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

Rizwan Nadim[1], Jie Tang[1, 2], Amena Dilmohamed[1], Siyang Yuan[1], Changhao Wu[3], Aishat T Bakre[1], Martin Partridge[1], Jindong Ni[4], John Copeland[5], Kaarin J. Anstey[6,7], Ruoling Chen[1]

[1] Institute of Health, Faculty of Education, Health and Wellbeing, University of Wolverhampton, UK

[2] School of Public Health, Guangzhou Medical University, China

[3] Faculty of Health and Medical Sciences, University of Surrey, UK

[4] School of Public Health, Guangdong Medical University, China

[5] Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK

[6] UNSW Ageing Futures Institute and School of Psychology, University of New South Wales

[7] Neuroscience Research Australia, Sydney, Australia

Rizwan Nadim and Jie Tang joint first author.

Correspondence: Professor Ruoling Chen, Institute of Health, Faculty of Education, Health and Wellbeing, University of Wolverhampton, Wolverhampton, WV1 1DT, UK. T: +44 (0)1902 328622, F: +44 (0)1902 321161, E: r.chen@wlv.ac.uk

Abstract

Objective: Periodontal disease (PD) is common and increases cardiovascular diseases. However, it is unclear whether PD is associated with increased risk of dementia. We carried out a systematic review and meta-analysis to investigate the influence of PD on dementia. We projected the number of dementia cases to be saved by reducing PD prevalence in the world.

Method: We searched cohort and case-control studies reporting the association of PD with all dementia (or any specific type of dementia) through PubMed, MEDLINE, PsycINFO, SocINDEX, CINHAL, and CNKI until 7th November 2018. Five cohorts and seven case-control studies were identified for review. We pooled eligible data to calculate relative risk (RR) of dementia in relation to PD and computed the number of dementia cases saved through reducing PD prevalence.

Results: Of 12 studies, six were undertaken in Asia, four in Europe and two in America. Eleven studies showed a positive association between PD and the risk of dementia, of which 10 were significant, and one reported a non-significant inverse association. Overall their quality was good. Pooled RR of dementia in relation to PD from all high quality studies was 1.38 (95%CI 1.01-1.90); in the five cohorts was 1.18 (1.06-1.31) and in the two case-control studies 2.25 (1.48-3.42). A 50% reduction in the current prevalence of 20% of PD in the population could save 850,000 (630,000-1,420,000) patients with dementia in the world.

Conclusions: PD could increase the risk of incident dementia. Preventing and treating PD could contribute to controlling the global epidemic of dementia.

Keywords: Oral health, Periodontitis, Periodontal disease, Dementia, Alzheimer's disease, Meta-analysis

Introduction

Periodontal disease (PD) is a chronic inflammatory disease, affecting the gums by infection of oral bacteria resulting in alveolar bone loss and eventually tooth loss [1]. PD includes both gingivitis and periodontitis, while periodontitis alone has been reported to be the sixth most prevalent condition worldwide, affecting around 20-50% of the global population [2].

PD can start from early life and then progress to chronic periodontitis in the 40-50 year age range [3]. Dental plaque (bacterial biofilm) forms on teeth and calcifies to become dental calculus, on which additional plaque can form. Sub-gingival biofilm and calculus cause PD [4] . As a source of chronic inflammation and bacterial infection, PD may affect other organ systems. There is evidence that PD increases the risk of cardiovascular diseases and all-cause mortality [5]. However, it is not clear whether PD is associated with increased risk of dementia. The current literature has shown inconsistent findings; some studies reported a significant increase in the risk of dementia among people with PD [6-9], and others did not [10]. Previous systematic reviews of the literature of PD and dementia [11, 12] have been limited by the inclusion of ineligible studies (one cross-sectional design [13], and another examined MCI rather than dementia [14]) or omission of articles [7, 10]. In this paper, we carry out what is to our knowledge the most comprehensive systematic literature review and a meta-analysis to investigate the association of PD with risk of developing dementia in population-based studies, and estimate the number of people to be saved from suffering dementia through preventing and treating PD in the world.

Methods

We (RN, JT and AB) searched MEDLINE, PubMed, CINAHL, PsycINFO and SocINDEX databases. Based on our unique position and increased prevalence of dementia in China [15], we (JT, RC) also searched a China National Knowledge Infrastructure (CNKI) database as

done previously [16]. The strategy for the database search was developed using the outlines of PICO: Population (adult patients having PD/or dementia), Intervention or exposure (PD), comparison (patients without PD in control) and outcome (dementia or any specific type of dementia) [17]. In each database search, we used the search terms: (oral health or oral hygiene or dental health or tooth loss or periodontal disease or periodontitis or gingivitis or periodontal infection or caries) AND (dementia or Alzheimer's disease or vascular dementia or cognitive impairment). The literature was searched from the earliest date to 7th November 2018 to identify topic-related articles including all studies with no language restriction. We read the title and abstract of the searched studies. Studies were included in the systematic review if they were original research published in peer-reviewed journals that met the criteria as follows. The study was (1) to investigate an association of PD with dementia or any type of dementia, (2) a cohort or case-control study from all settings including community-dwelling, care home or hospital, (3) to report any of the following periodontal parameters: periodontal pocket depth (PPD), clinical attachment loss (CAL), community periodontal Index (CPI), bleeding on probing (BOP), American Academy of Periodontology classification (AAP) and International Classification of Diseases, Ninth Revision, Clinical Modification codes 523.0-523.5 (ICD-9-CM), and (4) to have dementia diagnosis criteria and procedure elaborated. The grey literature was explored, including contact with the authors of potential eligible articles, e.g., non-English studies [18, 19]. Studies were excluded if they were a cross-sectional study, a case-report, commentaries, editorial, review, animal studies, or had the outcome of interest as mild cognitive impairment (MCI) only.

Searching six electronic datasets for literature, we had 3,099 hits. After eliminating duplicates, 1,829 remained. Review of titles and abstracts identified 17 articles that were potentially relevant. Detailed examination excluded other 5 articles and left a final number of

12 studies (five cohort studies and seven case-control studies) [6-10, 18-24] met the inclusion criteria for this systematic review (see the details in Figure 1).

The review was conducted according to the PRISMA guidelines [17]. Two pairs of reviewers (RN/JT and SY/AB, each pair including a dental professional) independently extracted data and assessed the quality of these studies. Discrepancies were resolved through face-to-face discussion, and where the differences remained, a 3rd reviewer (RC) made the final judgement. Following our previous study of systematic literature review of dementia in relation to overweight and obesity [25], we developed a standardized form to extract the following data from the selected articles: author, year of publication, study location, study design, participants' age range, sample size, measurement of PD, criteria of dementia diagnosis, the number of dementia cases in outcome, data analyses, variables adjusted and findings. We used the Newcastle-Ottawa Scale (NOS) [26] to assess the quality of the cohort and case-control studies separately. A star was assigned if there was a quality feature; scores of 1-9 were distributed (the comparability domain can score 1-2 stars). Studies with NOS scores of 1 to 3 were defined as poor quality, 4 to 6 intermediate and 7 to 9 high [26].

Meta-analysis

We pooled data of relative risk (RR) and its 95% Confidence Intervals (CIs) of dementia in relation to PD from each of the cohort or case-control studies. Since the odds ratio (OR) in the case-control study may overestimate the relative risk of dementia in relation to PD, we used a formula proposed by Zhang and Yu [27] to convert the OR into the RR. We analysed the data of each studied population from these articles as we did previously [28]. We pooled data, where available for, all types of dementia first (if the studied population did not provide data of all dementia, its subtypes data would be used), and then for Alzheimer's disease (AD) and vascular dementia (VaD) separately. If the study presented data of RRs for different

group of PD measured [7, 10, 21] or severity level of PD we took each individual RR for pooling data. In studies where RR of dementia in relation to PD was not presented, we calculated crude RR and its 95%CIs if the study provided necessary data. All these measures and their 95%CIs were pooled together as a relative risk (RR) with the assumption of attaining a common unit of comparison. RR was estimated using a random effect model, provided there was a statistically significant heterogeneity, indicative of differences among included studies; else, a fixed effect model. We used funnel plots to assess small-study effects, and evaluated the possibility of publication bias using Egger's regression asymmetry test [29].

We incorporated all studies which provided adjusted RR for the main analysis. We conducted subgroup analyses in terms of cohort and case-control studies, location of country (continents) and PD severity. We ran sensitivity analyses to evaluate the influence of studies with extreme value RRs and also the association of PD with dementia after including studies which had crude RR data.

Using the figure of the pooled RR of dementia in relation to PD, we estimated the number of dementia cases in the world that could be prevented by reducing PD prevalence, according to previous studies of preventable risk factors for dementia [30]. Currently there are approximately 50 million people suffering from dementia in the world [31]. The WHO Global Oral Health Data Bank [32] indicated that the prevalence of PD in population aged 35-44 years was around 5-20%, while a recent publication has suggested that 20-50% of the global population are affected by PD [2]. Thus we took 20% of PD occurring in a population of aged <65 years and computed the number of dementia cases that could be prevented if the current PD prevalence in the world could be halved through prevention or treatment of PD (i.e., the prevalence would be 10%) or it could be reduced to be at 5%. Population attributable risk (PAR) was estimated by multiplying the current PD prevalence estimated by 0.90 and

0.95 respectively and subtracting the revised number attributable cases from the original cases [30].

