Received: 4 January 2022 | Revised: 22 June 2022 | Accepted: 25 June 2022

DOI: 10.1111/jgs.17978

REVIEW ARTICLE

Journal of the
American Geriatrics Society

Periodontal health, cognitive decline, and dementia: A systematic review and meta-analysis of longitudinal studies

Sam Asher MPH[1] | **Ruth Stephen PhD**[2] | **Päivi Mäntylä PhD**[1,3] | **Anna Liisa Suominen PhD**[1,3] | **Alina Solomon PhD**[2,4,5]

[1]Institute of Dentistry, University of Eastern Finland, Kuopio, Finland

[2]Neurology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland

[3]Department of Oral and Maxillofacial Diseases, Kuopio University Hospital, Kuopio, Finland

[4]Division of Clinical Geriatrics, NVS, Karolinska Institute, Stockholm, Sweden

[5]Aging Epidemiology Research Unit, School of Public Health, Imperial College London, London, UK

Correspondence
Sam Asher, Institute of Dentistry, University of Eastern Finland, Yliopistonranta 1C, P.O. Box 1627, 70211 Kuopio, Finland.
Email: samash@uef.fi

Funding information
Ella ja Georg Ehrnroothin Säätiö; Juho Vainion Säätiö; Minerva Foundation; Päivikki ja Sakari Sohlbergin Säätiö; Suomen Aivosäätiö; Suomen Kulttuurirahasto; European Research Council, Grant/Award Number: 804371

Abstract

Background: Emerging evidence indicates that poor periodontal health adversely impacts cognition. This review examined the available longitudinal evidence concerning the effect of poor periodontal health on cognitive decline and dementia.

Methods: Comprehensive literature search was conducted on five electronic databases for relevant studies published until April 2022. Longitudinal studies having periodontal health as exposure and cognitive decline and/or dementia as outcomes were considered. Random effects pooled estimates and 95% confidence intervals were generated (pooled odds ratio for cognitive decline and hazards ratio for dementia) to assess whether poor periodontal health increases the risk of cognitive decline and dementia. Heterogeneity between studies was estimated by I^2 and the quality of available evidence was assessed through quality assessment criteria.

Results: Adopted search strategy produced 2132 studies for cognitive decline and 2023 for dementia, from which 47 studies (24 for cognitive decline and 23 for dementia) were included in this review. Poor periodontal health (reflected by having periodontitis, tooth loss, deep periodontal pockets, or alveolar bone loss) was associated with both cognitive decline (OR = 1.23; 1.05–1.44) and dementia (HR = 1.21; 1.07–1.38).

Further analysis, based on measures of periodontal assessment, found tooth loss to independently increase the risk of both cognitive decline (OR = 1.23; 1.09–1.39) and dementia (HR = 1.13; 1.04–1.23). Stratified analysis based on the extent of tooth loss indicated partial tooth loss to be important for cognitive decline (OR = 1.50; 1.02–2.23) and complete tooth loss for dementia (HR = 1.23; 1.05–1.45). However, the overall quality of evidence was low, and associations were at least partly due to reverse causality.

Preliminary results for the effect of periodontal health on cognitive decline were presented (poster presentation) at Alzheimer's Association International Conference (AAIC) 2020 in Amsterdam, the Netherlands.

Conclusions: Poor periodontal health and tooth loss appear to increase the risk of both cognitive decline and dementia. However, the available evidence is limited (e.g., highly heterogenous, lacking robust methodology) to draw firm conclusions. Further well-designed studies involving standardized periodontal and cognitive health assessment and addressing reverse causality are highly warranted.

KEYWORDS
cognitive decline, dementia, periodontitis, tooth loss

INTRODUCTION

Dementia is a syndrome characterized by progressive cognitive decline and functional incapacitation. Over 50 million people are affected by dementia worldwide and owing to an increase in aging population, the prevalence of dementia is expected to triple by 2050.[1] Less severe cognitive deterioration such as mild cognitive impairment (MCI) denotes a pathological cognitive decline in which functional independence is largely retained. MCI is a heterogeneous and still developing concept. Its prevalence varies significantly between different population groups ranging from 5% to 41%.[2] Same pathological processes underlie milder forms of cognitive deterioration (e.g., MCI) and dementia, partly explaining high conversion rate of MCI into dementia.[3] Moreover, both dementia and MCI are classified within the same cluster of neurocognitive disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5); MCI or other milder forms of pathological cognitive decline as mild neurocognitive disorders, and dementias represent major neurocognitive disorder.[4]

Dementias and even milder forms of pathological cognitive decline are debilitating conditions that significantly compromise the quality of life and impose an enormous socioeconomic burden on caregivers and healthcare systems.[1,2] Much research has been focused on identifying modifiable risk factors, for example, cardiovascular diseases, smoking, and unhealthy diet,[5] and targeting them through various interventions (e.g., pharmacotherapy and/or lifestyle modification).[5–7] Among the many risk factors for dementia and cognitive decline, oral health measures (e.g., periodontitis, tooth loss) have only started to be recently explored.[8–17]

Periodontitis is the inflammation of tooth-supporting tissues which in severe cases leads to tooth loss. It affects about 10%–15% of the world's adult population.[18] Periodontal health is an important health determinant linked to various systemic conditions (e.g., diabetes, cardiovascular diseases).[19] The available evidence on periodontal health and cognitive deterioration is insufficient and subject to limitations.[8–17,20–30] Most individual studies lack comprehensive exposure and outcome assessments and have a shorter duration. Also, in the past two years, several studies have been published[8–17] which warrant synthesis and evaluation. Previous literature reviews restricted their analysis by either exposure, outcome, or both, that is, they explored either periodontitis or tooth loss in relation to either cognitive impairment or dementia (but not all simultaneously). Moreover, meta-analyses had methodological limitations, for example, combined different effect estimates (odds ratio [OR], hazards ratio [HR], risk ratio [RR]) or effect estimates from different study designs,[20–30] and did not consider reverse causality (poor periodontal health due to cognitive decline/dementia). Therefore, this work aims to address these

Key points

- Poor periodontal health might contribute to the risk of both cognitive decline and dementia, although existing evidence has low quality and does not fully exclude reverse causality
- Tooth loss appears to be independently associated with poorer cognition
- This association might be mediated by different characteristics of periodontal health, for example, extent of tooth loss

Why does this paper matter?

This is a comprehensive systematic review with qualitative assessment and meta-analysis, investigating the effect of different measures of periodontal health, and highlighting the preventive potential of periodontal health for cognitive decline and dementia.

limitations, synthesize, and evaluate all updated evidence on this evolving topic.

METHODS

Definition of periodontal health

In this review, poor periodontal health was defined as having periodontitis or any of the clinical parameters by which periodontal deterioration is identified, including deeper periodontal pockets (PPDs), clinical attachment loss (CAL), or alveolar bone loss (ABL). Untreated/severe periodontal disease leads to tooth loss,[18,31] and is one of the leading causes of tooth loss among older adults.[32,33] Moreover, tooth loss is one of the most widely used surrogate measures of periodontal status in research. Therefore, low tooth count/tooth loss was also considered as an indicator of poor periodontal health in this review. However, since tooth loss can result from causes other than periodontal deterioration, tooth loss was also independently assessed for its impact on cognitive outcomes.

Definition of cognitive decline

Although there are several definitions and diagnostic criteria for MCI,[34,35] it is still a concept under development, and may not always be easily distinguishable from age-related cognitive decline. Due to the variety of definitions used in the literature, this review focused on the more general term "cognitive decline," to capture all relevant studies and ensure coverage of the full spectrum of pathological cognitive deterioration not severe enough to compromise functional independence (i.e., not meeting criteria for dementia).

Search strategy

Systematic search for English language studies, published until April 30, 2022, was conducted on five electronic databases, Medline via PubMed, Scopus, CINAHL, Web of Science, and PsycINFO. Search was applied separately for cognitive decline and dementia. For *cognitive decline*, "periodontitis," "tooth loss," "cognitive impairment," "cognitive deterioration," "cognitive decline," "prospective," "cohort," "retrospective," "follow-up," and "longitudinal" were used as keywords. For *dementia*, additional keywords such as "dementia," "Alzheimer's disease," and "vascular dementia" were used. Search strategy was applied according to Preferred Reporting Items for Systematic Reviews and Meta-analysis—PRISMA (Figure 1).

Inclusion criteria

Population (P)

Longitudinal studies were conducted on participants without dementia at baseline.

Exposure (E)

Studies with periodontal health assessment as exposure. All studies were considered regardless of the measure used to assess periodontal health. This also included studies with tooth loss as exposure.

Outcome (O)

Studies with cognitive decline and/or dementia diagnosis.

