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ORIGINAL ARTICLE

Periodontal conditions and incident dementia: A nationwide Swedish cohort study

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Abstract

Background: Periodontal disease has been proposed as a putative etiological factor for dementia. The aim of this investigation was to compare the incidence of dementia in individuals with or without deep probing pocket depths (DPPD), serving as a proxy for periodontitis.

Methods: In this cohort study, conducted in Sweden, we identified 7992 individuals with DPPD and 29,182 matched individuals without DPPD (non-DPPD), using the Swedish Quality Registry for Caries and Periodontal Diseases (SKaPa). The two groups were followed for incident dementia (mean follow-up time was 7.6 years) based on data from the Swedish Dementia Registry (SveDem). The exposure-outcome relationship was explored by applying the Royston-Parmar (RP) flexible parametric survival model.

Results: The incidence of dementia in the two groups was similar. In the DPPD group 137 (1.7%) developed dementia and 470 (1.6%) in the non-DPPD group. The incidence rate of dementia was estimated to be 2.3 per 1000 person-years (95% confidence interval [CI] 1.9 to 2.7) in the DPPD group and 2.1 per 1000 person-years (95% CI 1.9 to 2.3) in the non-DPPD group. The RP model disclosed no association between DPPD and dementia incidence after controlling for potential confounders (the exponentiated coefficient was estimated to 1.13 [95% CI = 0.39 to 3.24]).

Conclusion: In this sample, no association was revealed between deep probing pocket depths and the incidence of dementia.

KEYWORDS
dementia, epidemiology, neurocognitive disorders, oral health, periodontal disease

1 | INTRODUCTION

As the shift in global population structure continues towards an overrepresentation of older adults, there is a corresponding increase in the prevalence of dementia.[1,2] Apart from personal suffering and increasing numbers of disabled older adults, this altered demography will also challenge welfare systems.[3] The most common form of dementia is Alzheimer's disease (AD).[4] To date there is no treatment that modifies the disease. Following promising results of multidomain preventive trials, mainly targeting lifestyle factors, larger studies are now under way.[5,6] In recent decades, several risk (etiological) factors for dementia have been identified, but much remains unknown.[7] The AD therapeutic strategy targets the cholinergic system and provides symptomatic treatment. Recently, our group reported that modest cognitive benefits of treatment with cholinesterase inhibitors persist long-term.[8] Clinical trials targeting the accumulation of β-amyloid and tau protein, the pathological hallmarks of AD, have shown inconsistent outcomes and are yet to demonstrate a clear clinical improvement in cognitive function.[9] In the absence of effective medication, the exploration and proper identification of primary and secondary preventive strategies have been declared pivotal research priorities.[10] Oral diseases, because of their global omnipresence and systemic impact, are of interest as potentially modifiable risk factors for dementia.[11–13] There is emerging evidence that periodontitis, a common inflammatory disease of the tissues supporting the teeth, is associated with dementia.[14–16] The biological mechanisms that would explain this association are currently unclear. Both inflammatory and microbiological explanatory models have been proposed in the literature.[17]

There are few population-based longitudinal studies investigating the possible association between periodontitis and dementia. In the present study, using data from nationwide registers in Sweden and a longitudinal study design, the aim was to compare the incidence of dementia in individuals with or without signs consistent with periodontal disease, testing the hypothesis that the incidence of dementia is higher in those with signs of periodontal disease.

2 | MATERIALS AND METHODS

2.1 | Study design

This non-experimental cohort study compares the incidence of dementia in individuals with or without (exposed or unexposed to) deep periodontal/peri-implant probing pocket depths (regarded in this study as a proxy for periodontitis). The study participants were identified by data linkage of nationwide Swedish registers.[18] Individual record linkage was undertaken by the Swedish National Board of Health and Welfare, using personal identity numbers.[19] The data to undergo statistical analysis were pseudonymized before delivery to the researchers.

Ethical approval was obtained from the Regional Ethical Review Board in Stockholm, Sweden (registration number 2017/737-31). For reporting we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines.[20]

2.2 | Data sources and variable assessment

2.2.1 | Exposure

We used the Swedish Quality Registry for Caries and Periodontal Diseases (SKaPa) to identify individuals with or without periodontal/peri-implant disease.[21] We identified all individuals in SKaPa, aged 40 to 80 years in 2010, who had undergone a registered dental examination between January 1, 2010 and December 31, 2012. The age restriction was set to include mainly individuals at risk of dementia (the prevalence of dementia is low in younger age groups) and to reduce the influence of age-related comorbidities. To be eligible for inclusion in the study, it was a requirement that the dental examination included a completed probing pocket depth (PPD) registration chart. Date of dental examination represents the index date.

