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Periodontal disease and cognitive deficits: A systematic review and meta-analysis

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Abstract

Background: Previous studies showed controversial findings for correlation of periodontal disease and cognitive deficits. *Methods:* We searched systematically for studies pertaining to correlation of periodontal disease and cognitive deficits published between August 1980 and December 2019 on Web of Science and PubMed. We combined the data extracted from the included studies to determine the correlation between periodontal disease and cognitive deficits. *Results:* Our analysis indicated a higher risk of cognitive deficits in those with moderate to severe periodontal disease when compared to those with mild or no periodontal disease (odds ratio (OR) = 1.38 (95% confidence intervals (CI): 1.28-1.48). Subgroup analysis showed significant correlations in only case-control and cohort studies (case-control studies: OR = 1.49 (95% CI: 1.24-1.80); cohort studies: relative risk (RR) = 1.33 (95% CI: 1.22-1.45)). Subgroup analysis also indicated that moderate to severe periodontal disease was correlated to increased dementia and Alzheimer disease risks, whereas no significant correlation was found between periodontal disease and mild cognitive impairment (dementia: OR/RRs = 1.32 (95% CI: 1.22-1.44); Alzheimer disease: OR/RRs = 1.51 (95% CI: 1.20-1.90); Mild cognitive impairment: OR/RRs = 1.31 (95% CI: 0.89-1.94)). Furthermore, subgroup analysis showed significant correlations between cognitive deficits and tooth loss, periodontitis, whereas no significant correlation was found between deep periodontal pockets and cognitive deficits (tooth loss: OR/RRs = 1.57 (95% CI: 1.39-1.77); periodontitis: OR/RRs = 1.43 (95% CI: 1.03-2.00); deep periodontal pockets: OR/RRs = 1.24 (95% CI: 0.77-2.00)).
Conclusions: This review suggests a significant correlation between periodontal disease and cognitive deficits. Interventional studies for periodontal disease may be beneficial for patients with cognitive deficits.

Keywords: Periodontal disease, cognitive deficits, Alzheimer disease; dementia; meta-analysis

INTRODUCTION

Periodontal disease (PD) is a chronic inflammatory process induced by microorganisms. Epidemiological evidence indicates that PD may be seen between 20 and 50 percent of the general population globally. In addition, it is considered as one of the two most serious threats to the oral health and the main cause of tooth loss.[1,2]

Robust evidences has indicated a correlation between PD and systemic diseases such as cardiovascular disease, adverse pregnancy outcome, chronic kidney disease and diabetes mellitus.[3,4] However, the correlation between teeth loss and the risk of dementia are still under investigation. Dementia is a clinical syndrome; the common causes are Alzheimer disease (AD), vascular dementia (VD), frontotemporal dementia, dementia with Lewy bodies, and mixed dementia. Cognitive deficits include dementia and mild cognitive impairment (MCI). MCI represents a transitional stage between normal aging and dementia, especially, AD.[5] The correlation between PD and cognitive deficits may be related to the invasion of the brain through blood flow or peripheral nerves by the bacteria residing in the dental biofilm and their products.[6] Furthermore, a study has shown an increased levels of cytokines in both PD and cognitive deficits, suggesting the presence of overlapping mechanisms between the two diseases.[6,7] However, the relationship between PD and cognitive deficits remains unclear and controversial.

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There are increasing studies investigating the correlation between PD and cognitive deficits, with inconsistent results.[8,9] There has been some meta-analysis studies recently exploring the correlation between dementia or PD and tooth loss or periodontitis.[10-13] This study aims to explore the correlation between PD and cognitive deficits. In addition, subgroup analysis are were also performed to evaluate the correlations of different types or symptoms of PD (including tooth loss, deep periodontal pockets, periodontitis, alveolar bone loss, caries and chewing difficulty) and cognitive deficits (including dementia, AD, MCI, VD, other types of dementia except AD). Our study aims to be a comprehensive and systematic review and meta-analysis on PD and cognitive deficits. This was also the first meta-analysis for the correlation between PD and MCI.

METHODS

Search strategy and selection criteria

Web of Science and PubMed databases were searched for articles published in English between August 1980 and December 2019. A full list of search terms was included in the supplement. A total of 408 studies were included after the exclusion of duplicates. We included case-control or cohort studies, reporting relative risk (RR) or odds ratio (OR) and 95% confidence intervals (CI) related to PD and cognitive deficits. We excluded meta-analyses, case studies and reviews.

Data extraction and analysis

We independently extracted the following data: Author, publication year, numbers of participants, information of included participants (age, gender and MMSE), type of research, the ORs or RRs and 95% CI after multivariate adjustment, types or symptoms of PD and types of cognitive deficits. According to a previous study[14], the ORs or RRs and 95% CI were computed with STATA 12.0 software. The Q test and I^2 were used to examine heterogeneity between studies. Random effects models were conducted as pooling methods with invariably high heterogeneity (p value for Q test ≤ 0.05). Otherwise, fixed effects models were performed as pooling methods. Subgroup analyses (for types of PD and research designs) were conducted to detect source of the heterogeneity. In addition, we applied sensitivity analysis to assess the stabilization of the present study. Finally, publication bias was assessed with Begg's test and funnel plot.

