control group Non-impaired (n= 199) Mean age: 76.1 Group 1 Dementia (n= 501) Mean age: 82.6	Calculus/Plaque/Gingival bleeding(%) None Control: 0 Dementia: 0.3 Mild to moderate Control: 73.8 Dementia: 59.2 High: Control: 26.2 Dementia: 40.4	More than 40% of demented participants presented with heavy plaque, calculus or severe gingival bleeding, significantly more than that no-impaired group (26%, p < 0,01).	No	-
De Souza Rolim et al. 2014[56]	Case-Control Brazil	- Presence of gingivitis and periodontitis in percentage - NINCDS-ADRDA and MMSE (score from 18 to 26)	Control group Healthy subjects matched for age and gender (n= 30) Mean age: 61.17 Group 1 Mild Alzheimer's disease (n= 29) Mean age: 75.17	Gingivitis Control: 3 (10.0%) Mild Alzheimer's disease: 9 (31.0%) moderate periodontitis Control: 3 (10.0%) Mild Alzheimer's disease: 2 (6.9%) Severe periodontitis Control: 2 (6.7%) Mild Alzheimer's disease: 6 (20.7%)	Periodontal infections were more common in patients with mild AD than in healthy subjects	No	-
Martande et al. 2014[14]	Cross-sectional India	- Means of PI, BOP, PD and CAL - NINCDS-ADRDA and MMSE	Control group Cognitively normal (n= 60) Mean age: 64.5 Group 1 Mild Alzheimer's disease (n= 22) Group 2	PI: Control: 1.37 (SD: 0.29) Mild Alzheimer's disease: 1.96 (SD: 0.18) Moderate Alzheimer's disease: 2.62 (SD: 0.12) Severe Alzheimer's disease: 3.47 (SD: 0.27) BOP: Control: 29.17 (SD: 5.43) Mild Alzheimer's disease: 37.09	Individuals with Alzheimer's disease had an increase of all periodontal measures compared with cognitively normal individuals. Therefore, periodontal	Yes	Low risk of bias

			Moderate Alzheimer's disease (n = 18) Group 3 Severe Alzheimer's disease (n= 18) Mean age: group 1, 2 and 3: 65.2	(SD: 5.24) Moderate Alzheimer's disease: 55.44 (SD: 7) Moderate Alzheimer's disease: 67 (SD: 12.36) PD: Control: 2.39 (SD: 0.5) Mild Alzheimer's disease: 3.18 (SD: 0.35) Moderate Alzheimer's disease: 3.99 (SD: 0.32) Severe Alzheimer's disease: 5.02 (SD: 0.56) CAL: Control: 2.76 (SD: 0.55) Mild Alzheimer's disease: 3.58 (SD: 0.37) Moderate Alzheimer's disease: 4.52 (SD: 0.38) Severe Alzheimer's disease: 5.58 (SD: 0.58)	condition worsened as the disease level progressed from mild to moderate and severe.		
Gil-Montoya et al. 2015[4]	Case-Control Spain	- Means of PI, BI, PD and CAL. - Phototest And DSM-IV-TR	Control group No subjective memory loss and a score >30 in the Phototest cognitive test (n= 229) Mean age:78.5 Group 1 Mild cognitive impairment or dementia of any type or severity (n= 180) Mean age: 77	PI: Control: 1.55 (SD: 0.89) Mild cognitive impairment or dementia: 2.37 (SD: 0.65) BI: Control: 50.6 (SD: 34.2) Mild cognitive impairment or dementia: 63.0 (SD: 31.1) PD: Control: 2.6 (SD: 1.5) Mild cognitive impairment or dementia: 3.0 (SD: 0.7) CAL: Control: 4.5 (SD: 1.8) Mild cognitive impairment or dementia: 4.9 (SD: 1.6)	Individuals with cognitive impairment and with other types of dementia had an increased of all periodontal measures compared with subjective with no memory loss and a score >30 in the Phototest cognitive test.	Yes	Low risk of bias
Chu et al. 2015[3]	Case-Control China	- CPI - Not cited	Control Without dementia (n= 50) Mean age: 80.2 Group 1 Mild level of late-onset Alzheimer's disease (n= 47) Mean age: 79.8	CPI: Healthy: Control: 1 (2%) Alzheimer's disease 0 (0%) Reversible gingivitis: Control: 7 (14%) Alzheimer's disease: (11%) Calculus present: Control: 5 (10%) Alzheimer's disease: 5 (11%) Shallow pockets present: Control: 26 (52%) Alzheimer's disease: 24 (51%) Deep pockets present: Control: 11 (22%) Alzheimer's disease: 13 (27%)	There wasn't significant difference in the prevalence of periodontal pockets (CPI ≥3) between the two groups (78% vs 74%, *P* = 0.64). Other statistical analysis among periodontal measurements is not cited.	No	-
Cestari et al. 2016[17]	Case-control Brazil	- Percentages of PI and BI and means of PD and CAL	Control group Non demeted (n= 21) Mean age: 75.33 Group 1	PI: Control: 58.47% (SD: 26.52%) Alzheimer's disease: 71.87% (SD: 26.58%) Mild cognitive impairment:	There were no differences in the periodontal indexes	Yes	Low risk of bias