In SKaPa, it is not possible to discriminate between teeth and dental implants in the PPD registration charts (hence the use of the term "periodontal/peri-implant" throughout the text). SKaPa is a nationwide quality register where several different dental care providers deliver patient chart data to the register. Thus, the periodontal examination methodology is not standardized, and it may differ in how many sites the dental care professional registers per tooth in the PPD registration chart. Therefore, all PPD information is provided at tooth and dental implant level in this study. The PPD information was used to determine the presence of periodontitis.

The exposed group comprised individuals with deep periodontal/peri-implant PPD (DPPD). DPPD was defined as having ≥4 teeth and/or dental implants with PPD ≥6 mm. Using this definition, DPPD should represent a sufficient operationalization for periodontitis. In addition, the lower PPD cut-off point will exclude potential pseudopockets in gingivitis.

We created a matched unexposed group, which comprised individuals without deep periodontal/peri-implant PPD (non-DPPD). Non-DPPD was defined as having <4 teeth and/or dental implants with PPD 4 to 5 mm and no

PPD ≥6 mm. For each exposed individual, we matched four unexposed individuals by age, sex, index date and geographical area in Sweden.

Individuals were excluded if the following criteria were met prior to index date: registered in the Swedish Dementia Registry (SveDem), had a dementia diagnosis registered in the National Patient Register (International Classification of Diseases [ICD] codes: ICD-9 290 or 294, or ICD-10-SE F00-F04, F051, G30, G31, or A81.0) or had received treatment with anti-dementia drugs (cholinesterase inhibitors and/or memantine; Anatomic Therapeutic Chemical classification system [ATC] code N06D) in the Prescribed Drug Register.[22–24]

2.2.2 | Outcomes

Individuals were followed from index date until dementia diagnosis (all-cause dementia), defined as a first registration in SveDem (where individuals are registered at the time of dementia diagnosis and then followed up annually), or on treatment with anti-dementia drugs (cholinesterase inhibitors [donepezil, galantamine, or rivastigmine] and/or memantine; ATC code N06D) in the Prescribed Drug Register or dementia diagnosis in the National Patient Register (ICD-10 codes F00, F01, F02, F03, G30, and G31 [with subgroups]) until December 31, 2018. Other endpoints were migration, death as registered in the Cause of Death Register or end of follow-up (December 31, 2018).[25]

2.2.3 | Covariates

Baseline demographic and socioeconomic data (age, civil status, disposable income, education, geographical area, and sex) were retrieved from the Longitudinal Integrated Database for Health Insurance and Labor Market Studies maintained by the government agency Statistics Sweden.[26] The Charlson Comorbidity Index (CCI) was used to measure comorbidity using data retrieved from the National Patient Register (with dementia diagnoses excluded). CCI is an index which categorizes comorbidities of individuals, based on ICD-codes, and also includes diabetes mellitus. [27,28]

2.3 | Statistical methods

Age and disposable income were analyzed as continuous variables and sex as a binary variable. Civil status (widow/widower/surviving partner/divorced, married/registered partner, unmarried), education (9 years or less, 10 to 12 years, 13 years or more) and CCI (0, 1, 2, or more) were included as categorical variables with three levels. Categorical variables were described by the frequency and proportion, whereas continuous variables were described by median and interquartile range (IQR) or mean and standard deviation (SD).