All data analyses were performed using the statistical software package STATA version 15.

Results

Literature review

The identified 12 studies were published between 2012 and 2018, and 11 were in English and one in Chinese [19]. Six were conducted in Asia [6-9, 19, 24], four in Europe [10, 18, 20, 21], and two in America (North America [22] and South America [23] each). Nine studies were from high-income countries/regions (HICs) [6-10, 18, 20-22], and three studies [19, 23, 24] were from middle-income countries (MICs). Of the 12 studies, five were cohort studies [6-10], and their baseline ages of participants ranged from 20 to 80 years, sample size varied from 405 to 182,747, and were followed up between 10 and 15 years. Seven others were case-control studies [18-24], with sample sizes varied from 59 to 409 participants. The characteristics of 12 studies are shown in Supplementary Tables 1 and 2.

Six studies diagnosed PD by using PPD [18-23], of which 5 studies further examined BOP for diagnosis [18-22]. Among these six studies, three studies also used CAL [19, 21-23], two studies used AAP criteria [22, 23] and one study used both CAL and CPI [19]. In six other studies [6-10, 24], four studies used ICD-9-CM codes [6-9] and two studies did evaluation only by CPI [10, 24].

Of 12 studies, six studies analysed data of all types of dementia in relation to PD [6, 7, 9, 10, 21, 24], of which four studies further examined AD [7, 9, 10, 21] (among which two also examined VaD [7, 9]). In the studies measuring all types of dementia, three used Diagnostic

and Statistical Manual of Mental Disorders (DSM III, IV) [9, 10, 21] and two used ICD-9-CM codes [6, 7] to make dementia diagnosis. One case-control study [24] did not report the details of the methods of dementia diagnosis, but chose participants who were recruited with dementia diagnosed by medical doctors.

In six other studies which did not measure data from all types of dementia, five focused on AD [8, 19, 20, 22, 23] and one measured VaD [18]. In all, there were nine studies with an outcome of AD and three with VaD. In the studies of measuring AD, four used the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association- Alzheimer's Criteria (NINCDS-ADRDA) [10, 21-23], and three used ICD-9-CM codes [7-9]. One study used National Institute on Aging and Alzheimer's Association guidelines (NIA-AA) [20], and one used the clinical diagnostic criteria [19] for AD diagnosis. In three studies of VaD diagnosis, two used ICD-9-CM [7, 9] and one made the diagnosis from medical specialist through imaging evidence of cerebrovascular disease and additional clinical features [18].

The overall quality of these studies was good, with a mean score of 7.75 (Table 1). In the five cohort studies, one had a low risk of bias with 8 scores (13) and four got a full score of 9 points [6-9]. In the case control studies, five had low risk of bias reaching between 7-8 points [18-21, 23] and two had an intermediate risk of bias with 5 and 6 scores on Newcastle-Ottawa scale [22, 24].

In the 12 studies, 11 [6-9, 18-24] reported a positive association of PD with dementia (Supplementary Table 1 and 2), of which 10 were significant [24], while one study [10] showed a non-significant inverse association.

Meta-analysis

One study [22] did not yield any data available for the meta-analysis, while four studies [18, 19, 23, 24] provided crude data enabling only calculation of unadjusted risk of dementia in relation to PD. All of these studies were case-control (see Supplementary Table 2). Thus, seven studies [6-10, 20, 21], which provided multiple adjusted RR and 95% CIs of dementia, were used for meta-analysis. They included 13 studied populations for data analysis (Figure 2). The pooled data showed an overall significant association of PD with dementia (RR 1.38, 95% CI 1.01-1.90). There is no publication bias according to the Eggers' method (p=0.953) (Figure 3).

Subgroup analysis

Among the 13 studied populations, analysis of the 10 from cohort studies showed a RR of 1.18 (1.06-1.31) for incident dementia in relation to PD, and the three from case-control studies showed a RR of 2.25 (1.48-3.42) (Figure 2).

In analyses within geographical regions, pooled data of six studied populations in Asia showed an increased RR of 1.20 (1.08-1.33) for dementia in relation to PD, and of seven studies in Europe was 1.38 (0.84-2.27) (Table 2).

Sensitivity analysis

In Figure 3, we found one case-control study [20] had an extreme value of RR, and after excluding it the overall RR was 1.25 (1.11-1.40) (in the case-control 1.81, 1.35-2.43).

Four studies [18, 19, 23, 24] provided us with crude data to calculate unadjusted OR (see Supplementary Table 2). Pooling these four with above seven studies, we obtained an overall RR of 1.65 (1.28-2.13) (see Supplementary Figure 1). Of these 11 studies, six studies [7, 10, 19, 21, 23, 24] provided "dose-response" data in terms of three levels of PD. Table 3 showed

a pooled data of dose-response relationship; compared to no/minor PD, risk of dementia in moderate PD was 1.39 (0.97 – 1.99) and severe PD was 1.50 (0.97 – 2.33).

Estimated number of dementia cases prevented by reducing PD

Given the current prevalence of PD of 20% [2, 32], we estimated a Population Attributable Risk (PAR) of 3.47% of the total dementia cases worldwide, i.e., 1.735 million patients. Based on these estimates, a 50% reduction in the current prevalence of PD, i.e., 10%, could potentially reduce the number of people with dementia nearly 0.85 million cases worldwide; a 75% reduction in the current prevalence of PD, i.e., 5%, could remove 1.29 million people with dementia in the world (Table 4).

Discussion

We performed a comprehensive systematic review and a meta-analysis to evaluate the influence of PD on the risk of dementia in the population. Identifying and reviewing 12 peer-reviewed articles we found that there was an overall significant and positive association of PD with increased dementia. Data of seven studies which provided adjusted RR of dementia in relation PD showed a pooled RR of 1.38 (1.01-1.90); in the cohort study 1.18 (1.06-1.31) and in the case-control studies 2.25 (1.48-3.42). If the current prevalence of PD in the population could be halved, 850,000 dementia cases could be prevented globally.

Association between PD and dementia

In older adults, PD and dementia are more prevalent. Recent studies have linked these two diseases as both have possible common pathophysiological mechanisms (e.g., systematic inflammation) [33, 34]. Although an earlier cross-sectional study in USA [35] reported no statistically significant differences in any of the three periodontal parameters between AD patients and controls, recent research suggested a significant relationship between PD and

dementia. A cross-sectional study in India reported that all evaluated periodontal parameters were higher in people with dementia compared to those without dementia [36]. In Finland, Syrjala *et al* carried out a cross-sectional study of 354 participants age >75 years, and observed that people with AD or other types of dementia were more likely to have carious teeth, teeth with deep periodontal pockets, poor oral hygiene, and denture hygiene compared with non-demented people [13]. In a recent systematic literature, Kapellas *et al* [12] found a significant association of dementia with PD, but the association of PD with dementia has not well been investigated.

Some investigators tried to extract the evidence of the influence of PD on increased risk of incident dementia. In 2017, Leira and colleagues published a "systematic literature review and meta-analysis" paper, and reported that there was an increased risk of Alzheimer's disease in relation to PD; a pooled RR of 1.69 (1.21–2.35) [11]. However, although the authors claimed the paper as "systematic literature review", they did miss one eligible study [22] in the review, but included one cross-sectional study [13], which was unable to speak to the incidence of dementia in relation to PD. Recently Kapellas *et al* [12] also carried out a systematic literature review and a meta-analysis on the topic using the four cohort studies [6, 8, 9, 14]. Their meta-analysis for the cohort studies of PD predicting dementia missed two important studies [7, 10], but included one ineligible study which measured MCI rather than dementia [14].

Strength and Limitations of the Current Study

As far as we know, our study is the first to report the influence of PD on the risk of dementia in terms of reduced PD prevalence associated with the number of people with dementia. It has comprehensively searched topic-related literature and identified all eligible studies, based

on our mixed team's expertise on dental and epidemiology, including from non-English literature and research thesis [37] for systematic review and meta-analysis to investigate the impact of PD on the risk of dementia. The previous literature review [11, 12] included one cross-sectional study, which could not tell the causal-result relationship [13], and one study of examining MCI, which could not tell the influence of PD on dementia [14]. Strictly following PRISMA guidelines our review team (consisting of researchers with dental and epidemiology backgrounds) included neither the cross-sectional study nor the MCI paper for the systematic literature review and meta-analysis; otherwise, our pooled RR would be higher as the previous meta-analysis studies did [11, 12]. We also carried out the subgroup and sensitivity analyses. The findings of our study are robust.