Case reports, reviews, cross-sectional, and animal studies were excluded.

Quality assessment

Each study was assessed for risk of bias in 4 major and 1 minor domain. Quality assessment criteria were derived from previously published studies,[36,37] and are described in Supplementary Text S1.

Study selection and data extraction

Search strategy returned 2132 studies for cognitive decline and 2023 for dementia. After screening abstracts and removing duplicates, 77 studies for cognitive decline and 75 for dementia were obtained for full-text appraisal. Two authors (S.A. and R.S.) independently reviewed full texts and hand-searched references of included studies to identify any additional study meeting inclusion criteria. In cases of disagreements, a third author (A.S.) was consulted, and a consensus was reached. Relevant data including study duration, exposure-outcome assessment measures, and effect estimates were extracted.

Meta-analysis

Meta-analysis was conducted using RevMan 5.4 statistical program (Cochrane Collaboration Review Manager).[38] Individual studies used different effect estimates, which were considered statistically incomparable. Therefore,

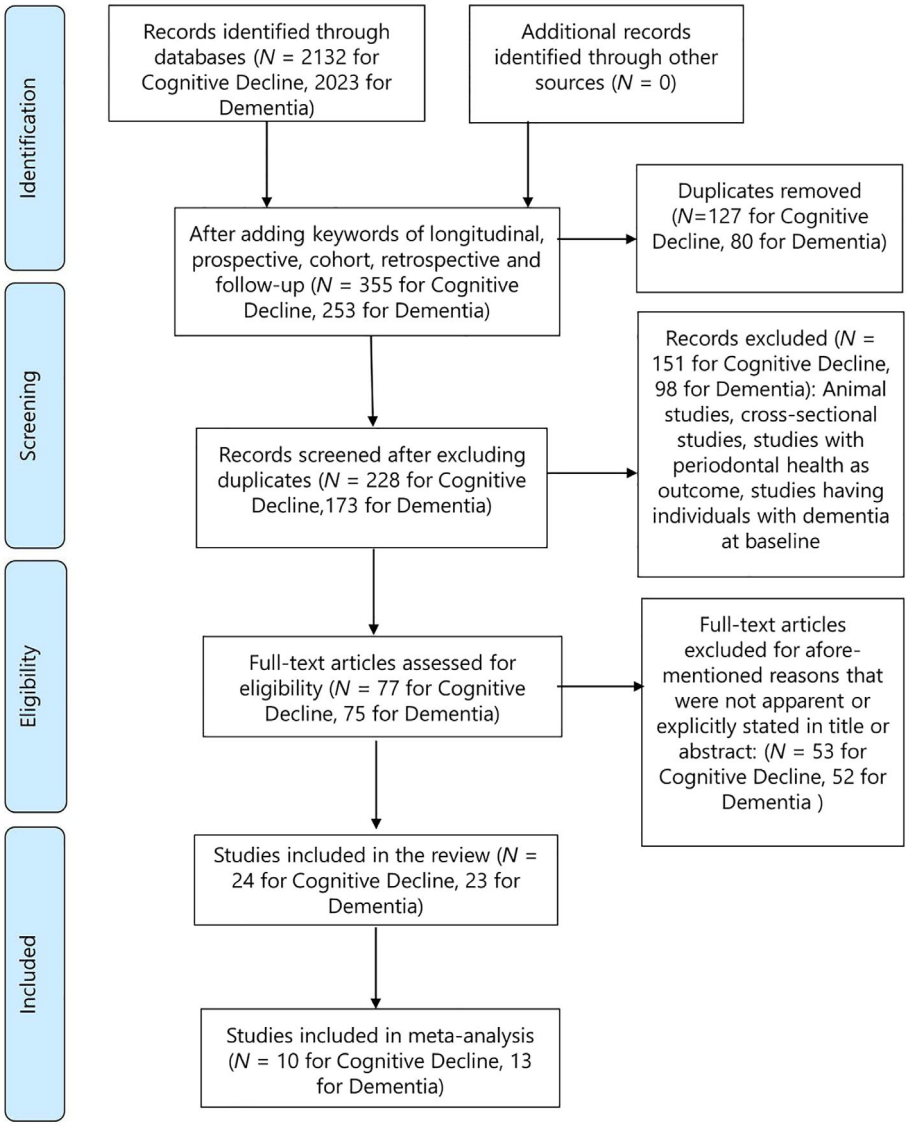

FIGURE 1 Search results (PRISMA flow diagram)

the most widely used effect estimate for each outcome, that is, OR for cognitive decline and HR for dementia were used to compute random effects pooled estimates with a corresponding 95% confidence interval (95% CI, $p = 0.05$) and degree of heterogeneity (I^2).

Multiple meta-analysis models (summarized in Table 1) were computed based on measures of periodontal health assessment to evaluate different aspects of periodontal-cognitive health association. For each study, only a single effect estimate was entered into each model. Therefore, for studies using multiple measures to assess periodontal health, only effect estimates corresponding to more accurate measures were selected (Supplementary Text S1). For example, periodontitis-specific measures (which includes periodontitis diagnosis, PPDs, ABL, and CAL) were used instead of tooth loss in primary models (Figures 2A and 3A).

Similarly, for studies where a particular measure of periodontal health was stratified into multiple categories (periodontitis into mild, moderate, and severe, or tooth loss into multiple tooth count categories), pooled estimates for individual studies were first generated and then entered into meta-analysis (Figures 2A–E and 3A–E). However, corresponding supplementary models were also computed with individual estimates (Figure S1A–E for cognitive decline; Figure S2A–E for dementia). Concerning cognitive decline, studies presenting estimates for >1 cognitive test, estimates corresponding to more sensitive or comprehensive tests were used, for example, mini-mental state examination (MMSE) over spatial coping test (SCT).

Addressing reverse causality

As cognitive decline may also lead to poor periodontal health, reverse causality may confound the association.[39,40] To account for this, only longitudinal studies

TABLE 1 Summary of meta-analysis models

Periodontal health assessment	Cognitive decline	Dementia
Poor periodontal health (Diagnosis of Periodontitis, PPDs, ABL, and tooth loss)	Figures 2A, S1A, S3A	Figures 3A, S2A, S4A
Periodontitis-specific measures (Periodontitis[a], PPDs, and ABL)	Figures 2B, S1B, S3B	Figures 3B, S2B, S4B
Tooth loss (low vs. high tooth count)	Figures 2C, S1C, S3C	Figures 3C, S2C, S4C
Complete tooth loss (0 teeth remaining vs. at least 1 tooth remaining)	Figures 2D, S1D, S3D	Figures 3D, S2D, S4D
Partial tooth loss (low vs. high tooth count, excluding 0 teeth remaining)	Figures 2E, S1E, S3E	Figures 3E, S2E, S4E

Abbreviations: ABL, alveolar bone loss; PPDs, periodontal pocket depths.
[a]Diagnosis of Periodontitis: International Statistical Classification of Disease (ICD), Centers for Disease Control and Prevention (CDC), American Academy of Periodontology (AAP), Community Periodontal Index (CPI), biofilm-gingival interface classification (BGI) criteria.

were included.[41] For dementia as an outcome, studies were restricted to dementia-free participants at baseline, and an additional meta-analysis was conducted restricting each main model (Figure 3A–E) to studies with ≥10 years of follow-up (Figure S4A–E). This was not possible for cognitive decline as most studies had <10 years of follow-up. Therefore, an additional meta-analysis was conducted excluding studies with unclear dementia/cognitive status of participants at baseline (Figure S3A–E).

RESULTS

Forty seven studies were included in this review: 24 for *cognitive decline*[8,9,15–17,42–60] and 23 for *dementia*[10–14,47,61–77] (Figure 1). Characteristics of included studies are summarized in Table S1.

Quality assessment

Quality assessment of included studies is summarized in Table S2 and Supplementary Text S2. For cognitive decline, the overall risk of bias was high; 1 study received "moderate"[56] and 23 "low"[8,9,15–17,42–55,57–60] for overall quality. For dementia, overall risk of bias was moderate; 2 studies receiving "good,"[67,70] 9 "moderate"[10,13,14,64,68,71,72,74,77] and 12 "low"[11,12,47,61–63,65,66,69,73,75,76] for overall quality. In general, studies with dementia as an outcome included younger participants, had a larger sample size and longer study duration, and had better exposure and outcome assessment.