RESULTS

Search results

Figure 1 is a summary of the selection progression

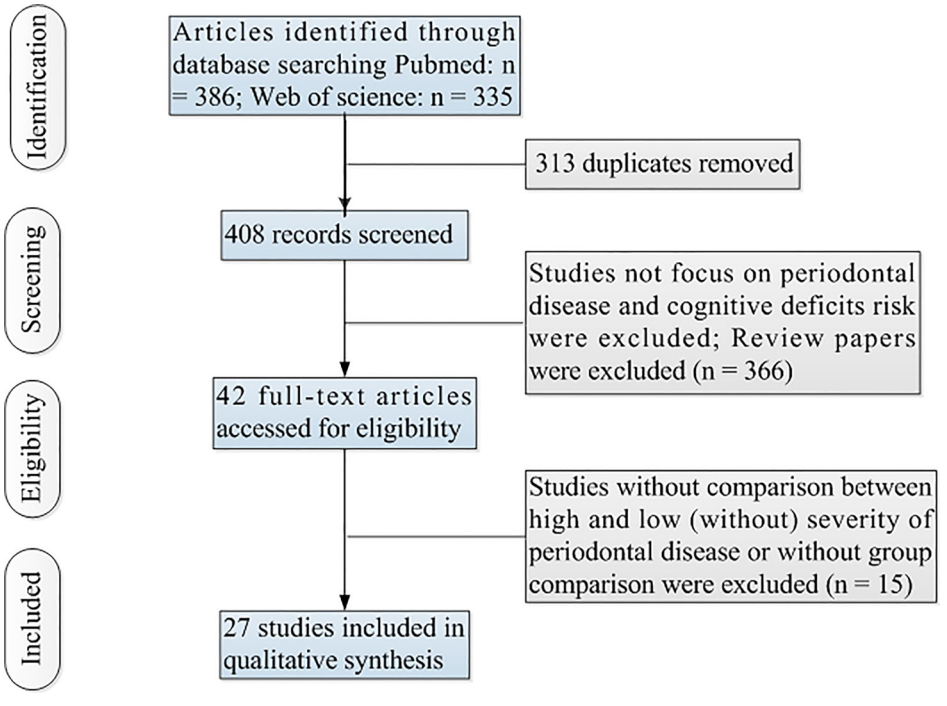

Figure 1. Flow of information through the different phases of a systematic review.

process. The final analysis was based on 27 articles on PD and cognitive deficits. Table 1 shows the study characteristics and results. There were 18 cohort studies with a total of 33,467 subjects and 9 case-control studies with a total of 4,088 subjects and 16,362 healthy controls. Among these studies, 3 studies reported results for cognitive deficits, 22 examined dementia as the endpoint, 4 studies reported results for AD, one study examined VD as the endpoint, one study showed results for dementia other than AD, 4 studies examined MCI as the endpoint. In addition, 22 studies explored the correlation between tooth loss and cognitive deficits, 3 studies reported results for deep periodontal pockets, 3 studies explored correlation between periodontitis and cognitive deficits, one study examined alveolar bone loss and another study explored correlation between caries and cognitive deficits; 2 studies examined chewing difficulty, and another study reported the correlation with gingival bleeding.

Meta-analysis results

The study indicated a higher risk of cognitive deficits in moderate to severe PD compared to that with mild or no PD (ORs = 1.38 (95% CI: 1.28-1.48); see Figure 2). Significant heterogeneities were showed between included studies. Subgroup analysis showed significant correlations in these case-control studies (ORs = 1.49 (95% CI: 1.24-1.80)). A significant correlation was detected in cohort studies (RRs = 1.33 (95% CI: 1.22-1.45); see Figure 3). Subgroup analysis indicated that PD was correlated to increased dementia and AD risks, whereas no significant correlation was found between PD and MCI (dementia: OR/RRs = 1.32 (95% CI: 1.22-1.44); AD: OR/RRs =

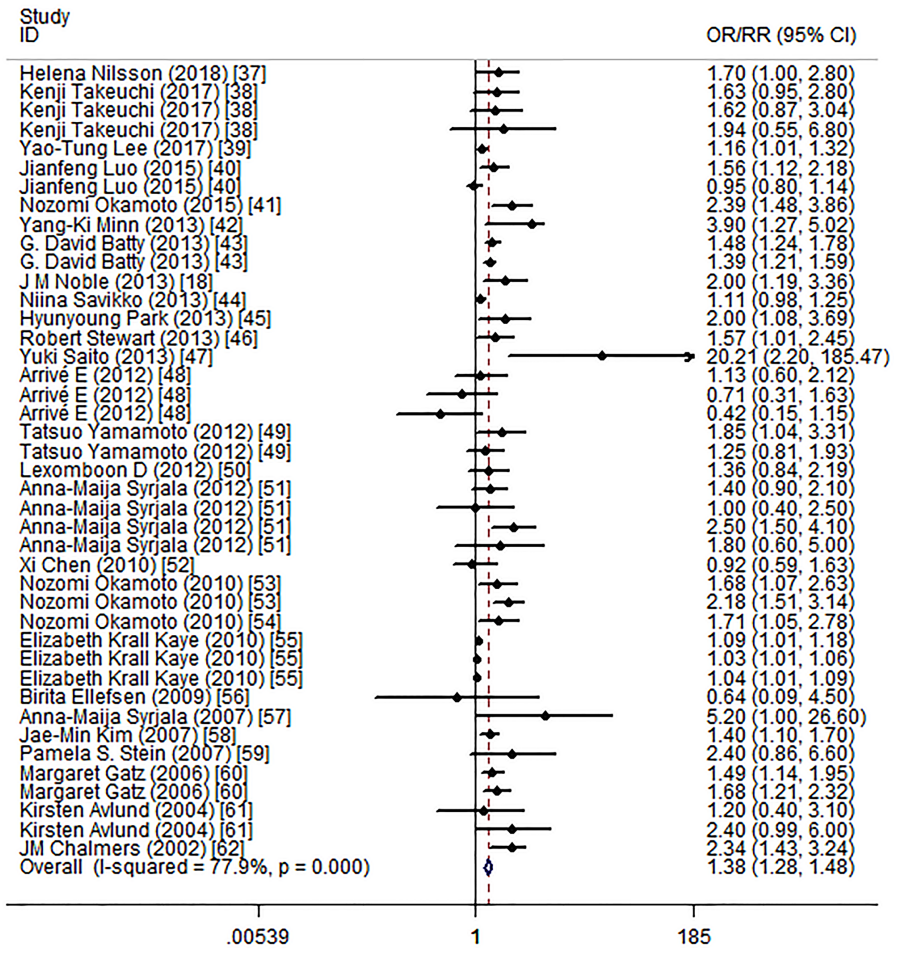

Figure 2. The combined OR/RRs and 95% CI of cognitive deficits risk in moderate to severe PD vs. that with mild or no PD. Abbreviations: CI, confidence intervals; OR, odds ratio; PD, periodontal disease; RR, relative risk.

