ISSN: 3068-918X
Journal of Neuro and Oncology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

The Oral-Brain Axis: Periodontal Pathogens, Neuroinflammation and Alzheimer's Disease: A Narrative Review

Lucia Argüello-Lacayo[1*], Marcela Paez-Sierra[2], Maria Arroyo-Hinojosa[3], Joanith Medina-Barreto[4], Karla Aholibama-Argueta[5], Paulina Ramos-Avila[6]

[1]UNINGA, Brasil, MSc. Bucomaxilofacial, Universidad Católica de Honduras
[2]Institución Universitaria Colegios de Colombia, Colombia
[3]Universidad Tecnológica de Mexico, Mexico
[4]Universidad de Carabobo, Venezuela
[5]Universidad Evangélica de El Salvador, El Salvador
[6]Universidad Autónoma del Estado de Hidalgo, Mexico

***Correspondence author:** Lucia Argüello-Lacayo, UNINGA, Brasil, MSc. Bucomaxilofacial, Universidad Católica de Honduras;
Email: research@idpathwaysllc.com

Citation: Argüello-Lacayo L, et al. The Oral-Brain Axis: Periodontal Pathogens, Neuroinflammation and Alzheimer's Disease: A Narrative Review. J Neuro Onco Res. 2026;6(3):1-10.

https://doi.org/10.46889/JNOR.2026.

Received Date: 27-08-2026

Accepted Date: 14-10-2026

Published Date: 21-10-2026

Copyright: © 2026 The Authors. Published by Athenaeum Scientific Publishers.

This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

License URL:

https://creativecommons.org/licenses/by/4.0/

Abstract

Periodontitis and Alzheimer's Disease (AD) are prevalent age-associated conditions increasingly linked through the proposed oral–brain axis, in which periodontal dysbiosis and persistent inflammation may compromise blood–brain barrier integrity, activate microglia and sustain neuroinflammation. This narrative review evaluates evidence connecting periodontal pathogens and inflammatory mediators to neurodegeneration, distinguishing cognitive decline, all-cause dementia and AD as separate outcomes and labeling preclinical and human evidence explicitly. Epidemiological data show a modest association between poor periodontal health and cognitive decline, with pooled estimates near RR 1.2 to 1.3 and a shallow severity gradient. Mechanistic work supports plausibility through hematogenous dissemination of bacterial products and transport along peripheral nerves, while systemic elevation of IL-1β, IL-6, TNF-α and IL-17 offers an inflammatory bridge to glial activation and oxidative stress. Detection of Porphyromonas gingivalis components in postmortem brain tissue does not establish viable infection. Countervailing evidence is substantial: two large prospective cohorts found no association with incident dementia, bidirectional Mendelian randomization found no genetic causal relationship and dementia itself increases subsequent periodontitis risk, supporting reverse causation. Periodontitis therefore represents a biologically plausible, potentially modifiable correlate of cognitive decline rather than an established cause of AD, pending adequately powered interventional trials with long-term cognitive endpoints.

Keywords: Alzheimer's Disease; Periodontitis; Oral–Brain Axis; Neuroinflammation; Periodontal Pathogens; Blood–Brain Barrier; Periodontal Therapy; Cognitive Decline; Dementia; Biomarkers

Introduction

This structured narrative review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) rather than as a systematic review. We searched PubMed and Europe PMC for English-language records published principally within the last five years, with seminal earlier work retained where it established a concept, metric or mechanism still in use, using combinations of the terms periodontitis, periodontal disease, periodontal pathogens, Porphyromonas gingivalis, oral–brain axis, oral microbiome, Alzheimer's disease, dementia, cognitive decline, neuroinflammation, blood–brain

barrier, microglia and periodontal therapy. We prioritized systematic reviews, meta-analyses, longitudinal cohorts, Mendelian randomization studies and randomized or interventional trials and hand-searched the reference lists of retrieved articles for additional records. Two authors screened records by title and abstract and assessed full texts against these criteria, resolving disagreements by discussion. Consistent with a narrative design, no formal risk-of-bias instrument, PRISMA flow diagram or quantitative synthesis was applied; the strength of each body of evidence is appraised qualitatively and preclinical and human findings are labeled explicitly throughout. [Authors: please confirm the exact month and year the final search was run.