Poor periodontal health and cognitive decline

All 24 studies were population-based longitudinal studies.[8,9,15–17,42–60] 23 studies included both male and female participants,[8,9,15–17,42,43,45–60] and 1 only male participants.[44] 15 studies included participants aged ≥65 years at baseline,[8,15–17,43,45,46,49–52,54,55,58,60] while 9 studies also included younger participants.[9,42,44,47,48,53,56,57,59] 8 studies had a sample size of <1000 participants,[15,44,46,49,50,52,55,56] 8 included 1000–5000 participants,[42,43,45,51,53,57–59] and 8 studies >5000 participants.[8,9,16,17,47,48,54,60] 16 studies had a follow-up period ≤6 years,[9,15,17,42,43,45–47,49–55,58] 7 between 7 and 13 years,[8,16,48,56,57,59,60] and 1 of 32 years.[44] 9 of the 24 studies had >40% subject attrition.[15,17,42,45,46,48,50,53,57] There was great variability in periodontal health assessment. Two studies used Centers for Disease Control and Prevention (CDC)/American Academy of Periodontology (AAP) criteria to diagnose periodontitis,[49,55] 2 used Community Periodontal Index (CPI),[51,52] and 1 Biofilm-gingival interface classification (BGI).[56] 4 studies used PPDs,[15,43,44,50] 2 ABL,[42,44] and 1 gingival bleeding[47] to assess periodontal health. Tooth loss was used by 21 studies,[8,9,16,17,42–48,50–54,56–60] with 11 using self-reported tooth count.[8,9,16,17,47,48,54,57–60]

Cognitive status was assessed through at least 1 cognitive test in 22 studies,[8,9,15,16,42–52,54–60] while 2 studies used subjective assessment.[17,53] 14 of the 22 studies used a single cognitive test[15,16,42,45–50,54,55,57–59] with MMSE used by 15 studies.[15,16,42–44,46–49,51,52,54,55,57,58] Others included some form of recall test,[51,52,59,60] digit symbol substitution test,[43,56] TICS-m,[8,60] Montreal cognitive assessment,[45,50] word fluency,[56] clock drawing test,[43] and SCT.[44] Most studies defined "cognitive decline" as the difference in scores between baseline and follow-up, without a validated well-defined threshold, without clearly using available MCI definitions, and without explicitly excluding

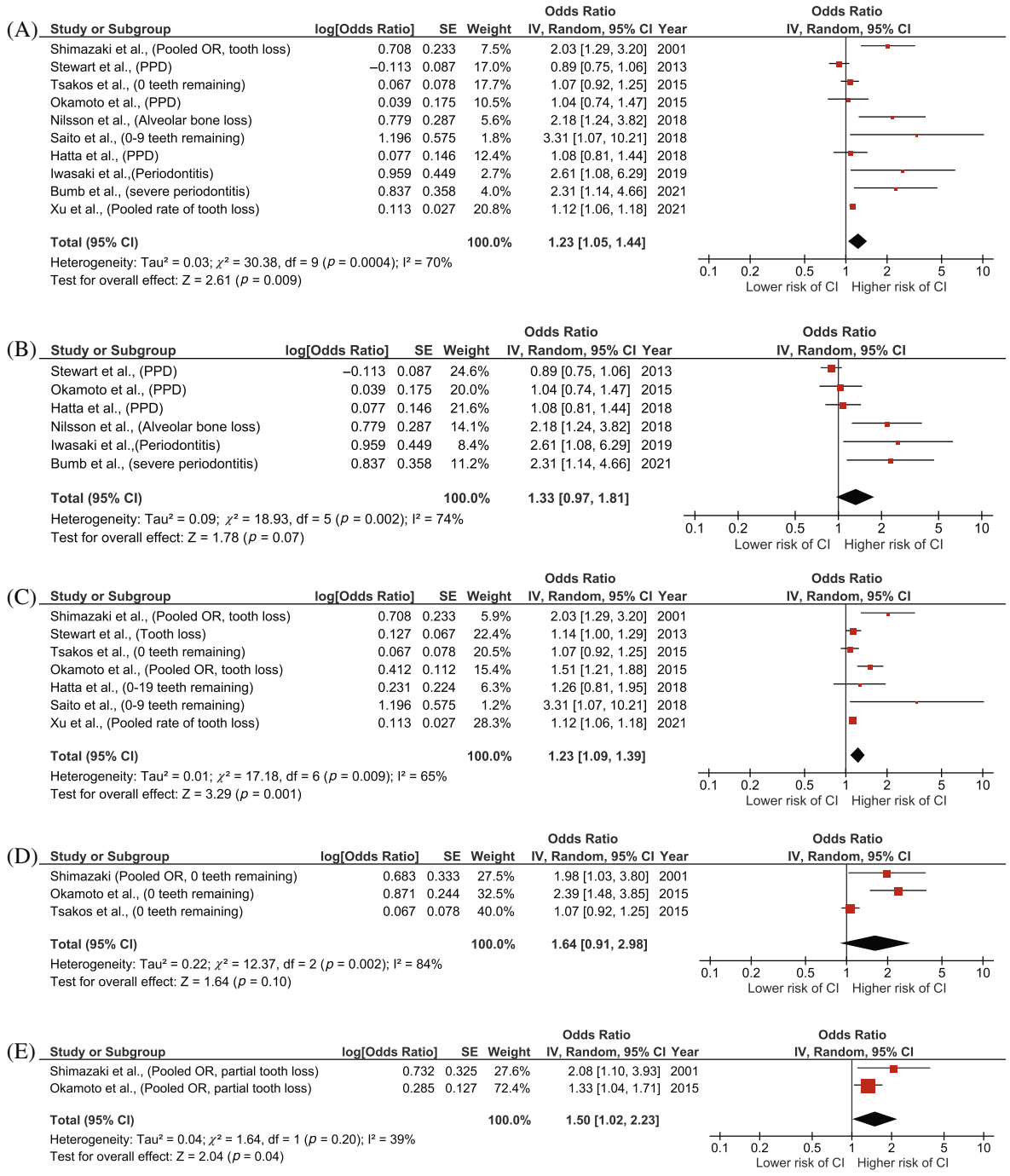

FIGURE 2 Meta-analysis for association between Poor Periodontal Health and Cognitive Decline. (A) Association of Poor Periodontal Health* and Cognitive Decline. *Periodontitis, PPDs, ABL, and tooth loss. (B) Association of Periodontitis-specific measures* and Cognitive Decline. *Periodontitis, PPDs, and ABL. (C) Association of Tooth Loss (low vs. high tooth count) and Cognitive Decline. (D) Association of Complete Tooth Loss (0 teeth remaining vs. at least 1 teeth remaining) and Cognitive Decline. (E) Association of Partial Tooth Loss (low tooth count vs. high tooth count, excluding 0 teeth remaining) and Cognitive Decline.

participants with incident dementia. Studies with "cognitive impairment" as an outcome used, for example, MMSE at follow-up with a threshold of <24 or <25, but no formal MCI diagnosis.

Associations

Twenty studies reported a significant association between at least 1 measure of periodontal health and cognitive decline,