Table 1: Characteristics of the studies included in the meta-analysis

Reference	Numbers of cases/controls	Age (years old)	Gender (male/ female)	MMSE	Research type	OR/RR (95% CI) (adjusted)	types of periodontal disease and cognitive deficits
Helena Nilsson (2018) [38]	775	NA	NA	NA	cohort study	1.7 (1.0–2.8)	Tooth loss (N = 13-31 vs. 0-12)/dementia
Kenji Takeuchi (2017) [39]	1566	≥ 60	691/875	NA	cohort study	1.63 (0.95–2.80)	Tooth loss (Edentulous vs. 0-12)/dementia
						1.62 (0.87–3.04)	Tooth loss (Edentulous vs. 0-12)/ Alzheimer's disease
						1.94 (0.55–6.80)	Tooth loss (Edentulous vs. 0-12)/Vascular dementia
Yao-Tung Lee (2017) [40]	6056	72.42	3270/2986	NA	cohort study	1.16 (1.01–1.32)	Periodontitis/dementia
Jianfeng Luo (2015) [41]	Dementia 120	80.9(7.4)	43/77	16.9(5.0)	case-control study	1.56 (1.12-2.18)	Tooth loss (N >16 vs. 0-3)/dementia
	HC 2389	70.0 (7.7)	1110/1279	28.5(1.7)			
	MCI 554	74.8 (8.4)	246/308	26.4(2.9)		0.95 (0.80–1.14)	Tooth loss (N >16 vs. 0-3)/MCI
	HC 2389	70.0 (7.7)	1110/1279	28.5 (1.7)			
Nozomi Okamoto (2015) [42]	2335	NA	NA	NA	cohort study	2.39 (1.48-3.86)	Tooth loss (Edentulous vs. 0-7)/dementia
Yang-Ki Minn (2013) [43]	438	63 (7.9)	NA	NA	cohort study	3.9 (1.27-5.02)	Tooth loss (N >10 vs. 0-5)/dementia
G. David Batty (2013) [44]	11140	55-88	NA	NA	cohort study	1.48 (1.24-1.78)	Tooth loss (Edentulous vs. 0-10)/dementia
						1.39 (1.21-1.59)	Tooth loss (Edentulous vs. 0-10)/CI
J M Noble (2013) [19]	2355	70.8 (70.0-71.6)	1005/1351	NA	cohort study	2.00 (1.19-3.36)	Individuals with the highest P gingivalis IgG vs those with lowest P gingivalis IgG/ CI
Niina Savikko (2013) [45]	Dementia 2316	84.9(7.4)	498/1818	NA	case-control study	1.109 (0.982-1.253)	Chewing Difficulty/dementia
	HC 848	82.7 (8.3)	217/631				
Hyunyoung Park (2013) [46]	438	64.1 (7.84)	123/315	26.37 (3.68)	cohort study	2.0 (1.08-3.69)	Tooth loss (N >10 vs. 6-10)/CI
Robert Stewart (2013) 47	1053	NA	NA	NA	cohort study	1.57 (1.01-2.45)	Periodontitis/dementia

Reference	Numbers of cases/controls	Age (years old)	Gender (male/ female)	MMSE	Research type	OR/RR (95% CI) (adjusted)	types of periodontal disease and cognitive deficits
Yuki Saito (2013) [48]	Dementia 26	73.7 (7.9)	12/14	21.0 (2.0)	case-control study	20.21(2.20-185.47)	Tooth loss (N = 22-32 vs. 0-10)/dementia
	HC 436	68.3 (6.2)	151/285	28.6 (1.7)			
Arrivé E (2012) [49]	405	70 (68-75)	184/221	NA	cohort study	1.13 (0.60-2.12)	Tooth loss (N ≥ 19 vs. < 4)/dementia
						0.71(0.31-1.63)	Gingival bleeding/dementia
						0.42 (0.15-1.15)	Deep periodontal pockets (≥ 6 mm vs. 4–5mm)/dementia
Tatsuo Yamamoto (2012) [50]	4425	≥ 65	NA	NA	cohort study	1.85 (1.04-3.31)	Tooth loss (with few teeth and without dentures vs. no loss)/dementia
						1.25 (0.81-1.93)	Chewing difficulty/dementia
Lexomboon D (2012) [51]	557	83.0 (4.7)	229/328	NA	cohort study	1.72 (1.05-2.80)	Chewing difficulty/dementia
						1.36 (0.84-2.19)	Tooth loss (Multiple tooth loss vs. natural teeth) /dementia
Anna-Maija Syrjala (2012) [52]	AD 49	84.8 (5.6)	NA	NA	case-control study	1.4 (0.9-2.1)	Deep periodontal pockets/AD
	HC 278	81.4 (4.6)				1.0 (0.4-2.5)	Tooth loss/AD
	other types of dementia 27	82.2 (4.7)				2.5 (1.5-4.1)	Deep periodontal pockets/other types of dementia
	HC 278	81.4 (4.6)				1.8 (0.6-5.0)	Tooth loss/other types of dementia
Xi Chen (2010) [53]	Dementia 119	81.5 (9.2)	30/89	NA	case-control study	0.92 (0.59-1.63)	Tooth loss/dementia
	HC 372	73.8 (10.7)	110/262				
Nozomi Okamoto (2010) [54]	MCI 121	74.0 (71.0, 79.0)	83/38	26.0 (25.0, 27.0)	case-control study	1.679 (1.073-2.627)	Tooth loss (N = 22-32 vs. 0-10)/MCI
	HC 3696	71.0 (68.0, 75.0)	1785/1911	28.0 (26.0, 30.0)			
	Dementia 214	74.0 (71.0, 78.0)	123/91	23.0 (22.0, 23.0)		2.177(1.510 - 3.140)	Tooth loss (N = 22-32 vs. 0-10)/dementia
	HC 3696	71.0 (68.0, 75.0)	1785/1911	28.0 (26.0, 30.0)			
Nozomi Okamoto (2010) [55]	MCI 101	71.0 (7.0)	69/32	26.0 (2.0)	case-control study	1.71 (1.05-2.78)	Tooth loss (N = 22-32 vs. 0-10)/MCI
	HC 2960	74.0 (9.0)	1478/1486	28.0 (4.0)			