Our study has limitations. First, the studies which we identified for review used different measurements of PD, which gave various information on PD, including its severity. There is no consensus regarding PD criteria, and to measure PD different cases definitions are used. The variation in the methods of measuring PD in the studies might influence our pooled data findings, but we could not analyse them separately due to the small number of studies in each of those methods. However, six of 12 studies provided the data of different measures of PD, giving moderate (acute) and severe (chronic) stages, and showed that there was slightly increased influence of severe PD on the risk of dementia compared to those moderate PD (Table 3). Other studies included in the meta-analysis consisted of a population of patients with PD at different stages except for one [8]. Thus the varied PD measures in those studies would not substantially change our current findings. With regards to different procedures for measuring dementia, we could not examine their impacts on the association of PD with increased risk of dementia, including separate data analysis due to the small number of studies. But all methods of diagnosing dementia in those studies are validated. Thus the impact of variation in diagnosing dementia on the association between PD and dementia

would be minimised. Second, three studies [19, 21, 24] included patients with minor PD in the reference group for analysis. This would attenuate the association. Also the authors of that study [21] combined 159 cases of dementia with 21 patients who had mild cognitive impairment as the case group for analysis, and this 11.7% misclassification may attenuate the association. Our finding of the influence of PD on the risk of incident dementia could be more conservative. Third, the adjusted confounders varied with the studies. Each of the studies adjusted for different sets of confounders, except four studies [18, 19, 23, 24] which only presented the crude data for calculating the RR. The adjusted confounders are not consistent across the studies (Supplementary Tables 1 and 2). In our meta-analysis, we included seven studies [6-10, 20, 21] which adjusted for confounders to produce the main findings. They adjusted for 7-12 numbers of most important confounders such as age, sex, socioeconomic status, lifestyles, social network and co-morbidities. We have found no association between the number of adjusted confounders and RR. In spite of it, only one study among these studies which adjusted for confounders included smoking for adjustment. The residual effect from smoking remained, which may lead the influence of PD on dementia towards hypothesis. But the studies adjusted for other smoking-related factors such as socioeconomic status and co-morbidities, and the residual effect from smoking would be minimised. Thus our findings in this main data analysis (e.g., RR 1.38) are preserved. However, the four studies [18, 19, 23, 24] with the crude RRs had the residual confounding and would have overestimated the RR. Adding them in the analysis (Supplementary Figure 1) could lead a higher RR in the pooled data than those of using their adjusted RRs. But we could not judge what effects of these crude RRs were on the finding of dose-response relationship between PD and dementia (Table 3). They should be interpreted cautiously, and the dose-response relationship needs further research, including more studies which presented adjusted RRs. Fourth, in nine studies which measured AD, only two [8, 20] presented the

results for the association of PD with AD. Thus we are not able to analyse the evidence of the impact of PD on AD. Future studies on the topic should report results separately for AD and other type of dementia, apart from all dementia for meta-analysis.

As the studies included in our systematic review and meta-analysis were observational, we considered causal relationship between PD and dementia using the Bradford Hill Criteria [38] to provide evidence.

How strong are the associations between PD and dementia?

The studies under consideration demonstrated an overall moderate association between PD and dementia. Most of them showed a RR of dementia > 1.14 in people with PD [6-9, 20, 21]. The cohort study conducted by Arrive *et al*, however, presents a non-significant inverse association between PD and incidence of dementia [10]. Chu *et al* [24] in a case-control study also found no significant association between PD and dementia, but data from two case-control studies [20, 21] has demonstrated a stronger association between PD and dementia; their pooled OR of 2.25 (1.48-3.42). Overall, our meta-analysis of all data from eligible studies has demonstrated a significant influence of PD on increased risk of incident dementia (RR1.38, 1.01-1.90).

How consistent are the reported studies?

The results from the studies we identified were quite consistent, despite using different methodologies in conducting the studies. Of twelve studies reviewed, 11 reported a positive association of PD with dementia [6-9, 18-24], and only one showed a non-significant inverse association [10]. Furthermore, the findings among these studies are consistent with those in a systematic literature review for the association of tooth loss with dementia (RR 1.34, 1.19-1.51) [39].

How specific is the response to proposed agents?

The specificity criterion requires that a cause leads to one effect and not to multiple effects. PD increases the risks of cardiovascular disease [5], such as coronary heart disease [40] and stroke [41]. Nowadays it is not difficult to find that one risk factor causes multiple effects; for example, cigarette smoking increases the risk of lung cancer, but also cardiovascular disease and dementia [5, 40, 42]. Similar to other chronic non-communicable diseases, dementia could have more than one cause, i.e., multiple causes [31, 42]. Thus, the findings of our study could suggest that PD is also associated with increased risk of incident dementia. If a study reported the association of PD with dementia, other risk factors should be considered for analysis. The independent influence of PD on the risk of dementia needed to be identified through adjustment for other factors. Although most of the studies included in our meta-analysis did not adjust for smoking, they adjusted for many other important factors such as socioeconomic status and co-morbidities, which were associated with smoking status. The pooled RR of 1.38 (1.01-1.90) for dementia in relation to PD appeared not to be substantially changed by other unmeasured confounders as those socioeconomic status and co-morbidities were adjusted, while PD shared common risk factors with a number of chronic diseases which include cardiovascular diseases [40, 43]. A significant association of PD with amyloid accumulation in AD patients' brain was found with confirming an increase in ^{11}C-PIB-PET uptake in Aβ vulnerable brain regions [44]. The current study could support an independent and potential causal effect of PD on dementia.

Is there a temporal relationship between exposure and response?

Exposure must precede outcome and this is best ascertained in cohort studies. All five cohort studies had long-term follow up. After removing one study with the shortest follow-up period (8 years approximately) [6], the pooled RR was 1.20 (1.05-1.36), which did not reduce the

association of PD with increased risk of dementia. Since most of the relevant studies, which we identified for review and meta-analysis, took chronic periodontitis in account in place of acute periodontitis, the exposure to PD should be earlier after experiencing certain duration (bacteria to deposit on tooth leading to plaque formation causing PD). Thus the temporal relationship has been ensured in our study.

Is there an exposure-response relationship?

The dose-response relationship between PD and dementia is observed in our pooled data from the studies, but it is not statistically significant, which could be due to the small number of studies included, of which half were those crude RRs. However, in a meta-analysis of examining the association of tooth loss with dementia, Chen *et al* [39] found a significant dose-response. This could support our finding of the dose-response association of PD with dementia.

Is the association biologically plausible?

There are several potential biological reasons for explaining the effect of PD on incident dementia. A plausible biologic mechanism has been proposed that periodontal infection lead to systemic inflammation, contributing to the pathogenesis of dementia [33, 45]. High inflammatory immune responses (C-reactive protein, tumor necrosis factor, interleukin-1, interleukin-6, a-1-antichymotrypsinin) can enter the blood brain barrier and influence priming or activation of the microglial cells in the cerebral regions which may contribute to the pathogenesis of dementia [33].

Recent research showed that neuronal damage in AD pathogenesis is caused by porphyromonas gingivalis infection through the secretion of gingipains [34]. Porphyromonas gingivalis enters the brain by direct infection, cranial nerves and infection of monocytes which also effect on AD development [34].

Other plausible mechanisms include shared genetic risk factors for PD and dementia. Porphyromonas gingivalis and host interactome related genes identified from genome-wide association studies (GWAS) overlap with susceptible genes involved in AD, suggesting that the Porphyromonas gingivalis interactome were significantly enriched in genes deposited in GWAS genes related to cognitive disorders, AD and dementia [46]. Also, it is possible that cardiovascular diseases, which are caused by PD [5, 40], link with dementia and converge into a common pathway leading to neurodegeneration and dementia [47].

Is the evidence coherent with knowledge of the natural history of disease?

Previous studies showed that PD increased the risks of stroke [41] and cognitive impairment[14], which are associated with dementia. The existing evidence [39, 48] has demonstrated that increased risk of dementia is associated with number of teeth lost, which is caused by PD. These could provide additional evidence in support of a causal association between PD and dementia.

Is there experimental evidence?

A number of animal studies have explored the relationship of PD with cognitive impairment and dementia. Kato *et al* [49] carried out an experiment of two groups of young rats; one group was made edentulous and other group was dentate. Both groups were given an identical nutritional powder. It was found that edentulous rats had poor spatial memory and decreased stimulated acetylcholine release in the parietal cortex. In another study, 12 mice were orally infected by polymicrobial bacteria (Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, and Fusobacterium nucleatum), and oral pathogen Porphyromonas gingivalis was able to access the ApoE of the brain of mice which contributed to activation neuronal injury [50].

Kawahata *et al* [51] observed a significant relationship between tooth loss and cognitive function in mice. They found that the loss of masticatory function in early life caused malnutrition and chronic stress that accelerated the aging process of the hippocampus [51]. In the amyloidogenic mouse model, dentate mice with experimental porphyromonas gingivalis periodontitis were found to develop impaired memory [52]. There was a significant increase in hippocampal, amyloid plaque loads in the whole brain and elevated levels of brain interleukin-1β and TNF-α [52]. Ilievski *et al* [53] have recently reported that long-term exposure to PD caused inflammation and neurodegeneration in the brain of mice, which similar to Alzheimer's disease in humans.