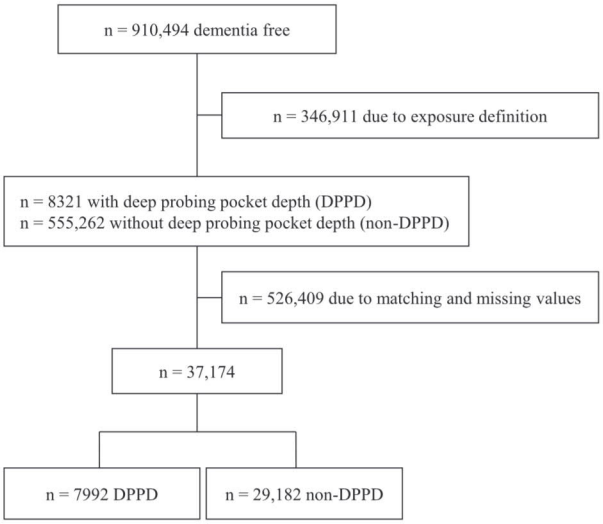

FIGURE 1 Study population selection

Initially, the survival data were explored using Kaplan-Meier plots. Cox proportional-hazards regression models were applied to investigate the relationship between the exposure and outcome. However, we found that the proportional-hazards assumption did not hold. Relaxing the proportional-hazards assumption, the Royston-Parmar (RP) flexible parametric survival model (RP model) was applied for modeling the cumulative hazard of dementia, using the function *flexsurvspline* in R package *flexsurv*.[29,30] Covariates assumed to influence both the exposure and outcome, and thus to confound the relationship under investigation, were chosen based on theoretical reasoning and subject matter knowledge in the potential causal network for this particular exposure-outcome relationship.

Sensitivity analyses were also undertaken by exploring a less stringent case definition for the exposed cohort (≥2 teeth and/or dental implants with PPD ≥6 mm). We also explored data using stratified analyses for age and sex, and different sets of covariates (with or without income and/or education). The resultant patterns and relationships between the two groups were similar, regardless of the definitions and analyses used (results not shown).

All statistical analyses were conducted using Stata release 16.1 and R version 4.0.1.[31,32]

3 | RESULTS

Baseline characteristics are presented in Table 1. The study population selection is depicted in Figure 1. The total study

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TABLE 1 Baseline characteristics of the study population (n = 37,174)

Sample characteristics[a]	Total (n = 37,174)	DPPD (n = 7992)	Non-DPPD (n = 29,182)
Age, years (median, IQR)	61 (52 to 68)	61 (53 to 68)	61 (52 to 68)
40 to 49	6418 (17.3)	1309 (16.4)	5109 (17.5)
50 to 59	10,762 (29.0)	2282 (28.6)	8480 (29.1)
60 to 69	12,682 (34.1)	2786 (34.9)	9896 (33.9)
≥70	7312 (19.7)	1615 (20.2)	5697 (19.5)
Sex			
Male	20,891 (56.2)	4584 (57.4)	16,307 (55.9)
Female	16,283 (43.8)	3408 (42.6)	12,875 (44.1)
Years of education[b]			
≤9	9439 (25.4)	2505 (31.3)	6934 (23.8)
10 to 12	17,019 (45.8)	3875 (48.5)	13,144 (45.0)
≥13	10,716 (28.8)	1612 (20.2)	9104 (31.2)
Disposable income[c] (median, IQR)			
Individual level	2140 (1459 to 2879)	1948 (1375 to 2642)	2197 (1495 to 2948)
Family level	3638 (2377 to 5360)	3109 (2092 to 4716)	3797 (2454 to 5533)
Marital status			
Widow/widower/surviving partner/divorced	7923 (21.3)	2102 (26.3)	5821 (19.9)
Married/registered partnership	22,713 (61.1)	4390 (54.9)	18,323 (62.8)
Unmarried	6538 (17.6)	1500 (18.8)	5038 (17.3)
Comorbidities			
Charlson's comorbidity index			
0	31,032 (83.5)	6588 (82.4)	24,444 (83.8)
1	2948 (7.9)	750 (9.4)	2198 (7.5)
≥2	3194 (8.6)	654 (8.2)	2540 (8.7)
Dental health status			
Number of teeth (median, IQR)	26 (23 to 28)	24 (20 to 27)	26 (23 to 28)
Number of dental implants			
0	35,976 (96.8)	7750 (97.0)	28,226 (96.7)
≥1	1198 (3.2)	242 (3.0)	956 (3.3)
Number of teeth/implants with PPD 4 to 5 mm (median, IQR)	1 (0 to 2)	2 (1 to 3)	1 (0 to 2)
Number of teeth/implants with PPD ≥6 mm (median, IQR)	0 (0 to 0)	6 (4 to 8)	0 (0 to 0)

Abbreviations: IQR = interquartile range; DPPD = individuals with deep periodontal/peri-implant PPD; Non-DPPD = individuals without deep periodontal/peri-implant PPD; PPD = probing (periodontal or peri-implant) pocket depth.

[a]Presented as frequencies (n) and proportions (%) unless otherwise specified.

[b]Nine years of schooling has been the minimum requirement in Sweden since 1962. It is equivalent to the 7-year school system that was used in Sweden during the 1930s and 1940s.