Reference	Numbers of cases/controls	Age (years old)	Gender (male/ female)	MMSE	Research type	OR/RR (95% CI) (adjusted)	types of periodontal disease and cognitive deficits
Elizabeth Krall Kaye (2010) [56]	597	24-84	NA	NA	cohort study	1.09 (1.01-1.18)	Tooth loss/dementia
						1.03 (1.01-1.06)	Alveolar bone loss /dementia
						1.04 (1.01-1.09)	Deep periodontal pockets/dementia
Birita Ellefsen (2009) [57]	106	NA	NA	NA	cohort study	0.64 (0.09-4.50)	Caries/AD
Anna-Maija Syrjala(2007) [58]	Dementia 131	NA	78/53	NA	case-control study	5.2 (1.0-26.6)	Tooth loss/dementia
	HC 2320		1334/986				
Jae-Min Kim (2007) [59]	686	NA	NA	NA	cohort study	1.4 (1.1-1.7)	Tooth loss (Edentulous vs. 0-4)/dementia
Pamela S. Stein (2007) 60	144	75-98	NA	NA	cohort study	2.4 (0.86-6.6)	Tooth loss/dementia
Margaret Gatz (2006) [61]	Dementia 310	78.95 (7.00)	85/225	NA	case-control study	1.49 (1.14-1.95)	Tooth loss (Lost all teeth vs. Has all teeth)/dementia
	HC 3063	79.23 (4.73)	1200/1863				
	AD 214	NA	NA	NA		1.68 (1.21-2.32)	Tooth loss (Lost all teeth vs. Has all teeth)/AD
	HC 3063	79.23 (4.73)	1200/1863				
Kirsten Avlund (2004) [62]	159	NA	NA	NA	cohort study	1.2 (0.4-3.1)	Tooth loss (N = 19-32 vs. 0-11)/MCI
						2.4 (0.99–6.0)	Tooth loss (N = 19-32 vs. 0-11)/dementia
JM Chalmers (2002) [63]	232	78.4 (21.6)	132/100	NA	cohort study	2.335 (1.429-3.241)	Tooth loss/dementia

Abbreviations: AD, Alzheimer's disease; CI, cognitive impairment; CI, confidence intervals; HC, healthy controls; MCI, mild cognitive impairment; N, number; NA, not available; OR, odds ratio; RR, relative risk.

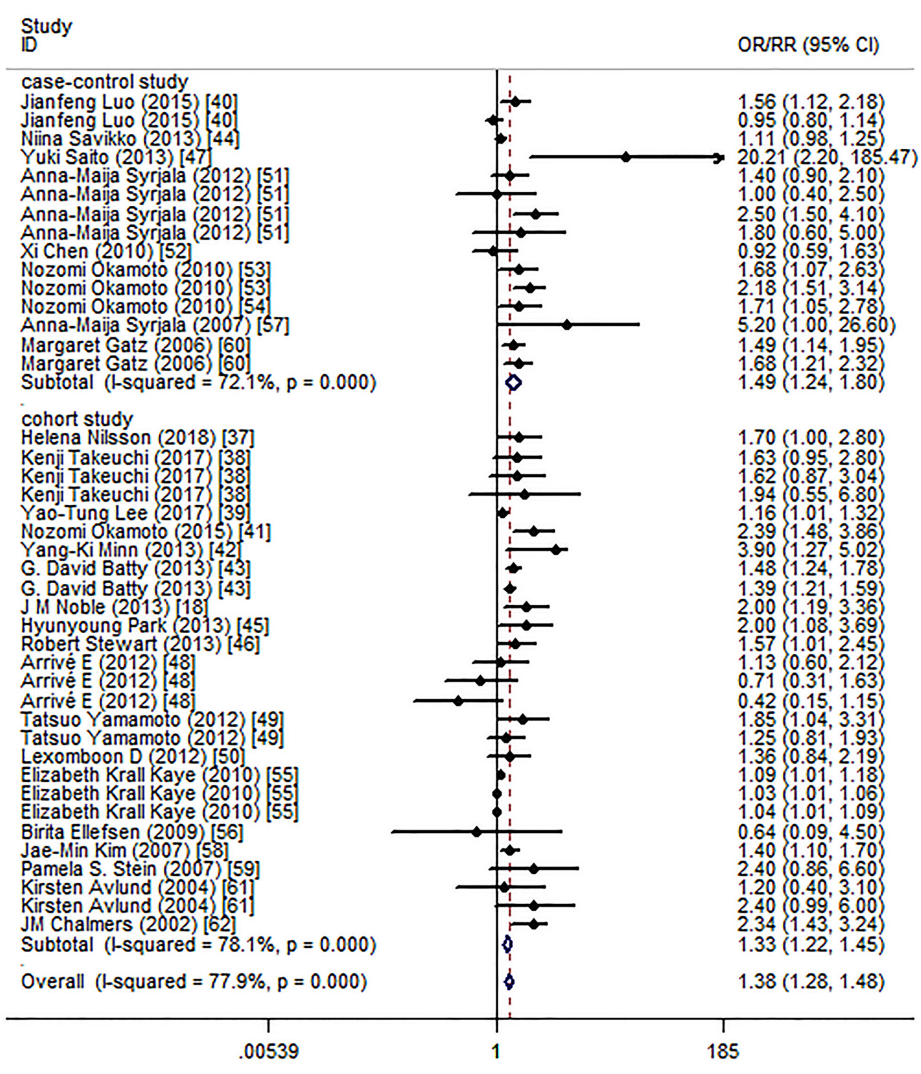

Figure 3. The combined OR/RRs and 95% CI of cognitive deficits risk in moderate to severe PD vs. that with mild or no PD for case-control studies and cohort studies. Abbreviations: CI, confidence intervals; OR, odds ratio; PD, periodontal disease; RR, relative risk.

1.51 (95% CI: 1.20-1.90); MCI: OR/RRs = 1.31 (95% CI: 0.89-1.94); see Figure 4). Subgroup analysis showed significant correlations between cognitive deficits and tooth loss, periodontitis, whereas no significant correlation was detected between deep periodontal pockets and cognitive deficits (tooth loss: OR/RRs = 1.57 (95% CI: 1.39-1.77); periodontitis: OR/RRs = 1.43 (95% CI: 1.03-2.00); deep periodontal pockets: OR/RRs = 1.24 (95% CI: 0.77-2.00); see Figure 5). The sensitivity analysis showed no alterations in the trend of effect when excluding any one of the studies (see supplementary figure 1). No significant publication bias was also found in these studies (Begg's test (p = 0.423); see supplementary Figure 2).

DISCUSSION

This study showed a correlation between PD and cognitive deficits. Significant correlation was shown in cohort and case-control studies. The correlation was significant between PD and dementia or AD, whereas no significant correlation was found between PD and MCI. There was also significant correlations between cognitive deficits and tooth loss, periodontitis, while no significant correlation was found between deep periodontal pockets and cognitive deficits.