An experimental study demonstrated that periodontal pathogen could penetrate the blood-brain-barrier into the brain tissue [54]. Most of existing studies have shown that oral porphyromonas gingivalis infection in mice resulted in brain colonization and increased production of Aβ1–42, a component of amyloid plaques. Gingipains have been found to mediate toxicity of Porphyromonas gingivalis in endothelial cells, fibroblast and epithelial cells [34]. Dominy *et al* [34] developed small inhibitor molecules to block gingipain to prevent neurodegeneration, which significantly reduced Porphyromonas gingivalis load in the mouse brain, and significantly decreased the host Aβ1–42 response to Porphyromonas gingivalis brain infection. These studies have provided evidence of plausible causal links between PD and AD/dementia in animal models.

Does the evidence accord by analogy with that from other fields?

Iwasaki *et al* [14] examined older people in the community in Japan, and found that severe periodontitis and periodontal inflammation were associated with incident MCI. In a cohort study, Kaye *et al* [55] observed that the risk of cognitive decline over a decade increased by 2–5% for every tooth that had progression of alveolar bone loss or probing pocket depth. The

association of tooth loss with increased risk of dementia have been confirmed in two systematic literature reviews [39, 48]. These have supported our findings of significant influence of PD on increased risk of dementia.

Implications

Our study has demonstrated that PD could be significantly associated with increased risk of incident dementia. It has projected the number of dementia cases to be saved through reducing the prevalence of PD in the world. If the current prevalence of PD in the world were halved, 0.85 million dementia cases would be saved based on our conservative estimation of RR of 1.18 for dementia in relation to PD from the cohort studies, or 1.70 million dementia cases would be saved if we used an estimation of RR of 1.38 from both the cohort studies and the case-control studies. Treating patients with PD could help reduce the risk of dementia [7]. Population-based prevention of PD and improved strategies can minimize dementia burden. All these would reduce huge economic burden and decrease financial constraint in health-care systems. Oral hygiene habits, including regular brushing and dental visits can reduce the risk of PD and should thus be promoted as public health interventions to reduce incident dementia in the world. Dental care must be included in the wider care plan for the general population, to improve oral health throughout each individual's life course, minimizing the negative effect of PD on the quality of life and reducing the potential risk of dementia in later life. It is imperative that all health and allied healthcare professionals, including dental teams, continue to promote and implement guidelines for the delivery of oral health that are tailored to support the various stages of dementia prevention.

In *conclusion*, our study could provide evidence of significant and positive association of PD with increased risk of incident dementia. PD is a potential modifiable risk factor for dementia

and AD. Globally reducing PD through timely intervention, enhanced screening services and efficient treatment and dental care would save the cases of dementia.

Acknowledgement

Professor Ruoling Chen and Dr Jie Tang thank an EU grant from Horizon 2020 MSCA – DEMAIRPO #799247. Dr Kaarin Anstey is funded by NHMRC Fellowship #1102694. Dr Wu is the recipient of BBSRC [BB/P004695/1] and NIA [1R01AG049321-01A1] grant for aging research. Dr Yuyou Yao, Associate Professor of Anhui Medical University, China is a visiting scholar at the Faculty of Education, Health and Wellbeing, University of Wolverhampton to support this study and has made valuable comments on the manuscript.

Conflict of Interest:

The authors declare that they have no conflict of interest.

References:

1. Van Dyke TE, Van Winkelhoff AJ. Infection and inflammatory mechanisms. J Clin Periodontol. 2013;40:S1-S7. https:// doi: 10.1111/jcpe.12088

2. Kassebaum N, Bernabé E, Dahiya M, Bhandari B, Murray C, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dent Res. 2014;93(11):1045-53. https://doi: 10.1177/0022034514552491

3. Schätzle M, Faddy MJ, Cullinan MP, Seymour GJ, Lang NP, Bürgin W et al. The clinical course of chronic periodontitis: V. Predictive factors in periodontal disease. J Clin Periodontol. 2009;36(5):365-71. https://doi: 10.1111/j.1600-051X.2009.01391.x.

4. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005 ;366 (9499):1809-20. https://doi.org/10.1016/S0140-6736(05)67728-8

5. Hansen GM, Egeberg A, Holmstrup P, Hansen PR. Relation of periodontitis to risk of cardiovascular and all-cause mortality (from a Danish nationwide cohort study). Am J Cardiol. 2016;118(4):489-93. https://doi: 10.1016/j.amjcard.2016.05.036

6. Lee YT, Lee HC, Hu CJ, Huang LK, Chao SP, Lin CP 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. doi:10.1111/jgs.14449. https:// doi.org/10.1111/jgs.14449.

7. Lee YL, Hu HY, Huang LY, Chou P, Chu D. Periodontal disease associated with higher risk of dementia: Population-based cohort study in Taiwan. J Am Geriatr Soc. 2017;65(9):1975-80. doi:10.1111/jgs.14944. https:// dx.doi.org/10.1111/jgs.14944.

8. Chen C-K, Wu Y-T, Chang Y-C. Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study. Alzheimer's Research & Therapy. 2017;9(1):56-. https:// doi:10.1186/s13195-017-0282-6.

9. Tzeng NS, Chung CH, Yeh CB, Huang RY, Yuh DY, Huang SY et al. Are Chronic Periodontitis and Gingivitis Associated with Dementia? A Nationwide, Retrospective, Matched-Cohort Study in Taiwan. Neuroepidemiol. 2016;47(2):82-93. https: //doi:10. 1159 /000449166.

10. Arrivé E, Letenneur L, Matharan F, Laporte C, Helmer C, Barberger-Gateau P 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. https://doi:10.1111/j.1600-0528 .2011 .00650.x.

11. Leira Y, Domínguez C, Seoane J, Seoane-Romero J, Pías-Peleteiro JM, Takkouche B et al. Is Periodontal Disease Associated with Alzheimer's Disease? A Systematic Review with Meta-Analysis. Neuroepidemiology. 2017;48(1-2):21-31. https://doi:10.1159/000458411.

12. Kapellas Kostas XJ, Xiaoyan Wang, Nicole Mueller, Lisa M Jamieson. The association between periodontal disease and dementia: a systematic review and meta-analysis. Dental Oral Biology and Craniofacial Research. 2019. https://doi: 10.31487/j.DOBCR.2019.01.005.

13. Syrjälä AM, Ylöstalo P, Ruoppi P, Komulainen K, Hartikainen S, Sulkava R et al. Dementia and oral health among subjects aged 75 years or older. Gerodontology. 2012;29(1):36-42. https:// doi:10.1111/j.1741-2358.2010.00396.x.

14. Iwasaki M, Kimura Y, Ogawa H, Yamaga T, Ansai T, Wada T et al. Periodontitis, periodontal inflammation, and mild cognitive impairment: A 5-year cohort study. J Periodontal Res. 2018. https:// doi: 10.1111/jre.12623

15. Chan KY, Wang W, Wu JJ, Liu L, Theodoratou E, Car J et al. Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990–2010: a systematic review and analysis. The Lancet. 2013;381(9882):2016-23. https:// doi: 10.1016/S0140-6736 (13) 60221-4.

16. Chen R, Hu Z, Chen R-L, Zhang D, Xu L, Wang J et al. Socioeconomic deprivation and survival after stroke in China: a systematic literature review and a new population-based cohort study. BMJ open. 2015;5(1):e005688. https:// doi: 10.1136/bmjopen-2014-005688.

17. Liberati A, Altman D, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions. BMJ. 2009 Jul 1;339. https://dx.doi.org/10.1136%2Fbmj.b2700

18. Bramanti E, Bramanti A, Matacena G, Bramanti P, Rizzi A, Cicciu M. Clinical evaluation of the oral health status in vascular-type dementia patients. A case-control study. Minerva Stomatol. 2015;64(4):167-75.

19. Jureti. R , Yiru W, Panlong H, Yue S, Awuti G. Survey on periodontal health status of Xinjiang Uygur and |Han patients with Alzheimer’s Disease. Journal of Chongqing Medical University. 2016; 41(12): 1267-1271.

20. Holmer J, Eriksdotter M, Schultzberg M, Pussinen PJ, Buhlin K. Association between periodontitis and risk of Alzheimer's disease, mild cognitive impairment and subjective cognitive decline: A case-control study. J Clin Periodontol. 2018. https://doi: 10. 1111 /jcpe.13016.

21. Gil-Montoya JA, Sanchez-Lara I, Carnero-Pardo C, Fornieles F, Montes J, Vilchez R et al. Is periodontitis a risk factor for cognitive impairment and dementia? A case-control study. J Periodontol. 2015;86(2):244-53. https://doi:10.1902/jop.2014.140340.

22. Stein PS, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E et al. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer’s disease. Alzheimer's & Dementia: J Alzheimer's Dis. 2012;8(3):196-203. https://doi:10.1016/j.jalz.2011.04.006.

