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Title: Influence of periodontal disease on risk of dementia: a systematic literature review and a meta-analysis

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Supplementary Table 1: Characteristics and findings of the cohort studies identified for systematic review

Authors (publication year); study location	**Type of study, participants' characteristics and recruitment**	**Sample Size**	**Follow up**	**Baseline measure of PD**	**Endpoint outcomes: Dementia cases and diagnosis criteria**	**Statistical analysis; Adjustment for confounders**	**Findings**
Arrive et al [10] (2012); France	Prospective cohort study Age: 66-80 years 2792 participants were recruited from PAQUID Study (1989–1990).	405 participants for final analyses	Median follow-up 10 years (Interquartile range: 6.5-13.7)	CPI	72 participants developed dementia, including 61 AD Dementia: DSM-III R criteria including AD: NINCDS-ADRDA criteria; and Vascular dementia: Hachinski score	Cox proportional hazard regression used. Age was used in model as time scale. It was adjusted for gender, hypertension, depression, body mass index, diabetes, and history of brain stroke/ ischemic cardiopathy	The adjusted HR for dementia in high educated patients (n=312) with tooth bleeding/calculus was 0.71(0.31-1.63) and periodontal pockets 0.42 (0.15-1.15) The matched HRs of dementia in low educated patients (n=92) were 1.24 (0.39-3.88) and 0.97 (0.29-3.19)
Tzeng et al [9] (2016); Taiwan, China	Retrospective matched cohort study Age: $\geq$ 20 years 2,888 patients with newly diagnosed CP and gingivitis, and age- sex	A total of 8,828 participants 2,207 patients with CP and gingivitis; after excluding 681 patients due to gingivitis/CP before 2000, gender unknown, aged <20	10 years	ICD-9-CM codes 523.4 (CP) and 523.1 (chronic gingivitis)	86 patients diagnosed with dementia include: - 25 patients with CP and gingivitis - 61 patients without CP or gingivitis Dementia:	Cox proportional hazard regression adjusted for age, gender, geographical area of residence, urbanization level of the residence, and monthly income, comorbidities (including hypertension, obesity, diabetes, hyperlipidemia, stroke,	Adjusted HR for dementia in patients with CP and gingivitis was 2.54 (95% CI 1.55–4.16)

	matched controls without CP and gingivitis; both recruited from Longitudinal Health Insurance Database (2000-2010) in Taiwan.	years and dementia diagnosed before first visit 6,621 controls without CP and gingivitis			DSM-IV or DSM IV Text Revision including AD, vascular dementia and non-vascular dementia: ICD-9-CM codes 290.0, 290.10–290.13, 290.20–290.21, or 290.3, 331.0, 290.41–290.43 and 290.8–290.9	traumatic brain injury and chronic kidney disease)	
Lee YL et al [7] (2017); Taiwan, China	Retrospective cohort study Age: ≥45 years 285,835 subjects were selected from the Longitudinal Health Insurance Database 2000 in Taiwan.	182,747 participants had PD according to ICD-9-CM diagnosis Patients were divided based on PD treatment codes: [1] Dental prophylaxis (n=97,802) [2] PD Intensive treatment (n=5,373) [3] PD with tooth extraction (n=59,898) [4] PD without treatment (n=19,674)	10 years	ICD-9-CM codes 523.0–523.5	6133 participants developed dementia Pre-senile dementia, vascular dementia, senile dementia, or AD: ICD-9-CM codes 290.X, 331.0	Cox proportional hazard regression adjusted for age, gender, income, job status, residential area (urban/rural) and comorbidities (diabetes, hypertension and hyperlipidemia)	Adjusted HR for dementia in PD patients who had teeth extracted was 1.10 (1.04-1.16), and 1.14 (1.04-1.24) in those who did not have treatments compared to 1.18 (0.97-1.43) in patients who received intensive treatments.
Lee YT et al [6] (2017); Taiwan, China	Prospective cohort study Age: ≥65 years One million subjects in National Health Insurance program (NHI) in Taiwan. Equal	6,056 participants in total including: -3,028 participants with periodontitis -3,028 participants without periodontitis	10 years (approximately)	ICD-9-CM codes 523.3–5	Dementia: ICD-9-CM codes 290.0–290.4, 294.1, 331.0–331.2	Cox proportional hazard regression adjusted for age, gender, geographic region, urbanization level, periodontitis, hypertension, diabetes mellitus, stroke, cardiovascular disease and chronic kidney disorder.	Adjusted HR for dementia in participants with PD versus those without PD was 1.16 (1.01–1.32).