AD is the most common cause of dementia involving 75% of cases. One possible pathophysiology link between PD and AD could be systemic inflammation. It has been reported that

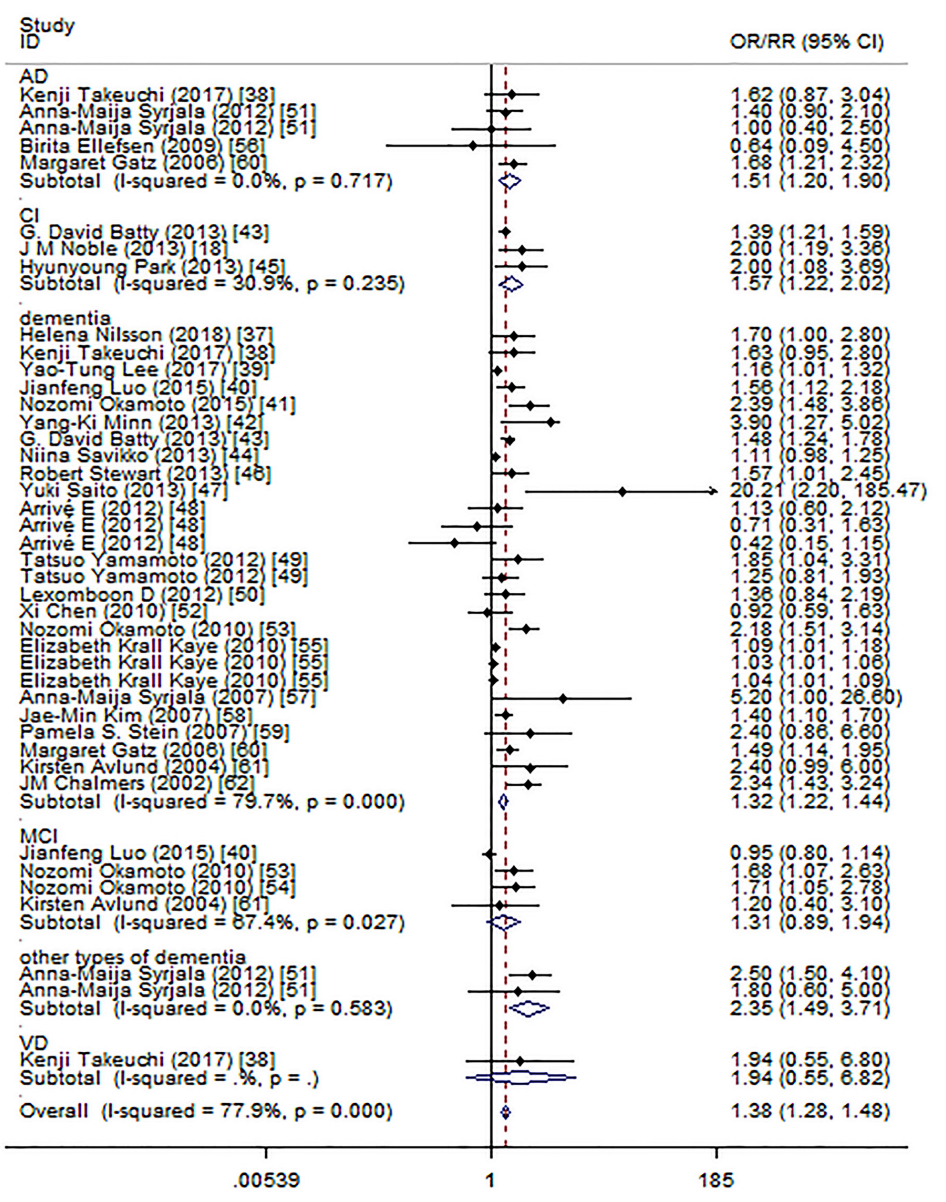

Figure 4. The combined OR/RRs and 95% CI of different types of cognitive deficits risk in moderate to severe PD vs. that with mild or no PD. Abbreviations: AD, Alzheimer's disease; CI, confidence intervals; CI, cognitive impairment; MCI, mild cognitive impairment; OR, odds ratio; PD, periodontal disease; RR, relative risk; VD, vascular dementia.

300 million organisms can be harboured in a single periodontal pocket.[15] Periodontopathogens can come into the systemic circulation via ulcerations in periodontal pocket lining. Also, periodontal pathogens could also incite pathology in the distant locations. For example, *P. gingivalis*, an actinomycetemcomitans, and *T. denticola* can invade multiple cell forms, thus evading the extracellular host defense system and replicating in the host tissues including brain tissues.[16,17] Previous studies have shown increased antibody levels of some periodontopathogens in the AD patients when compared to healthy controls.[18] In addition, patients with the highest *P. gingivalis* IgG showed poorer cognitive functions.[19] In the past two decades, emerging evidence suggests that inflammation may exacerbate or be part of the pathogenesis in AD. Postmortem brains of both AD transgenic animals and patients also showed elevated levels of inflammatory cytokines and chemokines.[20,21] Previous studies indicated that peripheral C-reactive protein (CRP) [22],