23. de Souza Rolim T, Fabri GM, Nitrini R, Anghinah R, Teixeira MJ, de Siqueira JT et al. Oral infections and orofacial pain in Alzheimer's disease: a case-control study. J Alzheimers Dis. 2014;38(4):823-9. https://doi:10.3233/jad-131283.

24. Chu CH, Ng A, Chau AMH, Lo ECM. Oral health status of elderly chinese with dementia in Hong Kong. Oral Health Prevent Dent. 2015;13(1):51-7. https:// doi: 10.3290/j.ohpd. a32343. .

25. Danat IM, Clifford A, Partridge M, Zhou W, Bakre AT, Chen A et al. Impacts of Overweight and Obesity in Older Age on the Risk of Dementia: A Systematic Literature Review and a Meta-Analysis. J Alzheimer's Dis. 2019(Preprint):1-13. https:// doi: 10.3233/ JAD-180763

26. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-5. https:// doi.org/10.1007/s10654-010-9491-z

27. Zhang J, Kai FY. What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998;280(19):1690-1. https://doi.org/10.1001 /jama.280.19.1690

28. Bakre AT, Chen R, Khutan R, Wei L, Smith T, Qin G et al. Association between fish consumption and risk of dementia: A new study from China and a systematic literature review and meta-analysis. Public Health Nutr. 2018;21(10):1921-32. https:// doi: 10. 1017/S136898001800037X.

29. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34. https://doi.org/10.1136/bmj.315.7109.629

30. Barnes D, Yaffe K. The projected impact of risk factor reduction on Alzheimer's disease prevalence. Alzheimer's & Dementia: The Journal Of The Alzheimer's Association. 2011;7(4):S511. https:// doi: 10.1016/S1474-4422(11)70072-

31. WHO. Dementia: Key facts. https://www.who.int/en/news-room/fact-sheets/detail/ dementia. 2017. Accessed 25 February 2019.

32. Petersen PE, Ogawa H. Strengthening the prevention of periodontal disease: the WHO approach. J Periodontol. 2005;76(12):2187-93. https://doi.org/10.1902/jop.2005.76.12.2187

33. Watts A, Crimmins EM, Gatz M. Inflammation as a potential mediator for the association between periodontal disease and Alzheimer's disease. Neuropsychiatr Dis Treat. 2008;4(5):865-76. https://doi:10.2147/ndt.s3610.

34. Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A et al. Porphyromonas gingivalis in Alzheimer’s disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Advan. 2019;5(1):eaau3333. https:// doi: 10 .1126/sciadv.aau3333

35. Ship JA. Oral health of patients with Alzheimer’s disease. J Am Dent Assoc. 1992;123(1):53-8. https://doi.org/10.14219/jada.archive.1992.0005

36. Martande SS, Pradeep A, Singh SP, Kumari M, Suke DK, Raju AP et al. Periodontal health condition in patients with Alzheimer’s disease. American Journal of Alzheimer's Disease & Other Dementias. 2014;29(6):498-502. https://doi: 10.1177/1533317514549650

37. Jureti R. Survey on periodontal health status of Xinjiang Uygur and Han patients with Alzheimer's diseases [Master]. Xinjiang Medical University; 2017.

38. Hill SB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965;58:295-300.

39. Chen J, Ren C-J, Wu L, Xia L-Y, Shao J, Leng W-D et al. Tooth loss is associated with increased risk of dementia and with a dose-response relationship. Frontiers in aging neuroscience. 2018;10:415. https:// doi: 10.3389/fnagi.2018.00415.

40. Janket S-J, Baird AE, Chuang S-K, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2003;95(5):559-69. https://doi.org/10.1067/moe.2003.107

41. Leira Y, Seoane J, Blanco M, Rodriguez-Yanez M, Takkouche B, Blanco J et al. Association between periodontitis and ischemic stroke: a systematic review and meta-analysis. Springer; 2017. https:// doi: 10.1007/s10654-016-0170-6.

42. Anstey KJ, von Sanden C, Salim A, O'kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol. 2007;166(4):367-78. https://doi.org/10.1093/aje/kwm116

43. Sheiham A, Watt RG. The common risk factor approach: a rational basis for promoting oral health. Community Dentistry and Oral Epidemiology: Commentary. 2000;28(6):399-406. https:// https://doi.org/10.1034/j.1600-0528.2000.028006399.x

44. Kamer AR, Pirraglia E, Tsui W, Rusinek H, Vallabhajosula S, Mosconi L et al. Periodontal disease associates with higher brain amyloid load in normal elderly. Neurobiol Aging. 2015;36(2):627-33. https:// doi: 10.1016/j.neurobiolaging.2014.10.038

45. Pizzo G, Guiglia R, Russo LL, Campisi G. Dentistry and internal medicine: from the focal infection theory to the periodontal medicine concept. Eur J Inter Med. 2010;21(6):496-502. https:// doi: 10.1016/j.ejim.2010.07.011

46. Carter CJ, France J, Crean S, Singhrao SK. The Porphyromonas gingivalis/host interactome shows enrichment in GWASdb genes related to Alzheimer's disease, diabetes and cardiovascular diseases. Front Aging Neurosci. 2017;9:408. https://doi.org/10.3389 /fnagi.2017.00408

47. Newman AB, Fitzpatrick AL, Lopez O, Jackson S, Lyketsos C, Jagust W et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. J Am Geriatr Soc. 2005;53(7):1101-7. https://doi.org /10.1111/j.1532-5415.2005.53360.x

48. Fang W-l, Jiang M-j, Gu B-b, Wei Y-m, Fan S-n, Liao W et al. Tooth loss as a risk factor for dementia: systematic review and meta-analysis of 21 observational studies. BMC Psychiatry. 2018;18(1):345. https://doi.org/10.1186/s12888-018-1927-0

49. Kato T, Usami T, Noda Y, Hasegawa M, Ueda M, Nabeshima T. The effect of the loss of molar teeth on spatial memory and acetylcholine release from the parietal cortex in aged rats. Behavioural Brain Research. 1997;83(1-2):239-42. https://doi:10.1016/s0166-4328(97)86078-0.

50. Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. J Alzheimer's Dis. 2013;36(4):665-77. https:// doi: 10.3233/JAD-121918.

51. Kawahata M, Ono Y, Ohno A, Kawamoto S, Kimoto K, Onozuka M. Loss of molars early in life develops behavioral lateralization and impairs hippocampus-dependent recognition memory. BMC Neurosci. 2014;15(1):4. https:// doi: 10.1186/1471-2202-15-4.

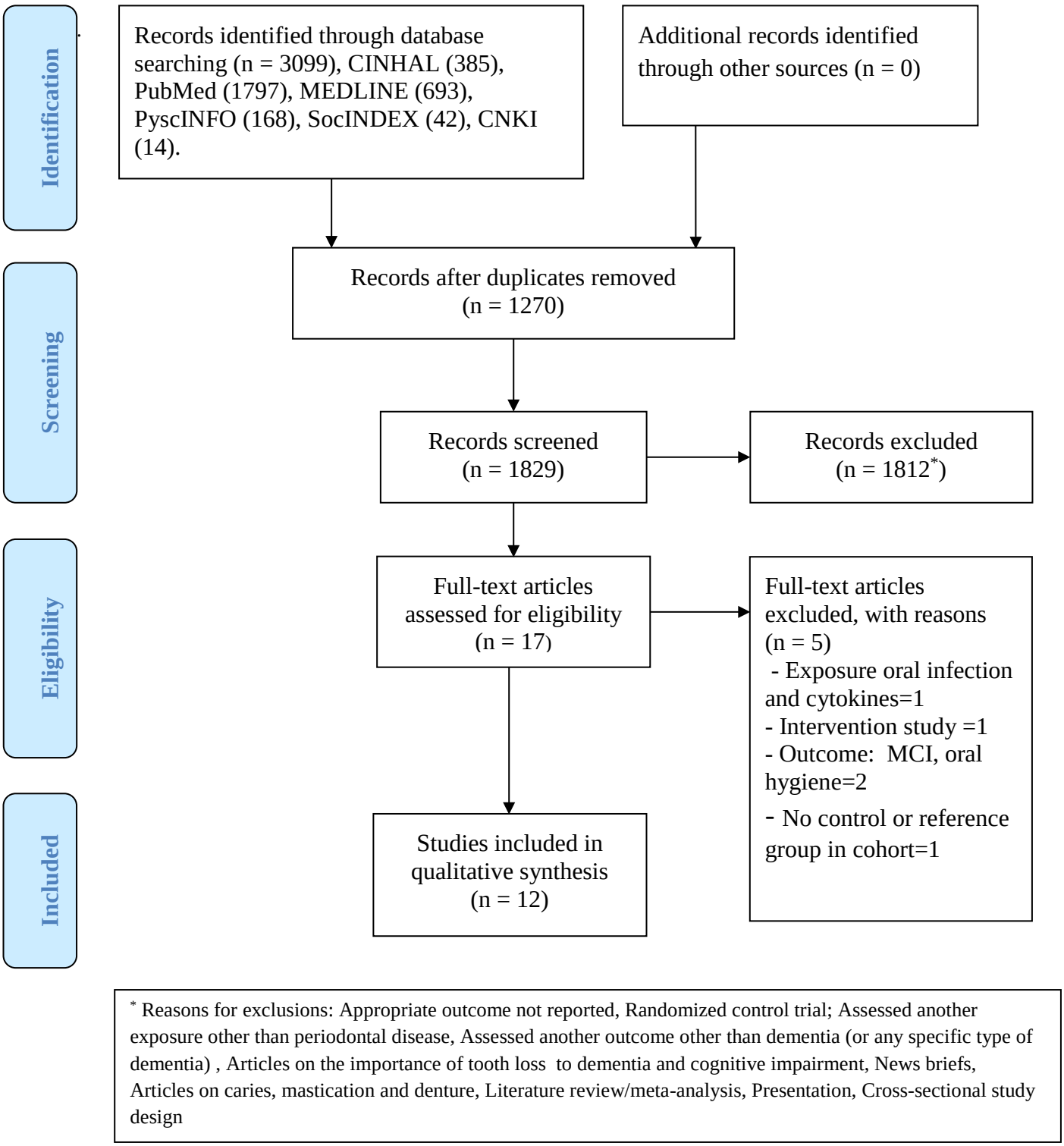
52. Ishida N, Ishihara Y, Ishida K, Tada H, Funaki-Kato Y, Hagiwara M et al. Periodontitis induced by bacterial infection exacerbates features of Alzheimer's disease in transgenic mice. NPJ aging and mechanisms of disease. 2017;3(1):15. https:// doi: 10.1038/s41514-017-0015-x.