	numbers of patients with newly diagnosed periodontitis and age-sex matched controls were recruited from Longitudinal Health Insurance Database 2000 which is a sub-database for NHI in Taiwan.						
Chen et al [8] (2017); Taiwan, China	Retrospective matched cohort study Age: ≥50 years 10,592 patients who had newly been diagnosed with CP. Age, sex, index year, co-morbidity and urbanisation level matched controls without CP, both recruited from NHI Research database in Taiwan.	27,963 participants including: -9291 participants with CP; after excluding 1301 patients due to having CP or AD prior to 1997 and AD prior to CP 1st visit, -18,672 patients without CP.	11.9 years (± 2.6) in participants with CP, 12.2 years (± 2.6) in participants without CP.	ICD-9-CM code 523.4	115 participants with CP and 208 participants without CP were diagnosed with AD. AD: ICD-9-CM code 331.0	Cox proportional hazards regression adjusted for urbanization level , hypertension, depression, diabetes mellitus, hyperlipidaemia, stroke , traumatic brain injury, chronic kidney disease and Charlson co-morbidity index score	In patients with 10 years of CP exposure, the adjusted HR for AD was 1.71 (1.15–2.53).

Supplementary Table 2: Characteristics and findings of the case-control studies identified for systematic review

Authors (publication year); study location	Type of study; Participants' characteristics and recruitment	Sample size	Baseline measure of PD	Endpoint outcomes: Dementia cases and diagnosis criteria	Statistical analysis; Adjustment for confounders	Findings
Stein et al [22] (2012); U.S.A	Case-control nested in cohort study. Mean age in controls = 70 years; MCI=72.1 years; AD= 74.1 years. Participants recruited from a subset of the BRAINS research who were cognitively intact at their baseline.	158 participants	BOP and AAP classification used for diagnosis of CP Serum Sample: Venous blood draws of the study participants	In 81 cases, 35 participants developed AD and 77 controls were cognitively intact AD: NINCDS-ADRDA criteria outlined by McKhann et al (1984) Serum Sample: The IgG antibody were analysed by using an enzyme-linked immunosorbent assay	Wilcoxon rank-sum test and general linear regression and adjusted for baseline age, gender, years of education, smoking status , diabetes, apolipoprotein epsilon 4 and baseline MMSE Bonferroni correction for multiple comparisons was used.	Antibody levels to F. nucleatum and P. intermedia were significantly increased (p=0.05) at baseline serum draw in the patients with AD compared with controls.
Chu et al [24] (2014); China	Population based case-control study Age ≥60 years Cases were recruited from day-care centres of the Hong Kong	118 participants	CPI	59 dementia cases and 59 controls matched for sex and age. Dementia: Diagnosed by medical doctors .	A parametric t-test and the chi-square were used for analysis. Adjusted RR was not presented.	RRs* in dementia patients compared to non- dementia patients were as follows: -Moderate PD: 1.10 (0.58-1.68) -Severe PD: 1.25 (0.63-1.81)

	Alzheimer's Disease Association and St. James' Settlement Kin Chi Dementia Care support service center Healthy controls without dementia from registered list who attended Prince Philip dental hospital were invited (not under current dental treatment).			47 dementia cases and 50 controls were examined for PD evaluation, after excluded 21 participants (edentulous and other reasons) CPI and PD levels as follows: -Healthy= 0; -Reversible gingivitis=1; -Calculus=2; -Shallow pockets/moderate PD =3; -Deep pockets/severe PD=4 **Crude data** **PD + CPI levels** / **Cases n=47** / **Controls n=50** 0 / 0 / 1 1 / 5 / 7 2 / 5 / 5 3 / 24 / 26 4 / 13 / 11		
De Souza et al [23] (2014); Brazil	Population based case-control study Mean ages: 75.17 years in cases and 61.17 years in controls Patients were recruited from the Cognitive Neurology and Behavior Group of the Neurology Department of the University of	59 participants	GBI, PPD and CAL Severity of PD was defined according to the AAP (CAL >3 mm)	29 AD cases and 30 controls matched for age and gender AD: NINCDS-ADRDA and MMSE score for severity. **Crude data** **PD** / **Cases n=29** / **Controls n=30** No PD / 12 / 22 Gingivit- / 9 / 3	One way ANOVA and non-parametric tests (Chi-square and Fisher's exact tests) were used. Adjusted RR was not presented.	RRs* in AD patients compared with control group were as follows: -Mild PD: 2.12 (1.15-2.63) -Moderate PD:1.13(0.25-2.32) -Severe PD: 2.12 (0.97-2.68)