The Oral–Brain Axis: Biological Basis Linking Periodontal Disease and Neurodegeneration

Periodontitis and Alzheimer's Disease (AD) are highly prevalent chronic disorders whose incidence increases substantially with aging. Periodontitis is characterized by dysbiotic microbial communities and a persistent host inflammatory response that progressively damages the periodontal supporting tissues, whereas AD is a multifactorial neurodegenerative disorder characterized by cognitive decline, amyloid-β accumulation, tau pathology, synaptic dysfunction and chronic neuroinflammation. Epidemiological and longitudinal evidence increasingly associates periodontal disease with cognitive impairment and dementia. Association alone, however, does not establish causality, because the two conditions share important determinants including advanced age, smoking, diabetes, hypertension, socioeconomic circumstance and altered immune regulation [1,2].

Three terms are distinguished throughout this review, because the literature often uses them interchangeably. Cognitive decline denotes a measurable worsening of cognitive performance that need not reach a diagnostic threshold; dementia denotes an acquired syndrome of cognitive impairment severe enough to compromise daily function, of which AD is the most common but not the only cause; and AD denotes the specific neuropathological entity defined by amyloid-β and tau pathology and, increasingly, by fluid or imaging biomarkers. Much of the epidemiological evidence links periodontitis to cognitive decline or all-cause dementia rather than to biomarker- or autopsy-confirmed AD and we retain each study's own outcome definition rather than conflating them [2,26].

The oral–brain axis describes the biological communication pathways through which oral microbial dysbiosis and periodontal inflammation may influence the Central Nervous System (CNS) and through which neurological deterioration may reciprocally impair oral health. Periodontitis is a particularly relevant model because the chronically ulcerated periodontal pocket offers repeated opportunity for bacterial products and locally generated inflammatory mediators to enter the systemic circulation. Periodontal inflammation may therefore extend beyond the oral cavity through two interconnected routes: hematogenous dissemination of microorganisms or their components and systemic propagation of inflammatory signals that can influence distant tissues [3,4].

The Blood–Brain Barrier (BBB) constitutes a critical interface within this axis. Under physiological conditions, brain microvascular endothelial cells, tight junctions, pericytes and astrocytic processes restrict entry of circulating pathogens, toxins and inflammatory molecules while maintaining CNS homeostasis. Chronic systemic inflammation may alter both endothelial function and barrier integrity. In a preclinical model, Porphyromonas gingivalis bacteremia increased BBB permeability through an Mfsd2a/Caveolin-1-mediated transcytosis pathway, providing biological plausibility for communication between periodontal infection and the cerebral environment [5]. Such observations should not, however, be read as proof that periodontal pathogens routinely invade the human brain or directly initiate AD.

Systemic inflammation supplies an additional mechanistic bridge. Periodontitis is associated with sustained production of inflammatory mediators that can enter the circulation and amplify neuroimmune signaling. Peripheral inflammatory stimuli may influence cerebral endothelial cells and activate resident immune populations, particularly microglia, creating conditions permissive to chronic neuroinflammation. Neuroinflammation has therefore been proposed as a distal consequence of periodontitis and a potential pathway through which persistent oral inflammation could modify susceptibility to neurodegenerative processes [4]. Preclinical evidence indicates that experimentally induced periodontitis or exposure to periodontal bacteria, can influence AD-related features, although heterogeneity among models limits direct extrapolation to humans [6].

Aging may strengthen this connection. Immunosenescence, characterized by progressive alteration of innate and adaptive

immune function, occurs alongside the chronic low-grade inflammation of aging often termed inflammaging. Together, these changes may reduce the efficiency of microbial control while promoting exaggerated or poorly resolved inflammatory responses and age-associated decline in vascular integrity and BBB function may further increase cerebral susceptibility to peripheral inflammatory signals. Periodontitis and AD may thus interact within an aging biological environment in which microbial dysbiosis, systemic inflammation, vascular dysfunction and impaired immune regulation converge [3,4].