53. Ilievski V, Zuchowska PK, Green SJ, Toth PT, Ragozzino ME, Le K et al. Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. PloS one. 2018;13(10):e0204941. https:// doi: 10.1371/journal.pone.0204941

54. Poole S, Singhrao SK, Chukkapalli S, Rivera M, Velsko I, Kesavalu L et al. Active invasion of Porphyromonas gingivalis and infection-induced complement activation in ApoE-/-mice brains. J Alzheimers Dis. 2015;43(1):67-80. https:// doi: 10.3233/JAD-140315

55. Kaye EK, Valencia A, Baba N, Spiro III A, 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. https:// doi: 10.1111/j.1532-5415.2010.02788.x

Figure 1: Flow chart for literature search, selection and inclusion of studies for review



* Reasons for exclusions: Appropriate outcome not reported, Randomized control trial; Assessed another exposure other than periodontal disease, Assessed another outcome other than dementia (or any specific type of dementia) , Articles on the importance of tooth loss to dementia and cognitive impairment, News briefs, Articles on caries, mastication and denture, Literature review/meta-analysis, Presentation, Cross-sectional study design

Figure 2: Forest plot for the pooled relative risk (RR) of PD and dementia risk

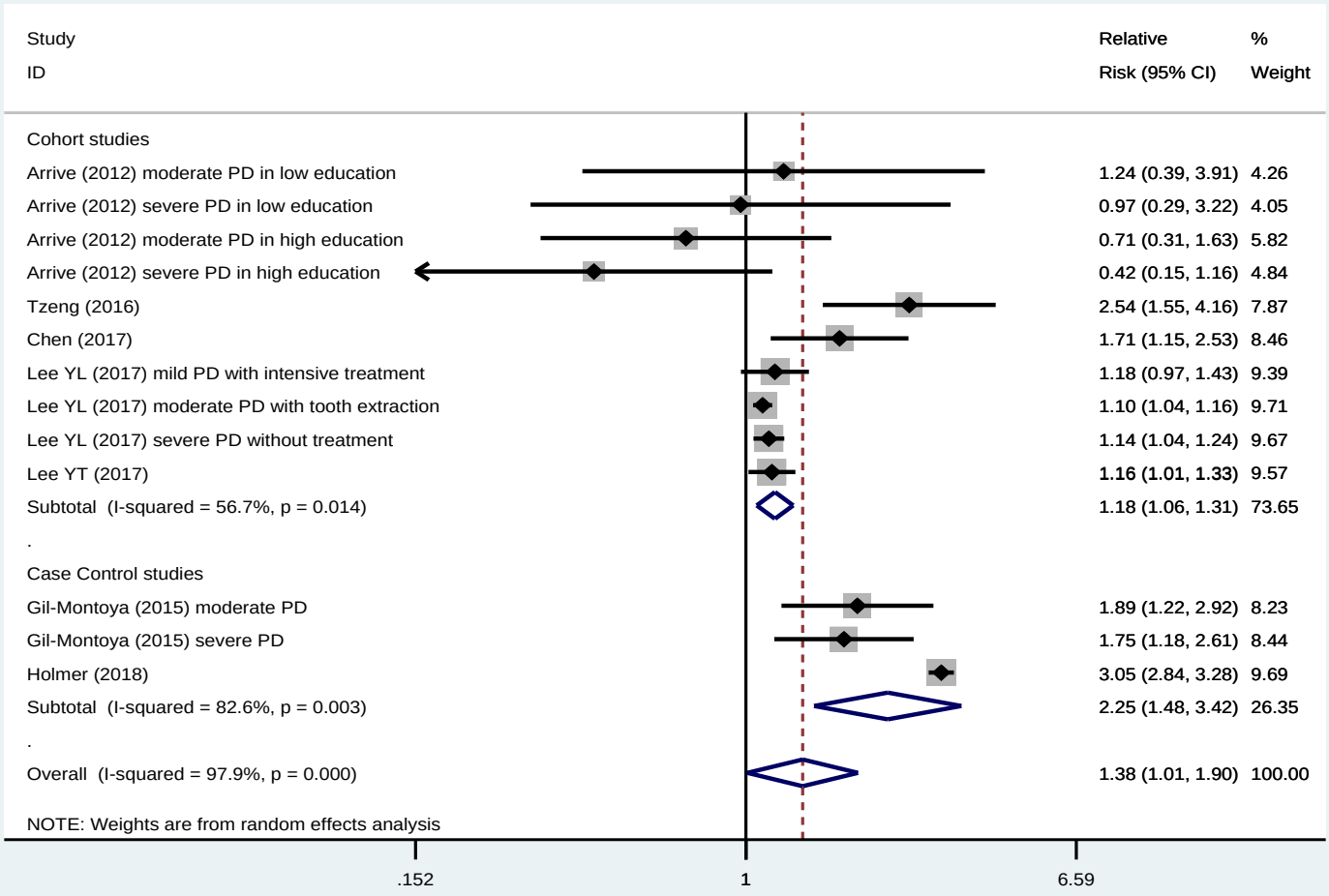


Figure 3: Funnel plot assessing publication bias

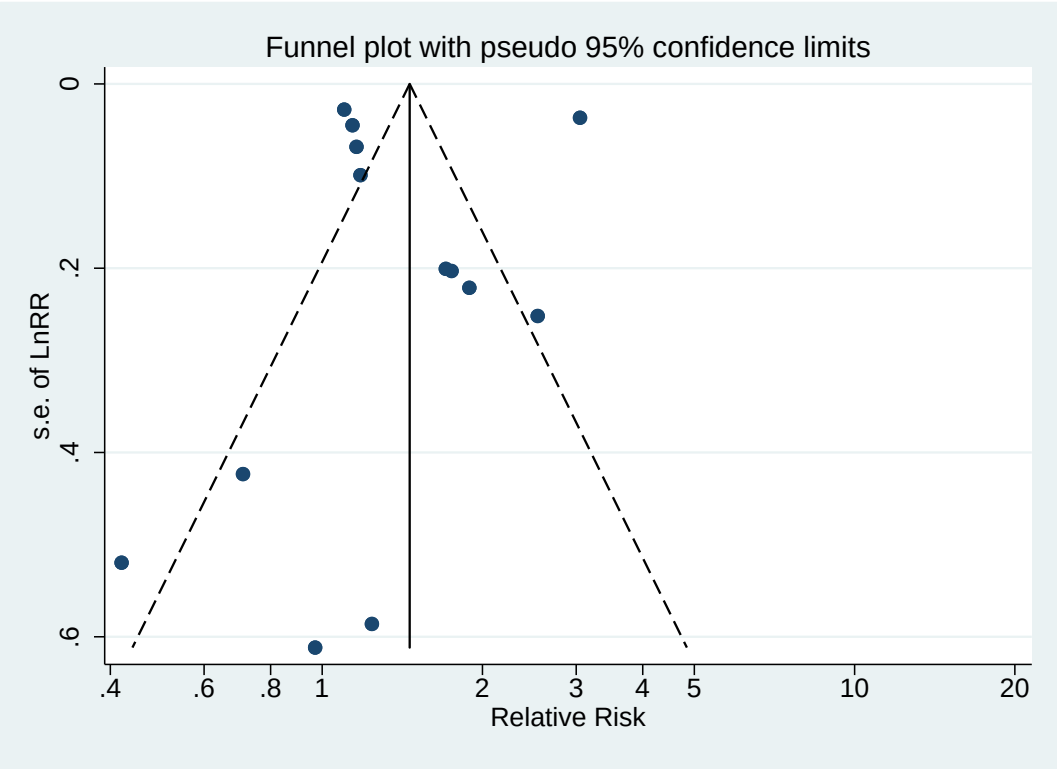


Table 1: Evaluation of the study quality using Newcastle-Ottawa Scales (NOS)