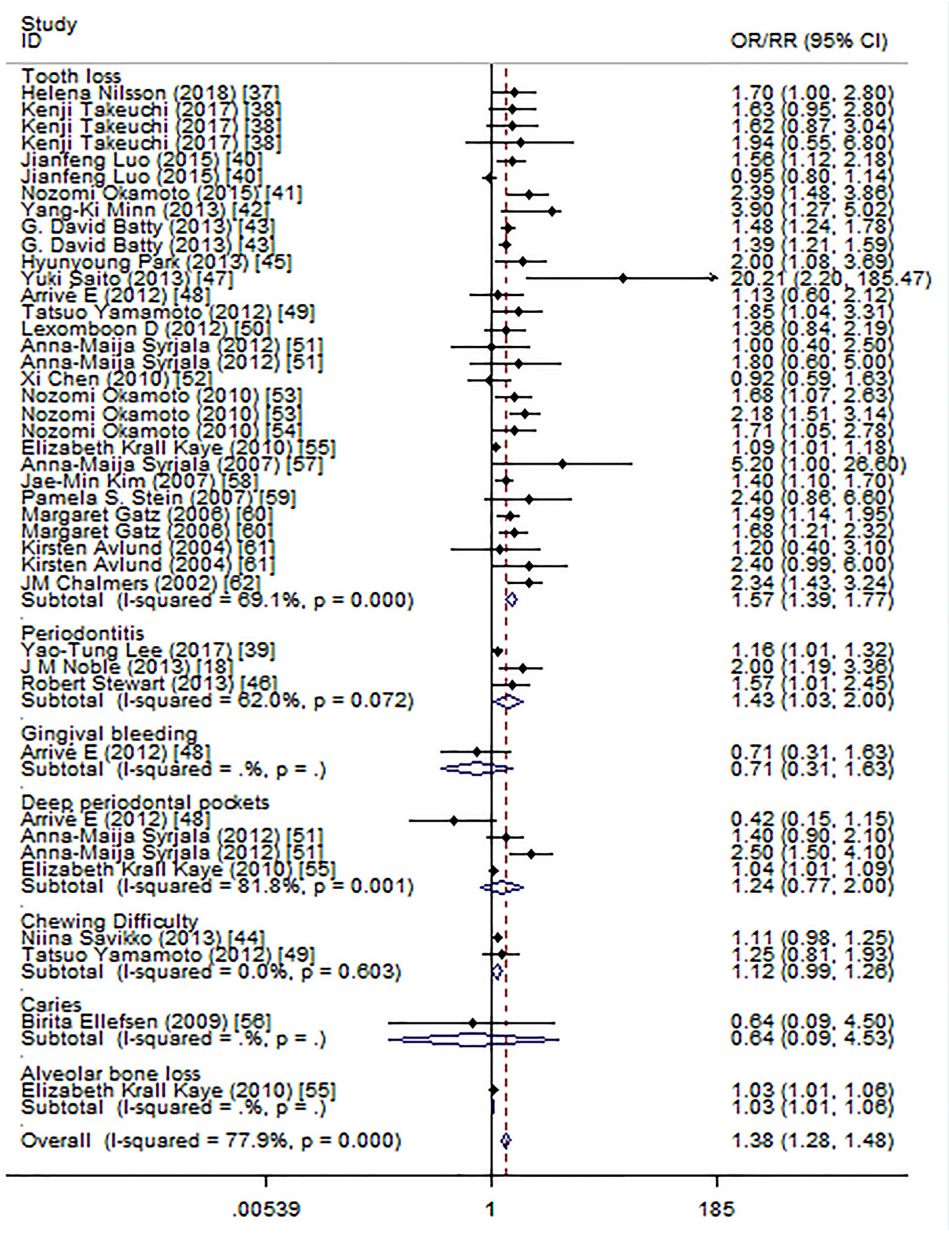

Figure 5. The combined OR/RRs and 95% CI of cognitive deficits risk in different types or symptoms of moderate to severe PD vs. that with mild or no PD. Abbreviations: CI, confidence intervals; OR, odds ratio; PD, periodontal disease; RR, relative risk.

Interleukin (IL) -1β[23,24], IL-6[25], IL-12[26], IL-18[26,27], IL-8[28] concentrations were negatively associated with Mini-Mental State Examination (MMSE) scores in AD patients. In addition, there were studies indicating that the use of non-steroidal anti-inflammatory drugs (NSAIDs) was associated with lower incidence of AD.[29] Furthermore, IL-1β levels were significantly lower in donepezil-treated AD patients.[30] These studies provid evidence for the concept that inflammation may exacerbate or be part of the pathogenesis process in AD.

Systemic inflammation in AD may exacerbate neurological deficit. Peripheral inflammation contributes to increased blood-brain barrier (BBB) permeability and extravasations of plasma proteins in the brain parenchyma.[31] Increased BBB permeability may allow some vasculotoxic and neurotoxic proteins (e.g. thrombin, fibrin and plasmin) to enter the brain.[32] BBB dysfunction contributes to the reduction of Aβ clearance at the BBB. Increased extravasations of plasma

proteins in the brain parenchyma may activate microglia and astrocytes. The accompanying edema contributes to a reduction of cerebral blood flow (CBF).[32] All these pathological process may initiate a cascade of events that precedes dementia, and contribute to the pathogenesis process of AD.

Our study has shown a significant correlation between PD and dementia or AD, which correspond to the result of some recent studies.[12,13] However, no significant correlation was seen between PD and MCI in our study. Some previous studies have indicated that systematic inflammation in MCI patients was more similar to healthy controls than to AD patients.[33-35] A systematic review has shown that older individuals with dementia has worse oral health (including root caries, coronal caries and retained roots), when compared to healthy older people.[36] Lee *et al*. also found that patients with dementia could not visit the dentists regularly, when compared to healthy controls.[37] This may be another reason contributing to the correlation between PD and dementia. This situation may not arise in MCI patients, which contributes to the absence of correlation between PD and MCI. Our study was the first meta-analysis to investigate the relationship between PD and MCI.

Our study have the following limitations: Only 4 studies were included for exploring the correlation between PD and AD or MCI; while only 3 studies reported results for deep periodontal pockets or periodontitis. It would be better to have more studies to evaluate the association between PD and cognitive deficits in the meta-analysis analysis.

In conclusion, the present meta-analysis demonstrates a significant correlation between PD and cognitive deficits. Interventional studies for PD, such as non-surgical periodontal therapy may be indicated in patients with cognitive deficits.