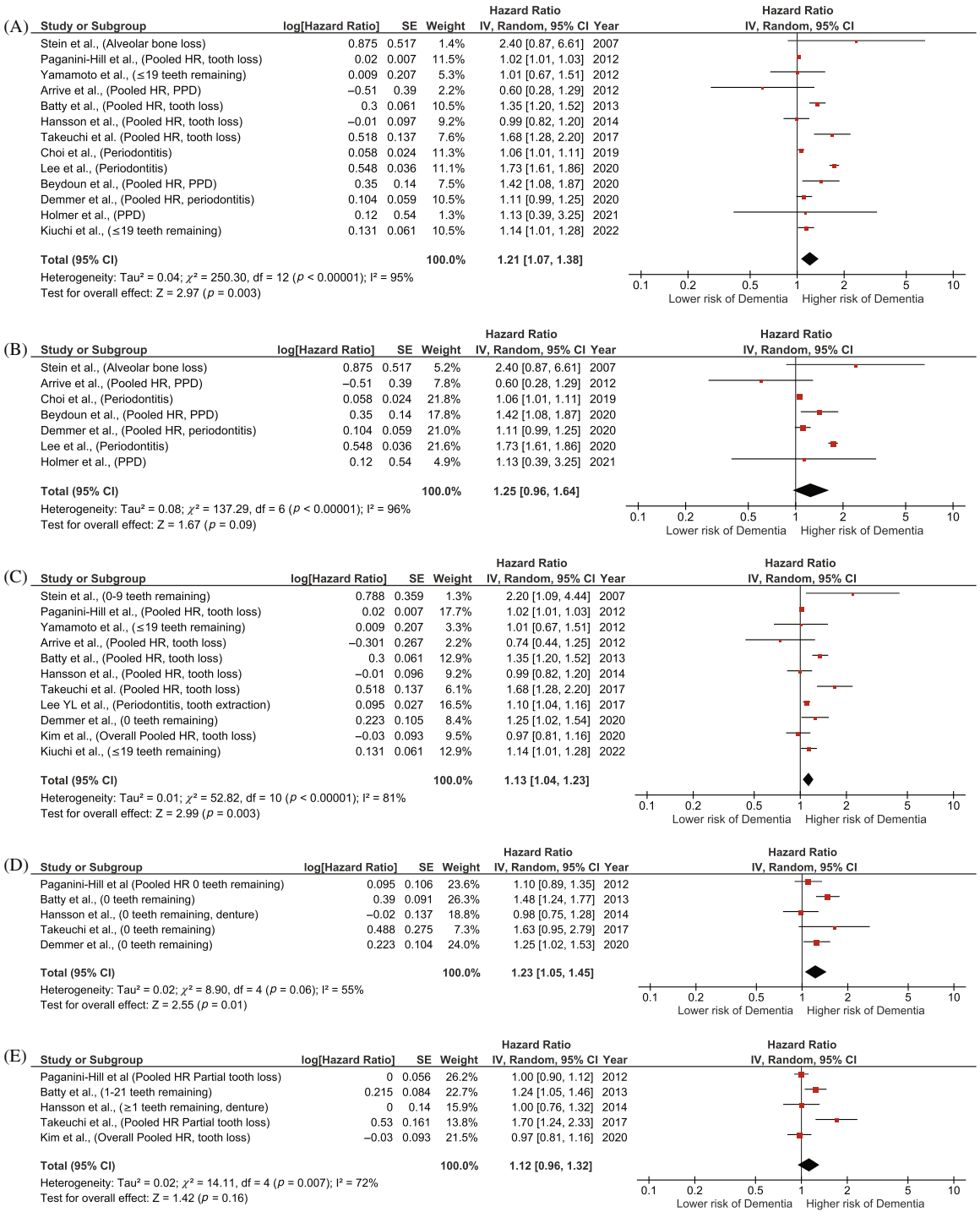

FIGURE 3 Meta-analysis for association between Poor Periodontal Health and Dementia. (A) Association of Poor Periodontal Health* and Dementia. *Periodontitis, PPDs, ABL, and tooth loss. (B) Association of Periodontitis-specific measures* and Dementia. *Periodontitis, PPDs, and ABL. (C) Association of Tooth Loss (low vs. high tooth count) and Dementia. (D) Association of Complete Tooth Loss (0 teeth remaining vs. at least 1 teeth remaining) and Dementia. (E) Association of Partial Tooth Loss (low tooth count vs. high tooth count, excluding 0 teeth remaining) and Dementia.

that is, higher risk of cognitive decline in individuals having either low tooth count, a higher number of extracted teeth, having periodontitis, deeper periodontal pockets, or alveolar bone loss[8,9,15–17,42,44–49,51,52,54–58,60] (Table S1).

Periodontitis-specific measures

Two of the 5 studies with periodontitis as exposure observed significant association.[49,55] Two of the 4 studies

with PPDs[15,44] and both studies with ABL[42,44] reported a significant association.

Tooth loss

Eighteen of the 21 studies with tooth loss as exposure observed significant association for at least 1 category of low tooth count.[8,9,16,17,42–48,51,52,54,56–58,60]

Poor periodontal health and dementia

All 23 studies were population-based longitudinal studies.[10–14,47,61–77] 21 studies were composed of male and female participants[10–14,47,61,62,64–68,70–77] and 2 had only female participants.[63,69] 8 studies included participants aged ≥65 years at baseline,[11,13,14,62,63,65,68,73] while 15 studies also included younger participants.[10,12,47,61,64,66,67,69–72,74–77] 4 studies had a sample size of <1000 participants,[62,63,65,69] 3 between 1000 and 5000,[61,66,73] 11 between 5000 and 100,000,[10–13,47,64,67,68,70,74,75] and five studies >100,000 participants.[14,71,72,76,77]

Study duration of 5 studies was ≤6 years,[11,12,47,61,66] 11 between 7 and 13 years,[13,14,62–64,68,71,72,74,76,77] and 7 of ≥14 years.[10,61,65,67,69,70,75] 21 of the 23 studies had <20% subject attrition.[10,12–14,47,61–69,71–77] There was great variability in periodontal health assessment. Six studies diagnosed periodontitis according to International Statistical Classification of Disease (ICD) criteria[64,68,71,74,76,77] and 1 by periodontal profile classes.[70] 3 studies used PPDs,[12,62,65] 1 ABL,[63] and 1 CAL.[62] 15 studies used tooth loss,[10,11,13,14,47,61,63,65–67,69,72,73,75,76] of which four studies assessed tooth loss through available data on tooth extraction[13,14,72,76] and 5 used self-reported tooth count.[11,47,61,73,75] All 23 studies diagnosed dementia according to standardized criteria: 11 used ICD,[10,12–14,62,64,68,71,72,76,77] 8 used DSM,[47,61,65,66,69,70,74,75] and 1 used Korean Classification of Disease (KCD) criteria.[67] 3 studies used other criteria/methods of identifying dementia, consistent with standardized criteria.[11,63,73]

Associations

Eighteen studies reported a significant association between at least 1 measure of periodontal health and dementia (Table S1).

Periodontitis-specific measures

All seven studies with periodontitis as exposure observed significant association.[64,68,71,74,76,77] 1 of the 3 studies with PPDs as exposure observed significant association.[62]

Tooth loss

Ten studies observed significant association between at least one category of low tooth count and dementia.[10,11,13,47,66,67,69,72,73,76] However, one study observed a significantly lower risk of dementia in individuals with low tooth count.[65]

Meta-analysis

Poor periodontal health and cognitive decline

For *cognitive decline*, pooled OR was generated (Figure 2A–E). Primary model (Figure 2A) included 10 studies and showed a significantly higher risk of cognitive decline in individuals with poor periodontal health, OR (95% CI) = 1.23 (1.05–1.44). Analysis based on measures of periodontal assessment found tooth loss to be independently associated with cognitive decline, OR (95% CI) = 1.23 (1.09–1.39) (Figure 2C). On stratification of tooth loss into complete (Figure 2D) and partial tooth loss (Figure 2E), only partial tooth loss (included only two studies) was associated with cognitive decline, OR (95% CI) = 1.50 (1.02–2.23). Apart from the model for partial tooth loss, all models carried high values of I^2 (>50) reflecting significant heterogeneity between studies. Figure S1A–E, where individual categories of periodontal health were entered, corroborated with the main analysis.

Poor periodontal health and dementia

For *dementia*, pooled HR was generated (Figure 3A–E). Primary model included 13 studies and showed increased dementia risk linked to poor periodontal health, HR (95% CI) = 1.21 (1.07–1.38). When the analysis was stratified into periodontitis-specific measures (Figure 3B) and tooth loss (Figure 3C), tooth loss was independently associated with dementia, HR (95% CI) = 1.13 (1.04–1.23) (Figure 3C). On stratification of tooth loss into complete (Figure 3D) and partial tooth loss (Figure 3E), complete tooth loss was significantly associated with dementia, HR (95% CI) = 1.23 (1.05–1.45) (Figure 3D). Although models for periodontitis-specific measures (Figure 3C) and partial tooth loss (Figure 3E) did not achieve statistical significance, they were in line with other models, however, all models carried high values of I^2 (>50).

Figure S2A–E, where individual categories of periodontal health were entered, corroborated with the main analysis.

Accounting for reverse causality

For dementia, the additional meta-analysis largely corroborated with the main analysis, associating periodontal heath with dementia (Figure S4A–E). However, the association between tooth loss and dementia became statistically non-significant (Figure S4C,D). Contrarily, for cognitive decline, the association became stronger and was significant across all models (Figure S3A–E), even for periodontitis-specific measures and complete tooth loss which were not significant in the main analysis (Figure 2B,D). Interestingly, these associations were stronger compared to the association between poor periodontal health and dementia.

DISCUSSION

We performed a comprehensive systematic review and meta-analysis and observed significant associations between poor periodontal health with risk of cognitive decline and dementia. Poor periodontal health, overall tooth loss, and complete tooth loss were associated with dementia; poor periodontal health, overall tooth loss, and partial tooth loss were associated with cognitive decline. However, overall quality of evidence was low. Most studies had a high risk of bias, particularly cognitive decline studies, which mainly involved participants aged ≥65 years, had a shorter follow-up, and involved heterogenous exposure (e.g., tooth count, PPDs, ABL) and outcome assessments (different cognitive tests).

Impact of reverse causality

Analysis of dementia studies with ≥10 years of follow-up showed an overall weakening of the effect of poor periodontal health on dementia as compared to the main analysis, with estimates for tooth loss becoming statistically non-significant. This indicates that part of the associations observed in the main analysis (which also included studies with a shorter follow-up) was due to reverse causality. Since neuropathological and cognitive changes leading to dementia develop over many years, a study duration <10 years is less likely to remove the potential effects of cognitive impairment on periodontal health.