Cohort studies							
Selection of cohort		**Chen *et al* [8]**	**Lee YL *et al* [7]**	**Lee YT *et al* [6]**	**Tzeng *et al* [9]**	**Arrive *et al* [10]**	
1	Representativeness of the exposed cohort	☆	☆	☆	☆	☆	
2	Selection of the non-exposed cohort	☆	☆	☆	☆	☆	
3	Ascertainment of exposure	☆	☆	☆	☆	☆	
4	Demonstration that outcome of interest was not present at start of study	☆	☆	☆	☆		
Comparability of cohorts							
1	Comparability of cohorts on the basis of the design or analysis	☆ ☆	☆ ☆	☆ ☆	☆ ☆	☆ ☆	
Outcome							
1	Assessment of outcome	☆	☆	☆	☆	☆	
2	Was follow-up long enough for outcomes to occur	☆	☆	☆	☆	☆	
3	Complete follow up- all subjects accounted for	☆	☆	☆	☆	☆	
Total score:		9/9	9/9	9/9	9/9	8/9	
Case –control studies							
Selection of case-control		**Holmer *et al* [20]**	**Jureti *et al* [19]**	**Brammati *et al* [18]**	**Gil Montoya *et al* [21]**	**Chu *et al* [24]**	**De Souza *et al* [23]**	**Stein *et al* [22]**
1	Is the case definition adequate?	☆	☆	☆	☆		☆	
2	Representativeness of the cases	☆	☆	☆	☆	☆	☆	☆

3	Selection of Controls	☆	☆				☆	☆
4	Definition of Controls	☆	☆	☆	☆	☆	☆	
Comparability								
1	Comparability of cases and controls on the basis of the design or analysis	☆ ☆	☆	☆ ☆	☆ ☆	☆ ☆	☆	☆
Exposure								
1	Ascertainment of exposure		☆	☆	☆	☆	☆	☆
2	Same method of ascertainment for cases and controls	☆	☆	☆	☆		☆	☆
3	Non-Response rate		☆		☆		☆	☆
Total score:		7/9	8/9	7/9	8/9	5/9	8/9	6/9

Table 2: Pooled risk of dementia in people with PD according to the continents where the studies were undertaken

Variable for subgroup data analysis	No. of studies	No. of cohort studies	No. of studied population	Number of participants	Number of dementia cases	RR	95%CI
Categorized country by continents							
Asia [6-9]	4	4	6	225,594	6542	1.20	1.08-1.33
Europe [10, 20, 21]	3	1	7	1034	283	1.38	0.84-2.27

Table 3: Dose –response between severity of periodontal disease and risk of dementia[*]

Periodontal disease (PD) Severity levels**	RR (95%CI)
0	**REF**
1	**1.39 (0.97-1.99)**
2	**1.50 (0.97-2.33)**

[*] Dose- response studies: [7, 10, 19, 21, 23, 24]

**PD severity levels:

0= Reference (REF): no PD (including minor PD [19, 21, 24])

1= Moderate PD: bleeding, calculus, gingivitis, shallow pockets.

2= Severe PD: deep pockets, PD without treatment.

Table 4: Estimated number of dementia cases attributable to periodontal disease in the world

Periodontal disease prevalence	Relative risk*	PAR %	No of cases attributable thousands (confidence range)	Estimated number of cases saved in thousands from 50 million dementia cases
current 20%	1.18 (1.06-1.31)	3.47 (1.86-5.84)	1,735 (930 – 2920)	
reduced to be 10%	1.18 (1.06-1.31)	1.77 (0.60-3.00)	885 (300- 1500)	850 (630-1420)
reduced to be 5%	1.18 (1.06-1.31)	0.89 (0.30-1.53)	445 (150-765)	1290 (780-2155)

* Based on the pooled data from all cohort studies (Figure 2)

EJEP-D-19-00779 Supplementary Tables and Figure (20-04-20)

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

Authors:

Rizwan Nadim[1], Jie Tang[1, 2], Amena Dilmohamed[1], Siyang Yuan[1], Changhao Wu[3], Aishat T Bakre[1], Martin Partridge[1], Jindong Ni[4], John Copeland[5], Kaarin J. Anstey[6,7], Ruoling Chen[1]

Rizwan Nadim and Jie Tang joint first author.

Correspondence: Professor Ruoling Chen, Email: r.chen@wlv.ac.uk

Affiliations:

[1]Institute of Health, Faculty of Education, Health and Wellbeing, University of Wolverhampton, UK

[2] School of Public Health, Guangzhou Medical University, China

[3] Faculty of Health and Medical Sciences, University of Surrey, UK

[4] School of Public Health, Guangdong Medical University, China

[5] Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK

[6] UNSW Ageing Futures Institute and School of Psychology, University of New South Wales

[7] Neuroscience Research Australia, Sydney, Australia

Journal: European Journal of Epidemiology

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	A total of 8,828 participants 2,207 patients with CP and gingivitis; after excluding 681	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	Cox proportional hazard regression adjusted for age, gender, geographical area of residence, urbanization level of the residence,	Adjusted HR for dementia in patients with CP and gingivitis was 2.54 (95% CI 1.55–4.16)

	2,888 patients with newly diagnosed CP and gingivitis, and age- sex matched controls without CP and gingivitis; both recruited from Longitudinal Health Insurance Database (2000-2010) in Taiwan.	patients due to gingivitis/CP before 2000, gender unknown, aged <20 years and dementia diagnosed before first visit 6,621 controls without CP and gingivitis			- 61 patients without CP or gingivitis Dementia: 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	and monthly income, comorbidities (including hypertension, obesity, diabetes, hyperlipidemia, stroke, 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 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.	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).
Chen et al [8] (2017); Taiwan, China	Retrospective matched cohort study Age: ≥50 years 10,592 patients	27,963 participants including: -9291 participants with CP; after excluding 1301	11.9 years (± 2.6) in participants with CP, 12.2 years (± 2.6) in participants	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,	In patients with 10 years of CP exposure, the adjusted HR for AD was 1.71 (1.15–2.53).

	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.	patients due to having CP or AD prior to 1997 and AD prior to CP 1st visit, -18,672 patients without CP.	without CP.			hyperlipidaemia, stroke , traumatic brain injury, chronic kidney disease and Charlson co-morbidity index score	

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);	Case-control nested in cohort study.	158 participants	BOP and AAP classification used for	In 81 cases, 35 participants developed AD and 77	Wilcoxon rank-sum test and general linear	Antibody levels to F. nucleatum and P. intermedia were

U.S.A	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.		diagnosis of CP Serum Sample: Venous blood draws of the study participants	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	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.	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 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	118 participants	CPI	59 dementia cases and 59 controls matched for sex and age. Dementia: Diagnosed by medical doctors . 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	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)

	Philip dental hospital were invited (not under current dental treatment).			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 Sao Paulo. Controls were older people without AD (relatives of the patients: wives,	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-is/mild PD / 9 / 3 Modera-te PD / 2 / 3 Severe PD / 6 / 2	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)

	husbands, brothers, and/or sisters).					
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 >4mm / 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)
Gil-Montoya et al [21] (2015); Spain	Population based case-control study Age: 51 to 98 years	409 participants	PPD, CAL and BI Degree of PD was	180 cases (159 dementia from mild to severe and 21 MCI) and 229 controls	Multiple logistic regression analysis adjusted for age, gender, education,	RRs* for dementia and MCI was as follows:

	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.		defined by the percentage of sites with CAL >3 mm as follows: - 0% = absent; - 0–32% = mild; - 33–66% = moderate; - 67–100% = severe	Dementia: DSM-IV including AD: NINCDS-ADRDA	smoking, alcohol, BI, PI, PD, CAL, number of teeth, oral hygiene habits, hyperlipidemia and hyperglycaemia	-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	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)

				Mode-rate PD 25 21 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.