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DISCLOSURE

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Conflict of interest: None

REFERENCES

1. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. *Int J Health Sci (Qassim)* 2017; 11(2): 72-80.
2. de Pablo P, Chapple IL, Buckley CD, Dietrich T. Periodontitis in systemic rheumatic diseases. *Nat Rev Rheumat* 2009; 5(4): 218-24.
3. Janket SJ, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. *Oral Surg Oral Med Oral Path Oral Radiol Endod* 2003; 95(5): 559-69.
4. Piscoya MD, Ximenes RA, Silva GM, Jamelli SR, Coutinho SB. Maternal periodontitis as a risk factor for prematurity. *Pediatrics Int* 2012; 54(1): 68-75.
5. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999; 56(3): 303-8.
6. Kamer AR, Dasanayake AP, Craig RG, Glodzik-Sobanska L, Bry M, de Leon MJ. Alzheimer's disease and peripheral infections: the possible contribution from periodontal infections, model and hypothesis. *J Alzheimers Dis* 2008; 13(4): 437-49.
7. Cestari JA, Fabri GM, Kalil J, *et al*. Oral infections and cytokine levels in patients with Alzheimer's disease and mild cognitive impairment compared with controls. *J Alzheimers Dis* 2016; 52(4): 1479-85.
8. Martande SS, Pradeep AR, Singh SP, *et al*. Periodontal health condition in patients with Alzheimer's disease. *Am J Alzheimers Dis Other Demen* 2014; 29(6): 498-502.
9. Gil-Montoya JA, Sanchez-Lara I, Carnero-Pardo C, *et al*. Is periodontitis a risk factor for cognitive impairment and dementia? A case-control study. *J Periodontol* 2015; 86(2): 244-53.
10. Leira Y, Dominguez C, Seoane J, *et al*. Is periodontal disease associated with Alzheimer's disease? A systematic review with meta-analysis. *Neuroepidemiology* 2017; 48(1-2): 21-31.
11. Shen T, Lv J, Wang L, Wang W, Zhang D. Association between tooth loss and dementia among older people: a meta-analysis. *Int J Geriatr Psychiatry* 2016; 31(8): 953-5.
12. Maldonado A, Laugisch O, Burgin W, Sculean A, Eick S. Clinical periodontal variables in patients with and without dementia-a systematic review and meta-analysis. *Clin Oral Investig* 2018.
13. Gusman DJR, Mello-Neto JM, Alves BES, *et al*. Periodontal disease severity in subjects with dementia: A systematic review and meta-analysis. *Arch Gerontol Geriatr* 2018; 76: 147-59.
14. Yan B, Zhang L, Shao Z. Consumption of processed and pickled food and esophageal cancer risk: A systematic review and meta-analysis. *Bulletin du Cancer* 2018; 105(11): 992-1002.
15. Socransky SS, Haffajee AD. Dental biofilms: difficult therapeutic targets. *Periodontology* 2000 2002; 28: 12-55.
16. Riviere GR, Riviere KH, Smith KS. Molecular and immunological evidence of oral Treponema in the human brain and their association with Alzheimer's disease. *Oral Microbiol Immunol* 2002; 17(2): 113-8.

17. Okuda K, Ishihara K, Nakagawa T, Hirayama A, Inayama Y, Okuda K. Detection of *Treponema denticola* in atherosclerotic lesions. *J Clin Microbiol* 2001; 39(3): 1114-7.
18. Sparks Stein P, Steffen MJ, Smith C, et al. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. *Alzheimers Dement* 2012; 8(3): 196-203.
19. Noble JM, Borrell LN, Papapanou PN, Elkind MS, Scarmeas N, Wright CB. Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III. *J Neurol Neurosurg Psychiatry* 2009; 80(11): 1206-11.
20. Cacabelos R, Barquero M, Garcia P, Alvarez XA, Varela de Seijas E. Cerebrospinal fluid interleukin-1 beta (IL-1 beta) in Alzheimer's disease and neurological disorders. *Methods Find Exp Clin Pharmacol* 1991; 13(7): 455-8.
21. Xia MQ, Qin SX, Wu LJ, Mackay CR, Hyman BT. Immunohistochemical study of the beta-chemokine receptors CCR3 and CCR5 and their ligands in normal and Alzheimer's disease brains. *Am J Pathol* 1998; 153(1): 31-7.
22. Ge X, Xu XY, Feng CH, Wang Y, Li YL, Feng B. Relationships among serum C-reactive protein, receptor for advanced glycation products, metabolic dysfunction, and cognitive impairments. *BMC Neurol* 2013; 13.
23. Forlenza OV, Diniz BS, Talib LL, et al. Increased serum IL-1beta level in Alzheimer's disease and mild cognitive impairment. *Dement Geriatr Cogn Disord* 2009; 28(6): 507-12.
24. Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry* 2010; 68(10): 930-41.
25. Huang CW, Wang SJ, Wu SJ, *et al*. Potential blood biomarker for disease severity in the Taiwanese population with Alzheimer's disease. *Am J Alzheimers Dis Other Demen* 2013; 28(1): 75-83.
26. Motta M, Imbesi R, Di Rosa M, Stivala F, Malaguarnera L. Altered plasma cytokine levels in Alzheimer's disease: correlation with the disease progression. *Immunol Lett* 2007; 114(1): 46-51.
27. Chen JM, Jiang GX, Li QW, Zhou ZM, Cheng Q. Increased serum levels of interleukin-18, -23 and -17 in Chinese patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* 2014; 38(5-6): 321-9.
28. Galimberti D, Schoonenboom N, Scarpini E, Scheltens P. Chemokines in serum and cerebrospinal fluid of Alzheimer's disease patients. *Ann Neurol* 2003; 53(4): 547-8.
29. Vlad SC, Miller DR, Kowall NW, Felson DT. Protective effects of NSAIDs on the development of Alzheimer disease. *Neurology* 2008; 70(19): 1672-7.
30. Gambi F, Reale M, Iarlori C, *et al*. Alzheimer patients treated with an AchE inhibitor show higher IL-4 and lower IL-1 beta levels and expression in peripheral blood mononuclear cells. *J Clin Psychopharmcol* 2004; 24(3): 314-21.
31. Zamolodchikov D, Chen ZL, Conti BA, Renne T, Strickland S. Activation of the factor XII-driven contact system in Alzheimer's disease patient and mouse model plasma. *Pro Natl Acad Sci U S A* 2015; 112(13): 4068-73.
32. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci* 2011; 12(12): 723-38.
33. Dursun E, Gezen-Ak D, Hanagasi H, *et al*. The interleukin 1 alpha, interleukin 1 beta, interleukin 6 and alpha-2-macroglobulin serum levels in patients with early or late onset Alzheimer's disease, mild cognitive impairment or Parkinson's disease. *J Neuroimmunol* 2015; 283: 50-7.
34. Yarchoan M, Louneva N, Xie SX, *et al*. Association of plasma C-reactive protein levels with the diagnosis of Alzheimer's disease. *J Neurol Sci* 2013; 333(1-2): 9-12.
35. Arik G, Cankurtaran M, Kara O, *et al*. The role of systemic inflammation on mild cognitive impairment. *Alzheimers Dementia* 2014; 10(4): P675-P6.
36. Delwel S, Binnekade TT, Perez RS, Hertogh CM, Scherder EJ, Lobbezoo F. Oral health and orofacial pain in older people with dementia: a systematic review with focus on dental hard tissues. *Clinical Oral Investig* 2017; 21(1): 17-32.
37. Lee KH, Wu B, Plassman BL. Dental care utilization among older adults with cognitive impairment in the USA. *Geriatr Gerontol Int* 2015; 15(3): 255-60.
38. Nilsson H, Berglund JS, Renvert S. Periodontitis, tooth loss and cognitive functions among older adults. *Clin Oral Investig* 2018; 22(5): 2103-9.
39. Takeuchi K, Ohara T, Furuta M, *et al*. Tooth loss and risk of dementia in the community: the Hisayama Study. *J Am Geriatr Soc* 2017; 65(5): e95-e100.
40. Lee YT, Lee HC, Hu CJ, *et al*. Periodontitis as a modifiable risk factor for dementia: A nationwide population-based cohort study. *J Am Geriatr Soc* 2017; 65(2): 301-5.
41. Luo J, Wu B, Zhao Q, *et al*. Association between tooth loss and cognitive function among 3063 Chinese older adults: a community-based study. *PloS One* 2015; 10(3): e0120986.
42. Okamoto N, Morikawa M, Tomioka K, Yanagi M, Amano N, Kurumatani N. Association between tooth loss and the development of mild memory impairment in the elderly: the Fujiwara-kyo Study. *J Alzheimers Dis* 2015; 44(3): 777-86.
43. Minn YK, Suk SH, Park H, *et al*. Tooth loss is associated with brain white matter change and silent infarction among adults without dementia and stroke. *J Korean Med Sci* 2013; 28(6): 929-33.
44. Batty GD, Li Q, Huxley R, *et al*. Oral disease in relation to future risk of dementia and cognitive decline: prospective cohort study based on the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial. *Eur Psychiatry* 2013; 28(1): 49-52.
45. Savikko N, Saarela RK, Soini H, Muurinen S, Suominen MH, Pitkala KH. Chewing ability and dementia. *J Am Geriatr Soc* 2013; 61(5): 849-51.
46. Park H, Suk SH, Cheong JS, *et al*. Tooth loss may predict poor cognitive function in community-dwelling adults without dementia or stroke: the PRESENT project. *J Korean Med Sci* 2013; 28(10): 1518-21.