[c]Presented as multiples of 100 Swedish krona (SEK; 100 SEK = ≈ 11.7 US Dollars on August 31, 2021).

population comprised 37,174 individuals with a median age of 61 years at baseline, contributing 283,373 person-years of time at risk, with a mean follow-up time of 7.6 years (SD 1.1). There were 7992 individuals in the DPPD group and 29,182 in the non-DPPD group. The mean follow-up time was 7.6 years (SD 1.1) for both groups. Compared to the non-DPPD group, the DPPD group had less education, lower disposable income, and more comorbidities.

Table 2 shows dementia incidence by exposure and related measures of disease occurrence. In the total study population, we identified 607 (1.6%) individuals diagnosed with dementia during follow-up. At the end of follow-up, 137 (1.7%) participants with DPPD had been diagnosed with dementia and 470 (1.6%) in the non-DPPD group. The incidence rate of dementia was estimated at 2.1 per 1000 person-years (95% confidence interval [CI] 2.0 to 2.3) in the

TABLE 2 Dementia incidence and association estimates for dementia by exposure (n = 37,174)

Sample characteristics[a]	DPPD (n = 7992)	Non-DPPD (n = 29,182)
Dementia		
None	7855 (98.3)	28,712 (98.4)
Follow-up	137 (1.7)	470 (1.6)
Person-time at risk (years)	60,525.5	222,847.5
Incidence rate (per 1000 person-years)[b]	2.3 (1.9 to 2.7)	2.1 (1.9 to 2.3)
Crude HR[c]	1.15 (0.40 to 3.28)	Reference
Adjusted HR[c]	1.13 (0.39 to 3.24)	Reference

Abbreviation: HR = hazard ratio; DPPD = individuals with deep periodontal/peri-implant PPD; Non-DPPD = individuals without deep periodontal/peri-implant PPD.

[a]Presented as frequencies (n) and proportions (%) unless otherwise specified.

[b]Incidence rates per 1000 person-years are presented with 95% confidence intervals.

[c]We applied the Royston-Parmar (RP) model, thus the estimates presented in this table are exponentiated coefficients derived from the RP model which are comparable to HR. Adjustments were made for age, sex, marital status, education, disposable income, and the Charlson comorbidity index. Point estimates are presented with 95% confidence intervals.

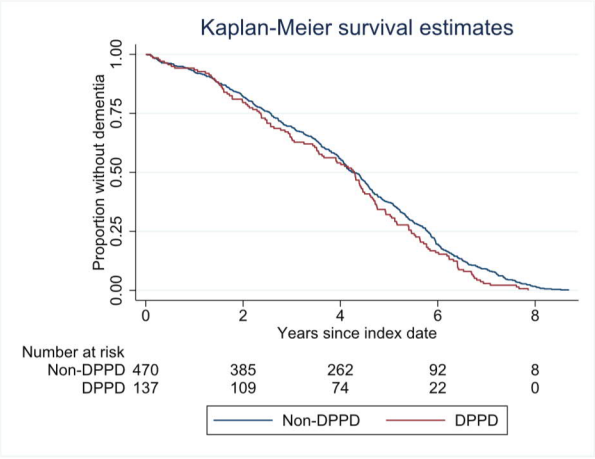

FIGURE 2 Kaplan-Meier plot of the exposure-outcome relationship, depicting incident dementia only. The deep probing pocket depths (DPPD) group were slightly more likely to develop dementia than those in the non-DPPD group

total study population, 2.3 per 1000 person-years (95% CI 1.9 to 2.7) in the DPPD group and 2.1 per 1000 person-years (95% CI 1.9 to 2.3) in the non-DPPD group. Approximately 2.1% in each exposure group died during follow-up.

Figure 2 represents a Kaplan-Meier plot indicating that individuals with DPPD at any time point during follow-up are slightly more likely to develop dementia than individuals in the non-DPPD group. RP model estimates and cumulative incidence of dementia are presented in Figure 3 and show marginal differences between the exposure cohorts. As shown in Table 2, non-significant differences emerged between the groups in dementia incidence. The crude RP model exponentiated coefficient (measure of association; comparable to hazard ratio) was 1.15 (95% confidence interval [CI] = 0.40 to 3.28) and adjusted (for age, sex, marital status, education, disposable income and CCI) estimates showed similar results (exponentiated coefficient 1.13, 95% CI 0.39 to 3.24). Thus, our analysis of this sample revealed no association between DPPD and dementia.

4 | DISCUSSION

The results of this study show a similar incidence of dementia in the two groups, with or without DPPD. After controlling for assumed confounders, no association was observed between DPPD and dementia. Nonetheless, a trend emerged indicating that at any time point during follow-up, individuals with DPPD were slightly more likely to develop dementia than those in the non-DPPD group.