Interestingly, in additional analyses excluding studies where dementia/cognitive status at baseline was unclear, poor periodontal health had stronger associations with cognitive decline across all models, that is, all measures of poor periodontal health, periodontitis-specific measures, overall tooth loss, complete tooth loss, and partial tooth loss. This unexpected finding may have two main explanations. It is possible that periodontal health is a risk factor for multiple types and severity levels of cognitive decline (not just dementia), and the broad definition of cognitive decline in available studies captured the full range of effects. However, the stronger associations may still partly reflect reverse causality, since participants with dementia at follow-up were not explicitly excluded from these studies, and the shorter follow-up (<10 years) predisposes them to reverse causality effects.

This pattern of stronger associations with shorter study duration has been previously described for other risk factors for cognitive decline and dementia, for example, depression (which can also be a prodromal dementia symptom).[78] Our findings emphasize the crucial need for improving the design of periodontal-cognitive health studies, with particular focus on sufficient follow-up time and thorough data analytical consideration of cognitive impairment and dementia status at both baseline and follow-up visits.

Mechanisms underlying periodontal-cognitive associations

The findings of this review might indicate the involvement of multiple mechanisms in the association between periodontal and cognitive health. Periodontitis is suggested to facilitate the development of neuroinflammation via systemic inflammation, evident by increased systemic proinflammatory mediators.[79] Systemic inflammation per se is an independent determinant of cognitive deterioration and links other risk factors including diabetes, hypertension, hypercholesterolemia, and even aging to cognitive deterioration.[80,81] Additionally, a more direct role of periodontal pathogens has been suggested, adding to the increasing body of evidence concerning possible infectious etiology of cognitive deterioration.[82,83]

Tooth loss may also independently impair cognition by reducing sensorimotor stimulation from masticatory apparatus which has been linked to atrophic brain changes. This association might depend on factors like magnitude/dose and length of exposure.[25,84] An insight into this possible dose-dependent effect is provided by our finding of somewhat higher ORs/HRs for complete versus partial tooth loss. Furthermore, non-traumatic/non-surgical causes of tooth loss (e.g., dental caries and periodontitis) lead to gradual and progressive tooth loss over decades. If the extent of tooth loss indicates chronicity of the underlying process (e.g., periodontitis) then higher chronicity (as

reflected by complete tooth loss) might be more likely to lead to cognitive deterioration. But current evidence concerning this is scant and lacks specific details (e.g., exact causes and time of tooth loss), however, it points to an important direction for future research.

The impact of periodontal health on cognition may also be more pronounced during a specific time window (e.g., midlife), as reported for other dementia risk factors.[85] This may explain the protective effect of low tooth count against dementia observed in individuals with lower education.[65] Low education is known to increase the risk of early tooth loss,[86] thus may decrease the periodontal inflammatory burden and its subsequent impact on cognition at midlife.[87] Furthermore, nutritional imbalances (e.g., antioxidants, vitamin B and E, etc.) and reduction in cerebral blood flow might also link tooth loss with cognitive deterioration.[88] The periodontal-cognitive health association may additionally be mediated by common risk factors such as systemic comorbidities, depression, lower education, and socioeconomic status.[5,89]

Strengths and limitations

While previous reviews mostly focused on either periodontitis or tooth loss alone, or on cognitive decline or

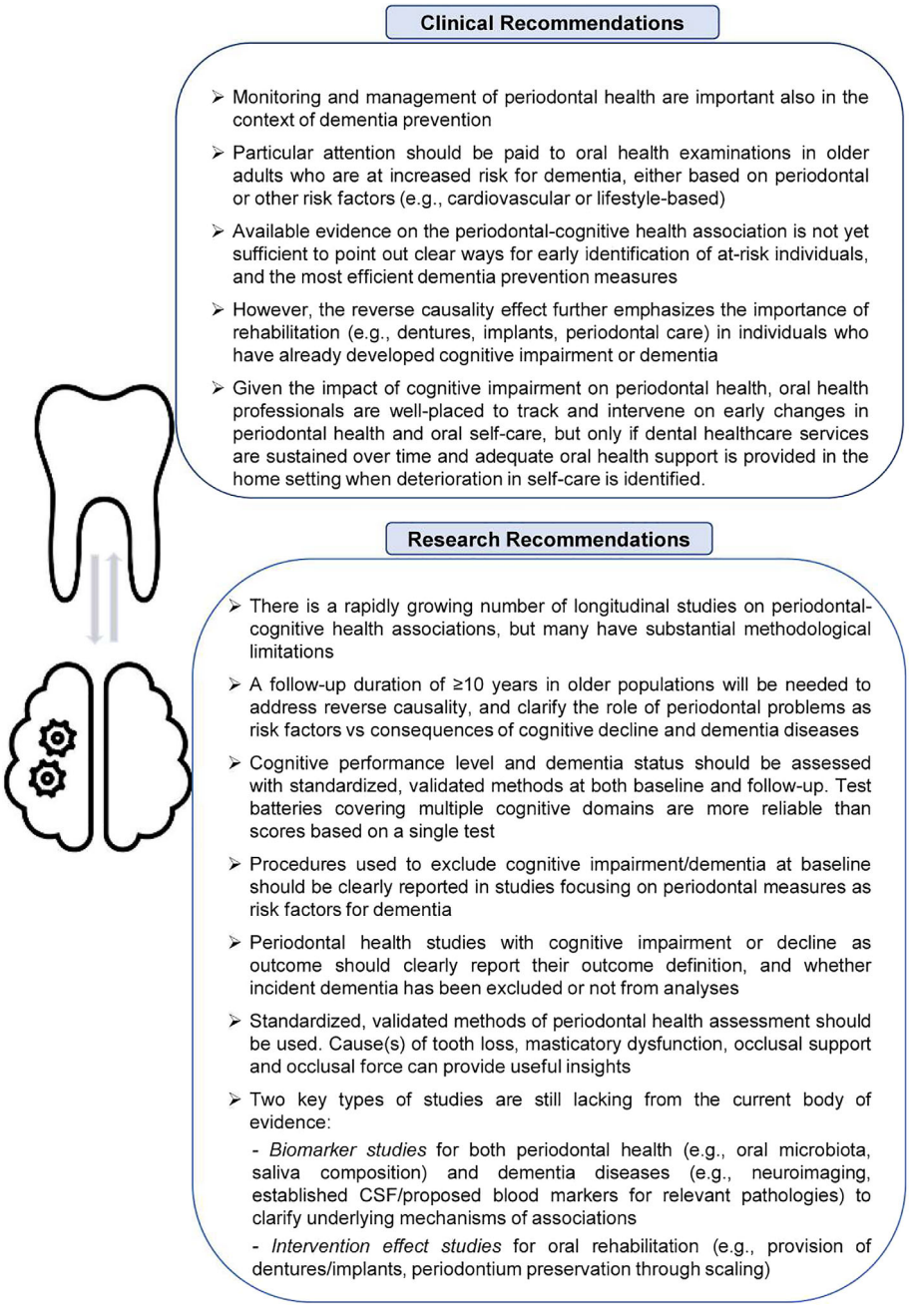

FIGURE 4 Research and clinical recommendations

dementia alone, this review covered the whole spectrum of periodontal deterioration including tooth loss. Although tooth loss may occur due to causes other than periodontitis, periodontal disease is one of the most common causes of tooth loss at older ages, when dementia is also most likely to occur. Furthermore, cognitive decline and dementia are part of a continuum, from normal aging to first asymptomatic, then prodromal, and later fully manifest disease. In this review, we examined both these outcomes and synthesized evidence across the cognitive functioning continuum.

To our knowledge, this systematic review included so far the largest number of longitudinal studies ($N = 47$), facilitating a better powered and more robust meta-analysis evaluating and strengthening the existing evidence. Previous meta-analyses did not account for multiple effect estimates originating from a single cohort and combined different effect estimate types, which may have affected the pooled estimates. We have addressed this by incorporating one estimate from each cohort and generating pooled estimates from comparable effect estimate types. We also accounted for reverse causality in our analysis.

The limitations of this work include consideration of English language publications only. Quality assessment criteria might also have limitations on internal validity. Moreover, it was not possible to account for periodontal treatment, severity, and length of exposure. In the case of tooth loss, the exact cause was not known. Due to substantial variability in cognitive tests and definitions of cognitive decline in included studies, it was not possible to reliably separate pathological impairment/MCI from other types of cognitive decline (e.g., age-related) that may not necessarily progress to dementia. Also, available cognitive decline studies did not clearly specify if incident dementia had been excluded from their analyses.