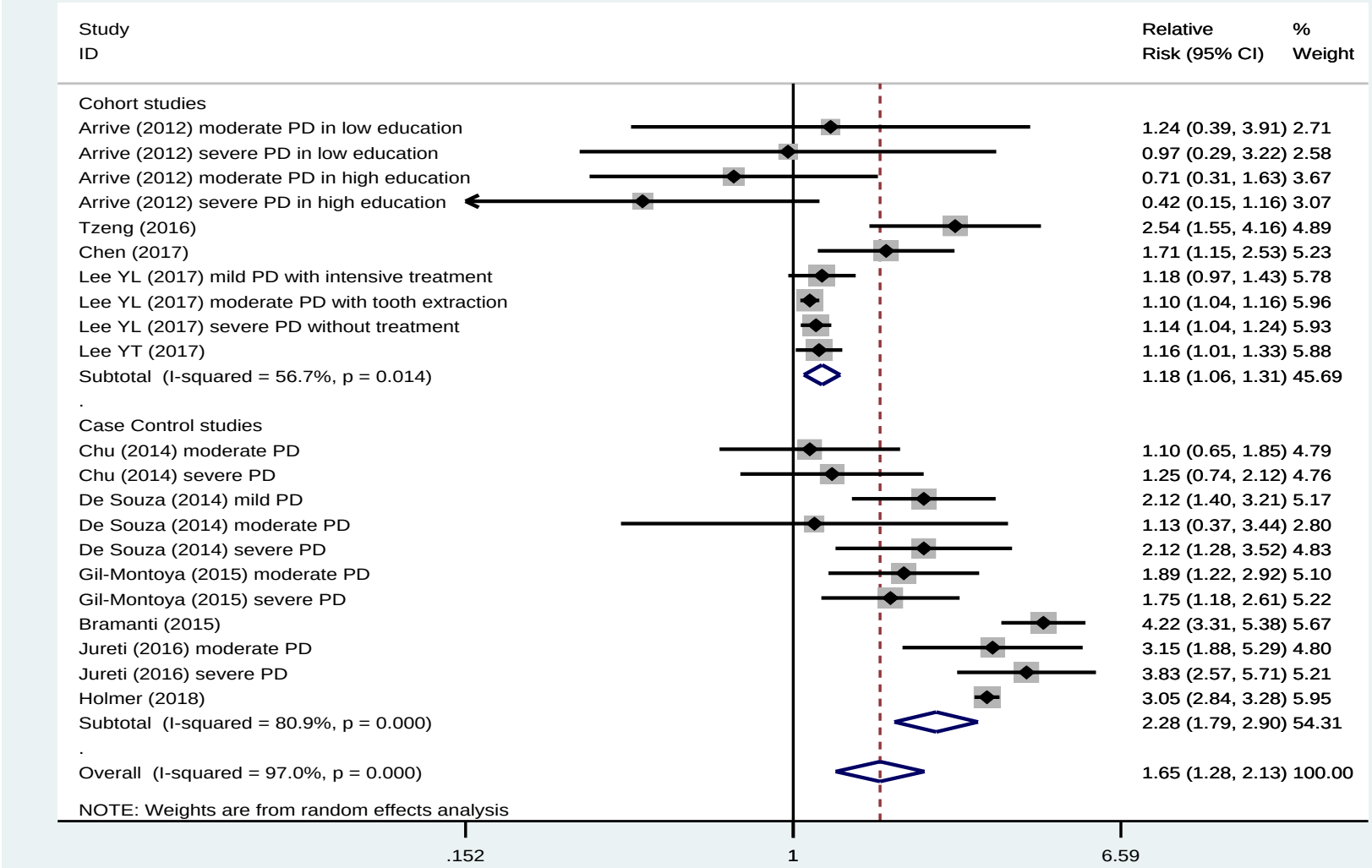
Abbreviations: AAP- clinical criteria of American Academy of Periodontology, AD- Alzheimer's disease, ANOVA- Analysis of variance, BI- Bleeding index, BOP-Bleeding on Probing, BMI- Body mass index, CAL/AL – clinical attachment loss, CP - chronic periodontitis, CPI- Community periodontal index, DSM-III 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]:

$$RR = \frac{\text{odds ratio}}{}$$

$1 - risk_0 + risk_0 \times \text{odds ratio}$

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


Study
ID
Relative
Risk (95% CI)
%
Weight
Cohort studies
Arrive (2012) moderate PD in low education
1.24 (0.39, 3.91) 2.71
Arrive (2012) severe PD in low education
0.97 (0.29, 3.22) 2.58
Arrive (2012) moderate PD in high education
0.71 (0.31, 1.63) 3.67
Arrive (2012) severe PD in high education
0.42 (0.15, 1.16) 3.07
Tzeng (2016)
2.54 (1.55, 4.16) 4.89
Chen (2017)
1.71 (1.15, 2.53) 5.23
Lee YL (2017) mild PD with intensive treatment
1.18 (0.97, 1.43) 5.78
Lee YL (2017) moderate PD with tooth extraction
1.10 (1.04, 1.16) 5.96
Lee YL (2017) severe PD without treatment
1.14 (1.04, 1.24) 5.93
Lee YT (2017)
1.16 (1.01, 1.33) 5.88
Subtotal (I-squared = 56.7%, p = 0.014)
1.18 (1.06, 1.31) 45.69
.
Case Control studies
Chu (2014) moderate PD
1.10 (0.65, 1.85) 4.79
Chu (2014) severe PD
1.25 (0.74, 2.12) 4.76
De Souza (2014) mild PD
2.12 (1.40, 3.21) 5.17
De Souza (2014) moderate PD
1.13 (0.37, 3.44) 2.80
De Souza (2014) severe PD
2.12 (1.28, 3.52) 4.83
Gil-Montoya (2015) moderate PD
1.89 (1.22, 2.92) 5.10
Gil-Montoya (2015) severe PD
1.75 (1.18, 2.61) 5.22
Bramanti (2015)
4.22 (3.31, 5.38) 5.67
Jureti (2016) moderate PD
3.15 (1.88, 5.29) 4.80
Jureti (2016) severe PD
3.83 (2.57, 5.71) 5.21
Holmer (2018)
3.05 (2.84, 3.28) 5.95
Subtotal (I-squared = 80.9%, p = 0.000)
2.28 (1.79, 2.90) 54.31
.
Overall (I-squared = 97.0%, p = 0.000)
1.65 (1.28, 2.13) 100.00
NOTE: Weights are from random effects analysis
.152
1
6.59

References numbering according to manuscript

6. Lee YT, Lee HC, Hu CJ, Huang LK, Chao SP, Lin CP 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. doi:10.1111/jgs.14449. https:// doi.org/10.1111/jgs.14449.

7. Lee YL, Hu HY, Huang LY, Chou P, Chu D. Periodontal disease associated with higher risk of dementia: Population-based cohort study in Taiwan. J Am Geriatr Soc. 2017;65(9):1975-80. doi:10.1111/jgs.14944. https:// dx.doi.org/10.1111/jgs.14944.

8. Chen C-K, Wu Y-T, Chang Y-C. Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study. Alzheimer's Research & Therapy. 2017;9(1):56-. https:// doi:10.1186/s13195-017-0282-6.

9. Tzeng NS, Chung CH, Yeh CB, Huang RY, Yuh DY, Huang SY et al. Are Chronic Periodontitis and Gingivitis Associated with Dementia? A Nationwide, Retrospective, Matched-Cohort Study in Taiwan. Neuroepidemiol. 2016;47(2):82-93. https: //doi:10. 1159 /000449166.

10. Arrivé E, Letenneur L, Matharan F, Laporte C, Helmer C, Barberger-Gateau P 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. https://doi:10.1111/j.1600-0528 .2011 .00650.x.

18. Bramanti E, Bramanti A, Matacena G, Bramanti P, Rizzi A, Cicciu M. Clinical evaluation of the oral health status in vascular-type dementia patients. A case-control study. Minerva Stomatol. 2015;64(4):167-75.

19. Jureti. R , Yiru W, Panlong H, Yue S, Awuti G. Survey on periodontal health status of Xinjiang Uygur and |Han patients with Alzheimer’s Disease. Journal of Chongqing Medical University. 2016; 41(12): 1267-1271.

20. Holmer J, Eriksdotter M, Schultzberg M, Pussinen PJ, Buhlin K. Association between periodontitis and risk of Alzheimer's disease, mild cognitive impairment and subjective cognitive decline: A case-control study. J Clin Periodontol. 2018. https://doi: 10. 1111 /jcpe.13016.

21. Gil-Montoya JA, Sanchez-Lara I, Carnero-Pardo C, Fornieles F, Montes J, Vilchez R et al. Is periodontitis a risk factor for cognitive impairment and dementia? A case-control study. J Periodontol. 2015;86(2):244-53. https://doi:10.1902/jop.2014.140340.

22. Stein PS, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E et al. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer’s disease. Alzheimer's & Dementia: J Alzheimer's Dis. 2012;8(3):196-203. https://doi:10.1016/j.jalz.2011.04.006.

23. de Souza Rolim T, Fabri GM, Nitrini R, Anghinah R, Teixeira MJ, de Siqueira JT et al. Oral infections and orofacial pain in Alzheimer's disease: a case-control study. J Alzheimers Dis. 2014;38(4):823-9. https://doi:10.3233/jad-131283.

24. Chu CH, Ng A, Chau AMH, Lo ECM. Oral health status of elderly chinese with dementia in Hong Kong. Oral Health Prevent Dent. 2015;13(1):51-7. https:// doi: 10.3290/j.ohpd. a32343. .

27. Zhang J, Kai FY. What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998;280(19):1690-1.

37. Jureti R. Survey on periodontal health status of Xinjiang Uygur and Han patients with Alzheimer's diseases [Master]. Xinjiang Medical University; 2017.