	Sao Paulo. Controls were older people without AD (relatives of the patients: wives, husbands, brothers, and/or sisters).			is/mild PD Modera-te PD 2 3 Severe PD 6 2		
Bramanti et al [18] (2015); Italy	Hospital based case-control study Recruited participant's from IRCSS staying at "Neurolesi Bonini-Pulejo" in Messina having mean age in VaD group was 86.7±6.2 years and control group was 80.2 ± 7.4 years.	168 participants	BOP and PPD	86 VaD cases and 82 healthy controls VaD: Imaging evidence of cerebrovascular disease and additional clinical features, MMSE (Italy version) was checked by specialist to grade cognitive and functional impairment of VaD patients. **Crude data** **PD evalut-ion** **Cases n=86** **Controls n=82** BOP + 76 32 PPD <4mm 8 69 PPD 78 13	Chi square and Fisher exact test were applied for categorical variables Adjusted RR was not presented.	RR* in VaD patients compared with control group was as follows: BOP positive: 4.22 (3.10-5.03)

				>4mm		
Gil-Montoya et al [21] (2015); Spain	Population based case-control study Age: 51 to 98 years Cases were recruited from the Neurology Departments of two hospitals. Controls were patients being seen in primary healthcare, for problems other than dental or neurological problems.	409 participants	PPD, CAL and BI Degree of PD was defined by the percentage of sites with CAL >3 mm as follows: - 0% = absent; - 0–32% = mild; - 33–66% = moderate; - 67–100% = severe	180 cases (159 dementia from mild to severe and 21 MCI) and 229 controls Dementia: DSM-IV including AD: NINCDS-ADRDA	Multiple logistic regression analysis adjusted for age, gender, education, smoking, alcohol, BI, PI, PD, CAL, number of teeth, oral hygiene habits, hyperlipidemia and hyperglycaemia	RRs* for dementia and MCI was as follows: -Moderate CAL: 1.89 (1.13-2.69) -Severe CAL: 1.75 (1.11-2.46)
Jureti et al [19] (2016); China	Hospital based case-control study Age: Cases =65.2±7.3 years Control=64.5±9.4 years Subjects were recruited from teaching hospitals of Xinjiang medical university from December 2015 to May 2016.	125 participants	CPI, BOP, GI, CAL and Probing Depth.	63 AD cases and 62 controls AD: Clinical diagnostic criteria using MMSE for severity In their research thesis [37] , it was reported that percentage of periodontitis as follows: **Crude data** **PD evalut-ion** / **Case n=63** / **Controls n=62** Mild PD: 5 / 24 Mode-: 25 / 21	One way ANOVA was used in the study, Adjusted RR was not presented.	RRs* in AD patients compared with control group were as follows: -Moderate PD: 3.15 (1.62-4.57) -Severe PD: 3.83 (2.24-4.98)