CONCLUSIONS AND FUTURE DIRECTIONS

Poor periodontal health may increase the risk of both cognitive decline and dementia. The overall quality of evidence was low, and several areas of periodontal-cognitive health interplay remain to be investigated. From a clinical perspective, our findings emphasize the importance of monitoring and management of periodontal health in the context of dementia prevention, although the available evidence is not yet sufficient to point out clear ways for early identification of at-risk individuals, and the most efficient measures to prevent cognitive deterioration. However, given the impact of cognitive deterioration on periodontal health, oral health professionals are well-placed to track and intervene in early changes in periodontal health and oral self-care, but only if dental healthcare services are sustained over time and adequate oral health support is provided in the home setting when deterioration in self-care is identified. Importantly, our results clearly indicate several key recommendations for future studies on periodontal and cognitive health to improve the state of current evidence and address these gaps (Figure 4).

AUTHOR CONTRIBUTIONS

Conceptualization: Sam Asher, Ruth Stephen, Anna Liisa Suominen, Päivi Mäntylä, and Alina Solomon. *Methodology*: Sam Asher, Ruth Stephen, Anna Liisa Suominen, and Alina Solomon. *Data analysis*: Sam Asher and Alina Solomon. *Supervision*: Anna Liisa Suominen, Päivi Mäntylä, and Alina Solomon. *Manuscript writing*: Sam Asher, Ruth Stephen, and Alina Solomon. *Reviewing*: Sam Asher, Ruth Stephen, Anna Liisa Suominen, Päivi Mäntylä, and Alina Solomon.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

SPONSOR'S ROLE

The funding sources had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

ORCID

Sam Asher https://orcid.org/0000-0003-3093-4720

REFERENCES

1. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7(2):e105-e125. doi:10.1016/S2468-2667(21)00249-8
2. Pais R, Ruano L, Carvalho OP, Barros H. Global cognitive impairment prevalence and incidence in community dwelling older adults-a systematic review. *Geriatrics (Basel)*. 2020;5(4):1-16. doi:10.3390/GERIATRICS5040084
3. McGrattan AM, Pakpahan E, Siervo M, et al. Risk of conversion from mild cognitive impairment to dementia in low- and middle-income countries: a systematic review and meta-analysis. *Alzheimers Dement (N Y)*. 2022;8(1):e12267. doi:10.1002/TRC2.12267
4. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol*. 2014;10(11):634-642. doi:10.1038/NRNEUROL.2014.181
5. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6

6. de Havenon A, Anadani M, Prabhakaran S, Wong KH, Yaghi S, Rost N. Increased blood pressure variability and the risk of probable dementia or mild cognitive impairment: a post hoc analysis of the SPRINT MIND trial. *J Am Heart Assoc*. 2021;10(18):e022206. doi:10.1161/JAHA.121.022206
7. Rosenberg A, Mangialasche F, Ngandu T, Solomon A, Kivipelto M. Multidomain interventions to prevent cognitive impairment, Alzheimer's disease, and dementia: from FINGER to world-wide FINGERS. *J Prev Alzheimers Dis*. 2020;7(1):29-36. doi:10.14283/JPAD.2019.41
8. Luo H, Tan C, Adhikari S, et al. Effects of the co-occurrence of diabetes mellitus and tooth loss on cognitive function. *Curr Alzheimer Res*. 2021;18(13):1023-1031. doi:10.2174/1567205019666211223093057
9. Khalaila R, Vitman-Schorr A, Cohn-Schwartz E. A prospective association between tooth status and cognitive performance among older adults in Europe. *Aging Ment Health*. 2022;26(3):499-506. doi:10.1080/13607863.2021.1891201
10. Kim JH, Oh JK, Wee JH, Kim YH, Byun SH, Choi HG. Association between tooth loss and Alzheimer's disease in a nested case-control study based on a National Health Screening Cohort. *J Clin Med*. 2021;10(17):3763. doi:10.3390/jcm10173763
11. Kiuchi S, Cooray U, Kusama T, et al. Oral status and dementia onset: mediation of nutritional and social factors. *J Dent Res*. 2022;101(4):420-427. doi:10.1177/00220345211049399
12. Holmer J, Eriksdotter M, Häbel H, et al. Periodontal conditions and incident dementia: a nationwide Swedish cohort study. *J Periodontol*. Published online January 31, 2022. 1. doi:10.1002/jper.21-0518
13. Tsai YC, Wang HJ, Wang LY, et al. Retrospective analysis of the association between tooth loss and dementia: a population-based matched case-control study. *Community Dent Health*. 2020;37(1):59-64. doi:10.1922/CDH_4609Tsai06
14. Lin JW, Chang CH, Caffrey JL. Examining the association between oral health status and dementia: a nationwide nested case-controlled study. *Exp Biol Med*. 2020;245(3):231-244. doi:10.1177/1535370220904924
15. Bumb SS, Govindan CC, Kadtane SS, Chawla R, Gupta R, Khoriya SS. Association between cognitive decline and oral health status in the aging population: a 5-year observational study. *GeroPsych: J Gerontopsychol Geriatr Psychiatry*. Published online 2021. doi:10.1024/1662-9647/a000271
16. Yang HL, Li FR, Chen PL, Cheng X, Chen M, Wu XB. Tooth loss, denture use and cognitive impairment in Chinese older adults: a community cohort study. *J Gerontol A Biol Sci Med Sci*. Published online 2021. doi:10.1093/gerona/glab056
17. Kiuchi S, Kusama T, Sugiyama K, et al. Longitudinal association between oral status and cognitive decline using fixed-effects analysis. *J Epidemiol*. Published online 2021. doi:10.2188/jea.je20200476
18. Petersen PE, Ogawa H. The global burden of periodontal disease: towards integration with chronic disease prevention and control. *Periodontol 2000*. 2012;60(1):15-39. doi:10.1111/J.1600-0757.2011.00425.x
19. Engebretson SP, Lalla E, Lamster IB. Periodontitis and systemic disease. *BDJ Team*. 2015;2(10):1-4. doi:10.1038/bdjteam.2015.163
20. Qi X, Zhu Z, Plassman BL, Wu B. Dose-response meta-analysis on tooth loss with the risk of cognitive impairment and dementia. *J Am Med Dir Assoc*. 2021;22(10):2039-2045. doi:10.1016/j.jamda.2021.05.009
21. Oh B, Han DH, Han KT, et al. Association between residual teeth number in later life and incidence of dementia: a systematic review and meta-analysis. *BMC Geriatr*. 2018;18(1):48. doi:10.1186/s12877-018-0729-z
22. Guo H, Chang S, Pi X, et al. The effect of periodontitis on dementia and cognitive impairment: a meta-analysis. *Int J Environ Res Public Health*. 2021;18(13):6823. doi:10.3390/IJERPH18136823
23. Hu X, Zhang J, Qiu Y, Liu Z. Periodontal disease and the risk of Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. *Psychogeriatrics*. 2021;21(5):813-825. doi:10.1111/PSYG.12743
24. Fang WL, Jiang MJ, Gu BB, 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. doi:10.1186/S12888-018-1927-0
25. Chen J, Ren CJ, Wu L, et al. Tooth loss is associated with increased risk of dementia and with a dose-response relationship. *Front Aging Neurosci*. 2018;10:415. doi:10.3389/FNAGI.2018.00415
26. Orr ME, Reveles KR, Yeh CK, Young EH, Han X. Can oral health and oral-derived biospecimens predict progression of dementia? *Oral Dis*. 2020;26(2):249-258. doi:10.1111/ODI.13201
27. Alvarenga MOP, Frazão DR, de Matos IG, et al. Is there any association between neurodegenerative diseases and periodontitis? A systematic review. *Front Aging Neurosci*. 2021;13:651437. doi:10.3389/FNAGI.2021.651437
28. Nangle MR, Riches J, Grainger SA, Manchery N, Sachdev PS, Henry JD. Oral health and cognitive function in older adults: a systematic review. *Gerontology*. Published online 2018. doi:10.1159/000496730
29. Nadim R, Tang J, Dilmohamed A, et al. Influence of periodontal disease on risk of dementia: a systematic literature review and a meta-analysis. *Eur J Epidemiol*. 2020;35:821-833. doi:10.1007/s10654-020-00648-x
30. Nascimento PC, Castro MML, Magno MB, et al. Association between periodontitis and cognitive impairment in adults: a systematic review. *Front Neurol*. 2019;10:323. doi:10.3389/FNEUR.2019.00323/BIBTEX
31. Oral Health Conditions, Division of Oral Health, CDC. Periodontal Disease. Accessed May 17, 2022. https://www.cdc.gov/oralhealth/conditions/periodontal-disease.html
32. Chan AKY, Tamrakar M, Jiang CM, Lo ECM, Leung KCM, Chu CH. Common medical and dental problems of older adults: a narrative review. *Geriatrics*. 2021;6(3):76. doi:10.3390/GERIATRICS6030076
33. National Institute of Dental and Craniofacial Research. Periodontal (Gum) Disease. Accessed June 8, 2022. https://www.nidcr.nih.gov/research/data-statistics/periodontal-disease
34. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med*. 2014;275(3):214-228. doi:10.1111/joim.12190
35. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256(3):240-246. doi:10.1111/J.1365-2796.2004.01380.x