Emerging human evidence supports an association but has not yet proven causation and the longitudinal data are frankly inconsistent. A large Swedish nationwide cohort found no significant association between deep probing pocket depths and incident dementia after accounting for potential confounders [2]. A prospective cohort, by contrast, reported that periodontitis was associated with cognitive decline and its progression, with blood-based AD biomarkers contributing to the observed relationship [7]. These divergent findings illustrate the heterogeneity of the current evidence base and the influence of differences in periodontal case definitions, cognitive outcome measures, follow-up duration, study populations and residual confounding. Collectively, the oral–brain axis provides a biologically plausible framework linking chronic periodontal inflammation with neurodegeneration, supporting periodontitis as a potentially modifiable contributor to neuroinflammatory burden rather than an established direct cause of AD.

Periodontal Pathogens and Bacterial Translocation to the Central Nervous System

Periodontitis is a chronic polymicrobial inflammatory disease in which ulcerated pocket epithelium creates a direct interface between the subgingival biofilm and the systemic circulation and this interface underlies the proposed oral–systemic axis [8]. Extending the framework to the CNS requires separating two distinct claims: that viable periodontal bacteria colonize the brain and that bacterial products alone reach it. Most available evidence addresses the latter. *P. gingivalis*, a Gram-negative anaerobe whose abundance tracks disease severity, dominates this literature [9,10]. Treponema denticola, Tannerella forsythia, Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans are implicated on mechanistic and ecological grounds rather than through demonstrated translocation [8,9,11]. Three virulence factors are central to the proposed pathways. Gingipains, arginine- and lysine-specific cysteine proteases, degrade host proteins and may weaken endothelial barrier integrity [9]. Lipopolysaccharide (LPS) enters the circulation during transient bacteremia and has been reported to increase BBB permeability [11]. Outer membrane vesicles package both, permitting delivery of concentrated bacterial cargo without viable organisms [12]. Two routes follow from these observations. Hematogenously, *P. gingivalis* may adhere to and cross brain microvascular endothelium, while gingipains and LPS disrupt tight junctions [9,11]. Alternatively, transport may proceed along peripheral nerves, bypassing the vasculature entirely [12]. A third, indirect pathway-systemic inflammation without physical transport of organisms-remains compatible with the same body of observations [8,4].

The strongest evidence is preclinical. In mice, *P. gingivalis*-derived extracellular vesicles applied to gingival tissue reached the trigeminal ganglia and hippocampus and produced cognitive impairment and migration was attenuated following trigeminal neurotomy; that interventional element distinguishes the finding from purely correlative detection [12]. Human data are considerably weaker: postmortem AD brain tissue has yielded *P. gingivalis* LPS, bacterial DNA, gingipain-related signals and treponemal material [9,10], none of which demonstrates viable infection. Two limitations constrain interpretation. Brain tissue is a low-biomass environment, highly susceptible to reagent contamination and false-positive sequencing and current methods cannot reliably discriminate viable organisms from residual microbial material [13]. Separately, the periodontitis–AD relationship appears bidirectional; cognitive decline degrades oral self-care, so periodontal disease in affected individuals may be a consequence rather than a cause and cross-sectional and postmortem designs cannot resolve that ambiguity [11]. In synthesis, dissemination of periodontal microbial products to the CNS is biologically plausible and mechanistically supported along at least two routes, but viable bacterial colonization of the human brain remains unproven and temporal precedence unestablished.