47. Stewart R, Weyant RJ, Garcia ME, *et al*. Adverse oral health and cognitive decline: the health, aging and body composition study. *J Am Geriatr Soc* 2013; 61(2): 177-84.
48. Saito Y, Sugawara N, Yasui-Furukori N, Takahashi I, Nakaji S, Kimura H. Cognitive function and number of teeth in a community-dwelling population in Japan. *Ann Gen Psychiatry* 2013; 12(1): 20.
49. Arrive E, Letenneur L, Matharan F, *et al*. Oral health condition of French elderly and risk of dementia: a longitudinal cohort study. *Community Dent Oral Epidemiol* 2012; 40(3): 230-8.
50. Yamamoto T, Kondo K, Hirai H, Nakade M, Aida J, Hirata Y. Association between self-reported dental health status and onset of dementia: a 4-year prospective cohort study of older Japanese adults from the Aichi Gerontological Evaluation Study (AGES) Project. *Psychosom Med* 2012; 74(3): 241-8.
51. Lexomboon D, Trulsson M, Wardh I, Parker MG. Chewing ability and tooth loss: association with cognitive impairment in an elderly population study. *J Am Geriatr Soc* 2012; 60(10): 1951-6.
52. Syrjala AM, Ylostalo P, Ruoppi P, *et al*. Dementia and oral health among subjects aged 75 years or older. *Gerodontology* 2012; 29(1): 36-42.
53. Chen X, Shuman SK, Hodges JS, Gatewood LC, Xu J. Patterns of tooth loss in older adults with and without dementia: a retrospective study based on a Minnesota cohort. *J Am Geriatr Soc* 2010; 58(12): 2300-7.
54. Okamoto N, Morikawa M, Okamoto K, et al. Relationship of tooth loss to mild memory impairment and cognitive impairment: findings from the Fujiwara-kyo study. *Behav Brain Funct* 2010; 6: 77.
55. Okamoto N, Morikawa M, Okamoto K, *et al*. Tooth loss is associated with mild memory impairment in the elderly: the Fujiwara-kyo study. *Brain Res* 2010; 1349: 68-75.
56. Kaye EK, Valencia A, Baba N, Spiro A, 3rd, Dietrich T, Garcia RI. Tooth loss and periodontal disease predict poor cognitive function in older men. *J Am Geriatr Soc* 2010; 58(4): 713-8.
57. Ellefsen B, Holm-Pedersen P, Morse DE, Schroll M, Andersen BB, Waldemar G. Assessing caries increments in elderly patients with and without dementia: a one-year follow-up study. *J Am Dent Assoc* 2009; 140(11): 1392-400.
58. Syrjala AM, Ylostalo P, Sulkava R, Knuuttila M. Relationship between cognitive impairment and oral health: results of the Health 2000 Health Examination Survey in Finland. *Acta Odontol Scand* 2007; 65(2): 103-8.
59. Kim JM, Stewart R, Prince M, *et al*. Dental health, nutritional status and recent-onset dementia in a Korean community population. *Int J Geriatr Psychiatry* 2007; 22(9): 850-5.
60. Stein PS, Desrosiers M, Donegan SJ, Yepes JF, Kryscio RJ. Tooth loss, dementia and neuropathology in the Nun study. *J Am Dent Assoc* 2007; 138(10): 1314-22; quiz 81-2.
61. Gatz M, Mortimer JA, Fratiglioni L, *et al*. Potentially modifiable risk factors for dementia in identical twins. *Alzheimers Dement* 2006; 2(2): 110-7.
62. Avlund K, Holm-Pedersen P, Morse DE, Viitanen M, Winblad B. Tooth loss and caries prevalence in very old Swedish people: the relationship to cognitive function and functional ability. *Gerodontology* 2004; 21(1): 17-26.
63. Chalmers JM, Carter KD, Spencer AJ. Caries incidence and increments in community-living older adults with and without dementia. *Gerodontology* 2002; 19(2): 80-94.