36. Stephen R, Hongisto K, Solomon A, Lönnroos E. Physical activity and Alzheimer's disease: a systematic review. *J Gerontol A Biol Sci Med Sci*. 2017;72(6):733-739. doi:10.1093/gerona/glw251
37. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394. doi:10.1016/j.jclinepi.2010.04.026
38. Manager CCR. RevMan. Accessed July 27, 2022. https://training.cochrane.org/online-learning/core-software/revman
39. Kaliamoorthy S, Nagarajan M, Sethuraman V, Jayavel K, Lakshmanan V, Palla S. Association of Alzheimer's disease and periodontitis - a systematic review and meta-analysis of evidence from observational studies. *Med Pharm Rep*. 2022;95(2):144-151. doi:10.15386/MPR-2278
40. Gusman DJR, Mello-Neto JM, Alves BES, et al. Periodontal disease severity in subjects with dementia: a systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2018;76:147-159. doi:10.1016/J.ARCHGER.2018.02.016
41. Besser LM, Brenowitz WD, Meyer OL, Hoermann S, Renne J. Methods to address self-selection and reverse causation in studies of neighborhood environments and brain health. *Int J Environ Res Public Health*. 2021;18(12):6484. doi:10.3390/IJERPH18126484
42. Nilsson H, Sanmartin Berglund J, Renvert S. Longitudinal evaluation of periodontitis and development of cognitive decline among older adults. *J Clin Periodontol*. 2018;45(10):1142-1149. doi:10.1111/jcpe.12992
43. Stewart R, Weyant RJ, Garcia ME, et al. Adverse oral health and cognitive decline: the health, aging and body composition study. *J Am Geriatr Soc*. 2013;61(2):177-184. doi:10.1111/jgs.12094
44. Kaye EK, Valencia A, Baba N, Spiro A, Dietrich T, Garcia RI. Tooth loss and periodontal disease predict poor cognitive function in older men. *J Am Geriatr Soc*. 2010;58(4):713-718. doi:10.1111/j.1532-5415.2010.02788.x
45. Hatta K, Gondo Y, Kamide K, et al. Occlusal force predicted cognitive decline among 70- and 80-year-old Japanese: a 3-year prospective cohort study. *J Prosthodont Res*. 2020;64(2):175-181. doi:10.1016/j.jpor.2019.07.002
46. Saito S, Ohi T, Murakami T, et al. Association between tooth loss and cognitive impairment in community-dwelling older Japanese adults: a 4-year prospective cohort study from the Ohasama study. *BMC Oral Health*. 2018;18(1):142. doi:10.1186/s12903-018-0602-7
47. Batty GD, Li Q, Huxley R, et al. Oral disease in relation to future risk of dementia and cognitive decline: prospective cohort study based on the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial. *Eur Psychiatry*. 2013;28(1):49-52. doi:10.1016/j.eurpsy.2011.07.005
48. Li J, Xu H, Pan W, Wu B. Association between tooth loss and cognitive decline: a 13-year longitudinal study of Chinese older adults. *PLoS ONE*. 2017;12(2):1-12. doi:10.1371/journal.pone.0171404
49. Iwasaki M, Kimura Y, Ogawa H, et al. Periodontitis, periodontal inflammation, and mild cognitive impairment: a 5-year cohort study. *J Periodontal Res*. 2019;54(3):233-240. doi:10.1111/jre.12623
50. Hatta K, Ikebe K, Gondo Y, et al. Influence of lack of posterior occlusal support on cognitive decline among 80-year-old Japanese people in a 3-year prospective study. *Geriatr Gerontol Int*. 2018;18(10):1439-1446. doi:10.1111/ggi.13508
51. Okamoto N, Morikawa M, Tomioka K, Yanagi M, Amano N, Kurumatani N. Association between tooth loss and the development of mild memory impairment in the elderly: the Fujiwara-kyo study. *J Alzheimers Dis*. 2015;44(3):777-786. doi:10.3233/JAD-141665
52. Okamoto N, Morikawa M, Amano N, Yanagi M, Takasawa S, Kurumatani N. Effects of tooth loss and the apolipoprotein E ϵ4 allele on mild memory impairment in the Fujiwara-kyo study of Japan: a nested case-control study. *J Alzheimers Dis*. 2017;55(2):575-583. doi:10.3233/JAD-160638
53. Shimazaki Y, Soh I, Saito T, et al. Influence of dentition status on physical disability, mental impairment, and mortality in institutionalized elderly people. *J Dent Res*. 2001;80(1):340-345. doi:10.1177/00220345010800010801
54. Xu S, Huang X, Gong Y, Sun J. Association between tooth loss rate and risk of mild cognitive impairment in older adults: a population-based longitudinal study. *Aging*. 2021;13(17):21599-21609. doi:10.18632/aging.203504
55. Iwasaki M, Yoshihara A, Kimura Y, et al. Longitudinal relationship of severe periodontitis with cognitive decline in older Japanese. *J Periodontal Res*. 2016;51(5):681-688. doi:10.1111/jre.12348
56. Naorungroj S, Schoenbach VJ, Wruck L, et al. Tooth loss, periodontal disease, and cognitive decline in the Atherosclerosis Risk in Communities (ARIC) study. *Community Dent Oral Epidemiol*. 2015;43(1):47-57. doi:10.1111/cdoe.12128
57. Dintica CS, Rizzuto D, Marseglia A, et al. Tooth loss is associated with accelerated cognitive decline and volumetric brain differences: a population-based study. *Neurobiol Aging*. 2018;67:23-30. doi:10.1016/j.neurobiolaging.2018.03.003
58. Reyes-Ortiz CA, Luque JS, Eriksson CK, Soto L. Self-reported tooth loss and cognitive function: data from the Hispanic established populations for epidemiologic studies of the elderly (Hispanic EPESE). *Colomb Med*. 2013;44(3):139-145. doi:10.25100/cm.v44i3.1248
59. Tsakos G, Watt RG, Rouxel PL, de Oliveira C, Demakakos P. Tooth loss associated with physical and cognitive decline in older adults. *J Am Geriatr Soc*. 2015;63(1):91-99. doi:10.1111/jgs.13190
60. Han SH, Wu B, Burr JA. Edentulism and trajectories of cognitive functioning among older adults: the role of dental care service utilization. *J Aging Health*. 2020;32(7-8):744-752. doi:10.1177/0898264319851654
61. Hansson P, Eriksson Sörman D, Bergdahl J, et al. Dental status is unrelated to risk of dementia: a 20-year prospective study. *J Am Geriatr Soc*. 2014;62(5):979-981. doi:10.1111/jgs.12814
62. Beydoun MA, Beydoun HA, Weiss J, Hossain S, El-Hajj ZW, Zonderman AB. *Helicobacter pylori*, periodontal pathogens, and their interactive association with incident all-cause and Alzheimer's disease dementia in a large national survey. *Mol Psychiatry*. Published online 2020. doi:10.1038/s41380-020-0736-2
63. Stein PS, Desrosiers M, Donegan SJ, Yepes JF, Kryscio RJ. Tooth loss, dementia and neuropathology in the Nun Study. *J*