Well-designed and carefully conducted studies are needed for proper assessment of a potential causal effect. The current state of evidence in periodontal-Alzheimer's disease interactions has recently been outlined.[11] Several cohort studies have demonstrated a positive association between signs of periodontal disease and dementia, but the methodology and exposure/outcome definitions lack consistency, which hinders further inference and interpretation.[33–36] Studies similar to the present, based on secondary data, have demonstrated associations between periodontitis and dementia. For instance, a study conducted in South Korea found a weak association (adjusted hazard ratio was 1.06 [95% CI 1.01 to 1.11]) between periodontitis and dementia when accounting for potential confounders.[34] Chen et al., also used nationwide data collected from the National Health Insurance Research Database in Taiwan and followed two cohorts (with or without periodontitis) and found that periodontitis was associated with AD (adjusted HR 1.71, 95% CI 1.15 to 2.53).[35]

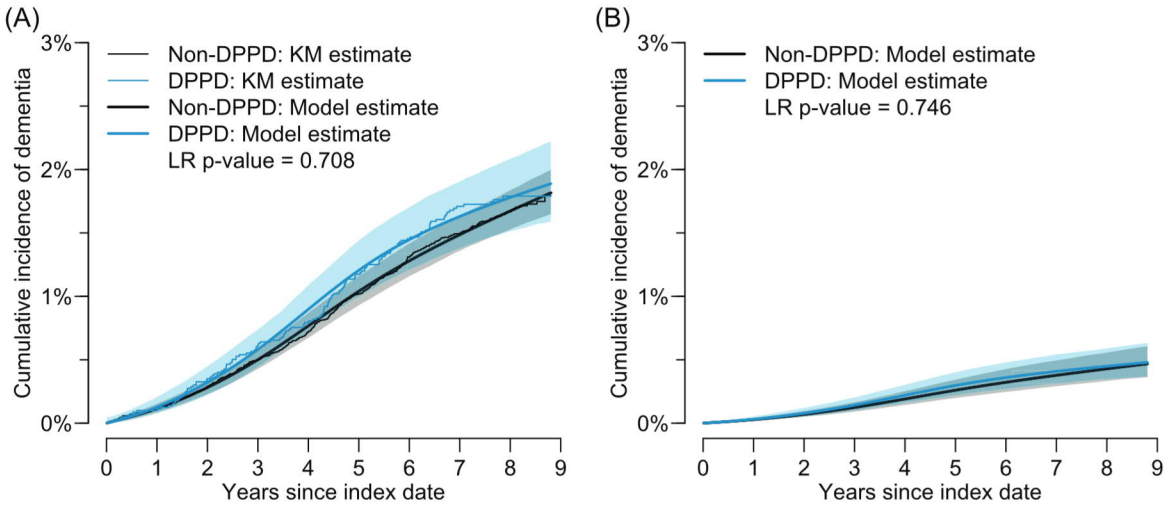

FIGURE 3 Royston-Parmar model estimates and cumulative incidence of dementia. Note: (**A**) crude estimates and (**B**) adjusted estimates (age, sex, marital status, education, disposable income and CCI). Note: KM = Kaplan-Meier curves; DPPD = individuals with deep periodontal/peri-implant probing pocket depths; Non-DPPD = individuals without deep periodontal/peri-implant probing pocket depths

Another Swedish study (Swedish National Study on Ageing and Care), based on primary data and using a clear-cut periodontal disease exposure definition, followed a larger cohort for 6 years.[36] It was shown that periodontal bone-loss was associated with cognitive decline (odds ratio was 2.2 [95% CI 1.2 to 3.8]).

The major strengths of this study are the large sample size, retrieved from nationwide registers, and the longitudinal design. We have also collected detailed information about potential confounders. Using secondary data, we can be confident that the exposure information was collected independently of the outcome, which eliminates the risk of observer bias. Another important strength is that the exposure measurements were based on PPD measurements at tooth or dental implant level, rather than the probably more arbitrary ICD codes or treatment codes for periodontitis case determination. This is unique in the context of published register-based studies exploring similar research questions.