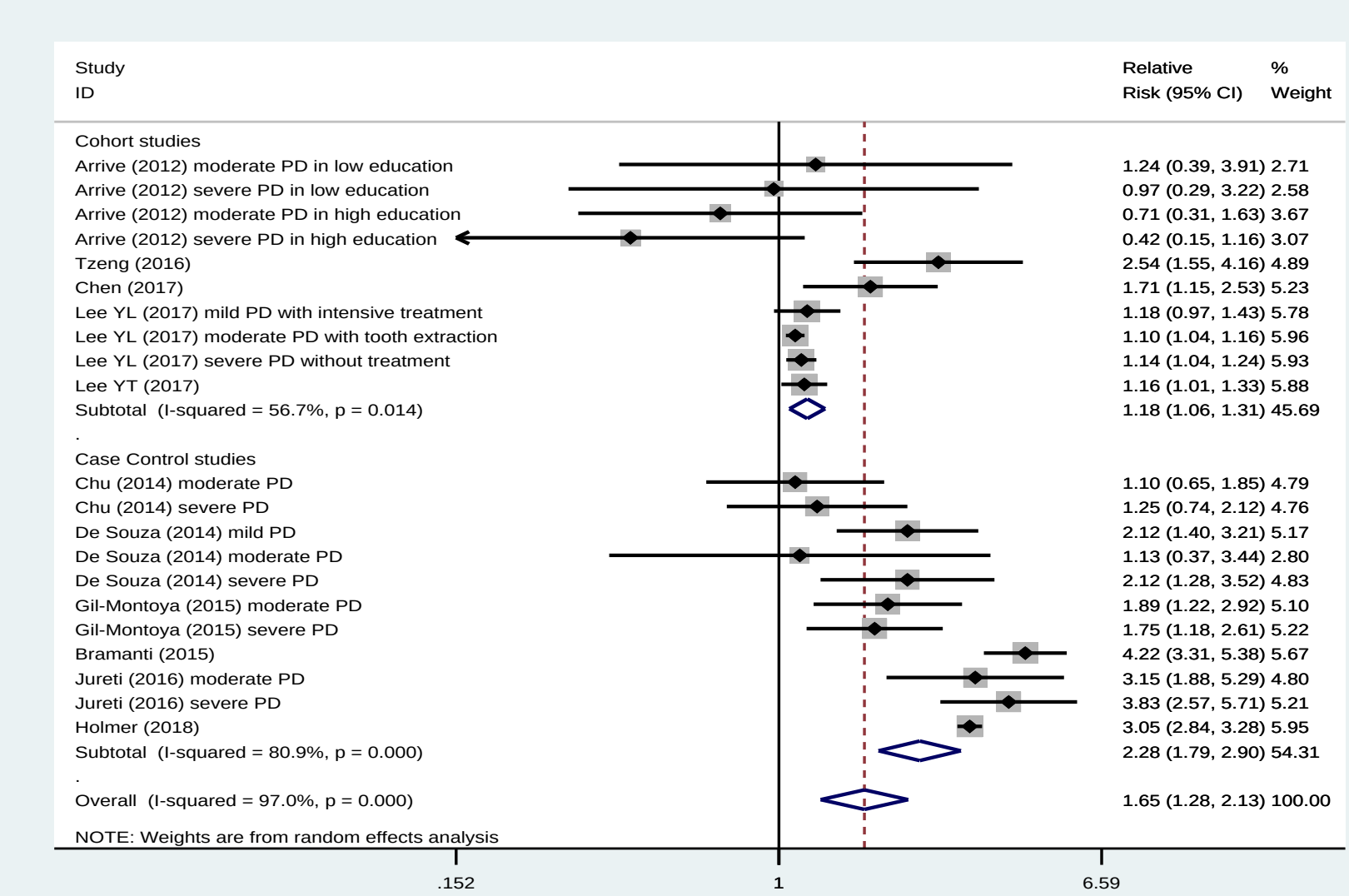
				rate PD Severe PD 33 17		
Holmer et al [20] (2018); Sweden	Population based case-control study. Subjects are aged 50-80 years. Cases were screened at the Karolinska Memory Clinic. Controls were recruited by a random sample from the Swedish population register.	220 participants.	PPD, BOP, suppuration, tooth mobility, furcation involvement and MABL using panoramic radiograph.	154 cases (including 52 participants with AD, 51 with MCI and 51 with SCD) and 76 controls. All cases: ICD-criteria (10^{th} revisions) including AD using NIA-AA diagnostic guidelines; and Mild AD using MMSE.	Multivariate logistic regression adjusted for age, gender, marital status, education, smoking, body mass index, and diabetes mellitus.	RR* in AD patients compared with control group was 3.05 (4.07 - 4.70) for those with more than 1 tooth with PPD ≥6mm.

Abbreviations: AAP- clinical criteria of American Academy of Periodontology, AD- Alzheimer's disease, ANOVA- Analysis of variance, BI- Bleeding index, BOP-Bleeding on Probing, BMI- Body mass index, CAL/AL – clinical attachment loss, CP - chronic periodontitis, CPI- Community periodontal index, DSM-III R- Diagnostic and Statistical, Manual of Mental Disorders, Third Edition, Revised, DSM IV - Diagnostic and Statistical Manual of Mental Disorders criteria, fourth edition, GBI-Gingival bleeding index , GI-gingival index, HR- Hazard ratio, ICD-9-CM - International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-10 -International Statistical Classification of Diseases and Related Health Problems 10th revision diagnostic criteria, LHID- Longitudinal Health Insurance Database, MABL- Marginal alveolar bone loss, MCI- Mild cognitive impairment, MMSE - Mini Mental State Examination, NIA-AA National Institute on Aging and Alzheimer's Association guidelines, NINCDS-ADRDA - National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer´s Disease and Related Disorders Association, NINDS-AIREN - National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences, NHIRD- National Health Insurance Research Database, OR- odds ratio, PD- periodontal disease, PI-Plaque Index PPD- probing pocket depth, RR-relative risk, SCD-subjective cognitive decline, VaD- Vascular dementia.

* Based on the original data, we calculated crude OR and converted OR to RR for dementia, AD and VaD based on following formula [27]:

$$RR = \frac{\text{odds ratio}}{1 - \text{risk}_0 + \text{risk}_0 \times \text{odds ratio}}$$

Supplementary Figure 1: Forest plot showing pooled relative risk (RR) of all included studies for PD and dementia risk.



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