Am Dent Assoc. 2007;138(10):1314-1322. doi:10.14219/jada.archive.2007.0046
64. Chen CK, Wu YT, Chang YC. Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study. *Alzheimer's Res Therapy*. 2017;9(1):1-7. doi:10.1186/s13195-017-0282-6
65. Arrivé E, Letenneur L, Matharan F, et al. Oral health condition of French elderly and risk of dementia: a longitudinal cohort study. *Community Dent Oral Epidemiol*. 2012;40(3):230-238. doi:10.1111/j.1600-0528.2011.00650.x
66. Takeuchi K, Ohara T, Furuta M, et al. Tooth loss and risk of dementia in the community: the Hisayama study. *J Am Geriatr Soc*. 2017;65(5):e95-e100. doi:10.1111/jgs.14791
67. Kim DH, Jeong SN, Lee JH. Severe periodontitis with tooth loss as a modifiable risk factor for the development of Alzheimer, vascular, and mixed dementia: National Health Insurance Service-National Health Screening Retrospective Cohort 2002-2015. *J Periodontal Implant Sci*. 2020;50(5):303-312. doi:10.5051/jpis.2000600030
68. Lee YT, Lee HC, Hu CJ, et al. Periodontitis as a modifiable risk factor for dementia: a nationwide population-based cohort study. *J Am Geriatr Soc*. 2017;65(2):301-305. doi:10.1111/jgs.14449
69. Stewart R, Stenman U, Hakeberg M, Hägglin C, Gustafson D, Skoog I. Associations between oral health and risk of dementia in a 37-year follow-up study: the prospective population study of women in Gothenburg. *J Am Geriatr Soc*. 2015;63(1):100-105. doi:10.1111/jgs.13194
70. Demmer RT, Norby FL, Lakshminarayan K, et al. Periodontal disease and incident dementia: the Atherosclerosis Risk in Communities Study (ARIC). *Neurology*. 2020;95(12):e1660-e1671. doi:10.1212/WNL.0000000000010312
71. Choi S, Kim K, Chang J, et al. Association of chronic periodontitis on Alzheimer's disease or vascular dementia. *J Am Geriatr Soc*. 2019;67(6):1234-1239. doi:10.1111/jgs.15828
72. Yoo JJ, Yoon JH, Kang MJ, Kim M, Oh N. The effect of missing teeth on dementia in older people: a nationwide population-based cohort study in South Korea. *BMC Oral Health*. 2019;19(1):1-10. doi:10.1186/s12903-019-0750-4
73. Yamamoto T, Kondo K, Hirai H, Nakade M, Aida J, Hirata Y. Association between self-reported dental health status and onset of dementia: a 4-year prospective cohort study of older Japanese adults from the Aichi Gerontological Evaluation Study (AGES) Project. *Psychosom Med*. 2012;74(3):241-248. doi:10.1097/PSY.0b013e318246dffb
74. Tzeng NS, Chung CH, Yeh CB, et al. Are chronic periodontitis and gingivitis associated with dementia? A nationwide, retrospective, matched-cohort study in Taiwan. *Neuroepidemiology*. 2016;47(2):82-93. doi:10.1159/000449166
75. Paganini-Hill A, White SC, Atchison KA. Dentition, dental health habits, and dementia: the Leisure World Cohort Study. *J Am Geriatr Soc*. 2012;60(8):1556-1563. doi:10.1111/j.1532-5415.2012.04064.x
76. 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):1975-1980. doi:10.1111/jgs.14944
77. Lee CY, Chang CC, Lin CS, et al. Risk of dementia in patients with periodontitis and related protective factors: a nationwide retrospective cohort study. *J Clin Periodontol*. 2020;47(12):1428-1436. doi:10.1111/jcpe.13372
78. Stafford J, Chung WT, Sommerlad A, Kirkbride JB, Howard R. Psychiatric disorders and risk of subsequent dementia: systematic review and meta-analysis of longitudinal studies. *Int J Geriatr Psychiatry*. 2022;37(5). doi:10.1002/GPS.5711. online ahead of print version.
79. Desta NT. Pathophysiological association between periodontal disease and Alzheimer's disease: importance of periodontal health in the elderly. *J Oral Biosci*. 2021;63(4):351-359. doi:10.1016/J.JOB.2021.08.007
80. Xie J, van Hoecke L, Vandenbroucke RE. The impact of systemic inflammation on Alzheimer's disease pathology. *Front Immunol*. 2022;12:796867. doi:10.3389/FIMMU.2021.796867
81. Miklossy J, McGeer PL. Common mechanisms involved in Alzheimer's disease and type 2 diabetes: a key role of chronic bacterial infection and inflammation. *Aging*. 2016;8(4):575-588. doi:10.18632/AGING.100921
82. Chi L, Cheng X, Lin L, et al. *Porphyromonas gingivalis*-induced cognitive impairment is associated with gut dysbiosis, neuroinflammation, and glymphatic dysfunction. *Front Cell Infect Microbiol*. 2021;11:755925. doi:10.3389/FCIMB.2021.755925
83. Romanenko M, Kholin V, Koliada A, Vaiserman A. Nutrition, gut microbiota, and Alzheimer's disease. *Front Psych*. 2021;12:712673. doi:10.3389/FPSYT.2021.712673
84. Wang X, Hu J, Jiang Q. Tooth loss-associated mechanisms that negatively affect cognitive function: a systematic review of animal experiments based on occlusal support loss and cognitive impairment. *Front Neurosci*. 2022;16:811335. doi:10.3389/FNINS.2022.811335
85. Wagner M, Grodstein F, Proust-Lima C, Samieri C. Long-term trajectories of body weight, diet, and physical activity from midlife through late life and subsequent cognitive decline in women. *Am J Epidemiol*. 2020;189(4):305-313. doi:10.1093/aje/kwz262
86. Ishikawa S, Konta T, Susa S, et al. Risk factors for tooth loss in community-dwelling Japanese aged 40 years and older: the Yamagata (Takahata) study. *Clin Oral Investig*. 2019;23(4):1753-1760. doi:10.1007/S00784-018-2604-X
87. Thomson WM, Barak Y. Tooth loss and dementia: a critical examination. *J Dent Res*. 2021;100(3):226-231. doi:10.1177/0022034520957233
88. Kossioni AE. The association of poor oral health parameters with malnutrition in older adults: a review considering the potential implications for cognitive impairment. *Nutrients*. 2018;10(11):1709. doi:10.3390/nu10111709
89. Genco RJ, Borgnakke WS. Risk factors for periodontal disease. *Periodontol 2000*. 2013;62(1):59-94. doi:10.1111/J.1600-0757.2012.00457.X

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Appendix S1. Supporting Information.
Text S1. Quality assessment criteria.
Text S2. Results of quality assessment.
Table S1. Descriptive table for included studies.
Table S2. Quality assessment of included studies.

Figure S1. Meta-analysis for association between poor periodontal health and cognitive decline (when individual exposure categories were entered). (A) Association of Poor Periodontal Health* and Cognitive Decline. *Periodontitis, PPDs, ABL, and tooth loss. (B) Association of Periodontitis-specific measures* and Cognitive Decline. *Periodontitis, PPDs, and ABL. (C) Association of Tooth Loss (low vs. high tooth count) and Cognitive Decline. (D) Association of Complete Tooth Loss (0 teeth remaining vs. at least 1 teeth remaining) and Cognitive Decline. (E) Association of Partial Tooth Loss (low tooth count vs. high tooth count, excluding 0 teeth remaining) and Cognitive Decline

Figure S2. Meta-analysis for association between Poor Periodontal Health and Dementia (when individual exposure categories were entered). (A) Association of Poor Periodontal Health* and Dementia. *Periodontitis, PPDs, ABL, and tooth loss. (B) Association of Periodontitis-specific measures* and Dementia. *Periodontitis, PPDs, and ABL. (C) Association of Tooth Loss (low vs. high tooth count) and Dementia. (D) Association of Complete Tooth Loss (0 teeth remaining vs. at least 1 teeth remaining) and Dementia. (E) Association of Partial Tooth Loss (low tooth count vs. high tooth count, excluding 0 teeth remaining) and Dementia.

Figure S3. Meta-analysis for association between poor periodontal health and cognitive decline (when only studies with clear exclusion of dementia and cognitive decline at baseline were included). (A) Association of Poor Periodontal Health* and Cognitive Decline. *Periodontitis, PPDs, ABL, and tooth loss. (B) Association of Periodontitis-specific measures* and Cognitive Decline. *Periodontitis, PPDs, and ABL. (C) Association of Tooth Loss (low vs. high tooth count) and Cognitive Decline. (D) Association of Complete Tooth Loss (0 teeth remaining vs. at least 1 teeth remaining) and Cognitive Decline. (E) Association of Partial Tooth Loss (low tooth count vs. high tooth count, excluding 0 teeth remaining) and Cognitive Decline.

Figure S4. Meta-analysis for association between Poor Periodontal Health and Dementia (when studies with <10 years of follow-up were excluded). (A) Association of Poor Periodontal Health* and Dementia. *Periodontitis, PPDs, ABL, and tooth loss. (B) Association of Periodontitis-specific measures* and Dementia. *Periodontitis, PPDs, and ABL. (C) Association of Tooth Loss (low vs. high tooth count) and Dementia. (D) Association of Complete Tooth Loss (0 teeth remaining vs. at least 1 teeth remaining) and Dementia. (E) Association of Partial Tooth Loss (low tooth count vs. high tooth count, excluding 0 teeth remaining) and Dementia.

How to cite this article: Asher S, Stephen R, Mäntylä P, Suominen AL, Solomon A. Periodontal health, cognitive decline, and dementia: A systematic review and meta-analysis of longitudinal studies. *J Am Geriatr Soc*. 2022;70(9): 2695-2709. doi:10.1111/jgs.17978