Some important limitations which may influence interpretation, should however be noted. This investigation represents an effort to study a larger population longitudinally. Follow-up time is limited by the date that the registers were established (SveDem in 2007 and SKaPa in 2008). Although we had access to a large population (see Figure 1), we could not fully exploit the entire population because of the strict definition of the groups, which rendered many potential study participants ineligible. This may be a source of bias if the included participants were not representative of other subjects. Moreover, data from SveDem show that 75% of the dementia population is >74 years and older at the time of dementia diagnosis.[37] With a mean age of 61 and 7 years follow-up a large proportion of the sample here would thus not reach the ages where dementia is more prevalent.

We cannot preclude residual confounding, inherent in an observational study design. For example, we were unable to assess the influence of smoking, which may represent an influential confounder. Another hinder to causal interpretations is the possibility of reverse causality, as the true onset of the two diseases is not known.

As mentioned earlier, our exposure measurement is a strength, but it may also be considered a limitation. The PPD information was retrieved from SKaPa. SKaPa continuously collects data from numerous dental clinics and clinicians across Sweden. The dental examination data collected from real-world clinical practice will possibly influence the validity of the exposure measurements. In this study there is a risk of misclassification of exposure, which is likely to be non-differential.

Periodontal/peri-implant disease in this study is defined by the presence of deepened PPDs, which typically represents current inflammation and edema in the periodontal or peri-implant tissues. PPD measurements seldom give an accurate estimate of the clinical attachment level (CAL), even though a deep PPD is often regarded as a reflection of attachment loss.[38] In Sweden, CAL is rarely measured in daily clinical practice because it is a time-consuming and technique sensitive endeavor. Thus, at present, SKaPa does not include information on CAL (or radiographical signs of marginal alveolar bone loss). This is an important limitation and prevents periodontitis classification according to the new EFP/AAP case definition and the widely used CDC–AAP case definition.[39,40] In an effort to compensate for this lack of information, we applied a strict operationalization for periodontitis (consistent with severe

periodontitis) by using four or more teeth/dental implants with PPD ≥6 mm. The reported prevalence of dental implants in our sample was 3.2%. Hence, the great majority of PPDs are observed on teeth, not implants, and reflect periodontal status. The unexposed cohort definition was used to ensure that the individual in fact had undergone a periodontal examination.

If we compare exposure or case definitions among studies with similar methodology, it is obvious that the criteria differ. For instance, both Choi et al., and Chen et al., used ICD-codes (in the study by Choi et al., also treatment codes) for their periodontitis case definitions.[34,35] We on the other hand, based our case definition on PPD measurements. Together with differences in study setting and design and statistical method, the approach to periodontitis case definition in this study could explain why we did not find an association between periodontal disease and dementia.

Repeated cross-sectional studies in Sweden have provided prevalence estimates since the 1970s.[41] Recently, periodontal health in those studies has been carefully described. The findings showed that the prevalence of having at least one 6 mm PPD in 2013 was 17% for 40-year-olds, which varied depending on age up to 35% for 80-year-olds.[42] Information on periodontitis prevalence may also be collected from SKaPa and their annual reports on oral health in Sweden.[43] In 2018, 10% had at least one 6 mm PPD, of which 10% to 20% had four or more affected teeth with 6 mm PPD. This is in good agreement with our figures.

Because periodontitis is a slowly progressive disease, some of the unexposed become exposed during late follow-up. However, it is likely that a certain amount of time would need to elapse for an individual's periodontitis to affect the risk of dementia, that is, an induction period. It is still unclear how long an induction period would be necessary (under the premise that we assume causality). This is further complicated by the fact that both diseases (i.e., periodontitis and dementia) are of complex etiology and often take a long time to become manifest (long latent period).

As with the exposure measurements, there are potential shortcomings with respect to the outcome ascertainment. The coverage of SveDem based on the estimated incidence of dementia in the population was about 33%.[37] However, many individuals with dementia do not seek help for their problems. We also used the Prescribed Drug Register and the National Patient Register to identify individuals who were treated with anti-dementia drugs and/or diagnosed with dementia but were not registered in SveDem. Taken together, all these measures gave us good chances to identify most incident dementia cases during the observation period.

We recently showed that the number of dental care visits significantly declined when diagnosed with dementia.[44,45] Therefore, individuals with dementia may be less prone to seek dental care also in years preceding the dementia diagnosis resulting in overall low dementia incidence in both exposure groups.

5 | CONCLUSIONS

The findings in this large register study show no apparent association between deep probing pocket depth and dementia. Population-based longitudinal studies with reliable, well-defined case definitions and conducted among other populations are required to clarify the possible link between periodontitis and dementia.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare related to this study.

DATA AVAILABILITY STATEMENT

No additional data are available because of Swedish regulations.

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