		- NINCDS-ADRDA and MMSE	Alzheimer's disease (n= 25) Mean age: 77.68 Group 2 Mild cognitive impairment (n= 19) Mean age: 73.11	67.69% (SD: 28.41%) BI: Control: 29.17% (SD: 26.58%) Alzheimer's disease: 46.00% (SD: 33.32%) Mild cognitive impairment: 44.6%1 (SD: 34.26%) PD: Control: 2.63 (SD: 3.25%) Alzheimer's disease: 2.82 (SD: 1.68) Mild cognitive impairment: 3.05 (SD: 1.61) CAL: Control: 3.92 (SD: 1.44) Alzheimer's disease: 4.15 (SD: 3.90) Mild cognitive impairment: 4.32 (SD: 3.12)			
Zenthofer et al. 2016[57]	Cohort study Germany	- Means of GBI and CPITN -MMSE	Non-dementia (n= 60) Mean age: 83.4 Dementia (n= 33) Mean age: 81.7	Baseline GBI: Control: 38.1 (20.1) Dementia: 52.1 (29.2) CPITN Control: 3.1 (0.6) Dementia: 3.3 (0.6) 6 months after carer have followed a dental education programme, and after use of ultrasonic devices for denture cleaning GBI: Control: 42.6 (28.6) Dementia: 37.7 (24.5) CPITN Control: 2.9 (0.6) Dementia: 3.0 (0.7)	The other oral health indices (PCR, GBI, and CPITN) were stable for participants without dementia and improved significantly for participants with dementia.	No	-
Gil-Montoya et al. 2017[15]	Case-control Spain	- Means of PI and BI - DSM-IVR, NINCDS-ADRDA, criteria for MCI of the Neurology and Behavioral and Dementia Study Group of the Spanish Neurology Society and phototest	Control group without cognitive impairment (n = 324) Mean age: 79.8 (8.3) Group 1 Mild Cognitive Impairment/Mild Dementia (n= 107) Group 2 Moderate/severe Dementia (n= 133) Group 1 and 2 mean age: 78.25 (7.6)	PI Control: 1.55 (0.89) Mild Cognitive Impairment/Mild Dementia: 2.26 (0.70) Moderate/severe Dementia : 2.45 (0.59) BI Control: 50.6 (34.2) Mild Cognitive Impairment/Mild Dementia: 57.8 (28.4) Moderate/severe Dementia: 67.5 (32.6)	The plaque index and bleeding index were higher (worse) with more severe cognitive impairment	No	-
Zenthofer et al.	Cohort study	- Means of GBI and	Control group Non-dementia (n= 83)	GBI: Control: 48.8 (SD: 28.9)	Dementia not showed	No	-

2017[58]	Germany	CPITN - MMSE	Mean age: 80.7 Group 1 Dementia (n= 136 Mean age: 84.6	Dementia: 53.8 (SD 27.6) CPITN Control: 2.7 (DP 0.6) Dementia: 3.1 (DP 0.7)	statistical difference in gingival bleeding compared to the control group, however, Periodontal Index of Treatment Needs was significantly higher in dementia group.		
Gil-Montoya et al., 2017[16]	Case-control Spain	- Means of PI, BI, AL - Criteria of Neurology and Behavioral and Dementia Study Group of the Spanish Neurology Society, DSM-IVR, NINCDS-ADRDA or Phototest	Control group Without cognitive impairment (n= 122) Mean age: 75.7 Case group Mild cognitive impairment or dementia (n= 166) Mean age: 77.3	PI Control: ± 0.8 Case: 2.4 ± 0.5 BI Control: 52.3 ± 37.2 Case: 67.3 ± 36.0 CAL (n,%) Control Mild/moderate: 62 (50.8) Severe: 60 (49.2) Case Mild/moderate: 34 (20.5) Severe: 132 (79.5)	Periodontitis was severe in 79.5% of cases and 49.2% of controls and was mild or moderate in 20.5% of cases and 50.8% of controls	No	-

PI: Plaque index; BOP: Bleeding on probing; PD: Probing depth; CAL: Clinical attachment loss; BI: bleeding index; SD: Standard deviation; GBI: Gingival bleeding index; CPI - community periodontal index; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; MMSE: Mini-Mental State Examination; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV; GDS: Geriatric Depression Scale short version; DSM-III R: Diagnostic and Statistical Manual of Mental Disorders III; CPITN: Community Index of Periodontal Treatment Needs.