Neuroinflammation: Cytokines, Microglial Activation and Alzheimer's Pathology

The relationship between periodontal pathogens and neurodegeneration does not depend solely on the physical presence of bacterial components within the CNS. Toxic bacterial products and inflammatory mediators released from the periodontium can activate inflammatory responses well beyond the oral cavity, altering CNS homeostasis [14]. These are biologically plausible pathways; they do not demonstrate that periodontal disease directly causes AD [15]. AD is a multifactorial disorder in which chronic, poorly regulated innate immune activation contributes to amyloid-β accumulation, synaptic loss and neurodegeneration

[16]. Microglia occupy an ambiguous position: they initially serve a protective function by facilitating phagocytosis and amyloid-β clearance, but their behavior shifts as the disease advances and the direction of that shift depends on disease stage and the local inflammatory environment [17]. Astrocytes participate alongside them, amplifying or restraining the response through cytokine release and oxidative signaling while continuing to support neuronal and synaptic homeostasis [17,18].

Periodontitis drives elevated circulating inflammatory mediators, including IL-1β, IL-6, TNF-α and CCL2 [4] and this elevation is measurable independently of comorbidities [18]. Sustained elevation of IL-1β, TNF-α, IL-6 and IL-17 may in turn amplify inflammatory signaling within the CNS and alter neuronal function by promoting synaptic dysfunction and glial activation [18,19]. IL-17 merits particular attention: at elevated circulating concentrations it has been implicated in disruption of the BBB, thereby facilitating neuroinflammation and neuronal injury [16,18,19]. IL-6, likewise elevated in periodontal inflammation, has been linked to neuroinflammatory change and barrier disruption, though it is by no means the only mediator implicated in AD and should not be treated as a specific marker of the relationship [20].

Oxidative stress represents a second convergent mechanism. It arises from an imbalance between the production of oxidizing species and cellular antioxidant capacity, sustaining chronic inflammation and rendering the brain more vulnerable to neuronal damage. In AD, oxidative stress appears early: mitochondrial function declines, lipid peroxidation increases, synaptic integrity is compromised and proteins involved in amyloid-β clearance are altered [20,21]. Inflammation coupled to oxidative stress and mitochondrial dysfunction can disturb cerebral homeostasis before clinical AD emerges and persistent stimulation converts what began as a protective response into a process driving synaptic loss and neurodegeneration [22]. Human data are consistent with this: reduced antioxidant capacity and elevated protein oxidation products have been reported in individuals with both periodontitis and AD [23]. No single mechanism accounts for the relationship: cytokine signaling, glial activation, oxidative stress, mitochondrial dysfunction and altered amyloid-β and tau handling are interconnected and a microglial response skewed toward neurotoxicity may alter amyloid metabolism and tau phosphorylation [24,25]. An important distinction remains unresolved whether periodontal-origin neuroinflammation initiates disease or accelerates established disease and the available evidence more strongly supports acceleration of established disease than initiation [25]. That framing carries clinical relevance, because neurodegenerative disease cannot presently be cured, whereas chronic periodontitis can be treated [26,27].

From Association to Causation: Evaluating the Evidence Linking Periodontitis and Alzheimer's Disease

The inflammatory and microbial mechanisms described above establish a biologically plausible pathway through which periodontal disease could influence AD progression. Biological plausibility, however, does not establish causality [28]. Determining whether periodontitis directly contributes to AD requires integrating epidemiological, longitudinal, genetic and mechanistic evidence while accounting for confounding, reverse causation and shared susceptibility. The principal human studies and their distinct outcomes are summarized in Table 1 and the overall evidence is weighed against the Bradford Hill considerations in Table 2.

Longitudinal epidemiological evidence supports temporality, although the observed associations are modest. A systematic review and meta-analysis of 47 longitudinal studies found poor periodontal health associated with cognitive decline (OR 1.23, 95% CI 1.05–1.44) and dementia (HR 1.21, 95% CI 1.07–1.38); the overall quality of evidence was nonetheless rated low [26]. A meta-analysis of 39 observational studies reported increased risks of cognitive decline (RR 1.33, 95% CI 1.13–1.55) and dementia or AD (RR 1.22, 95% CI 1.14–1.31), with a modest gradient by severity, from RR 1.14 for moderate disease to RR 1.25 for severe disease [27]. These findings support consistency and a possible biological gradient, but the small effect sizes weaken any argument for a strong independent causal effect.

Confounding is a major limitation. Periodontitis and AD share multiple determinants including aging, smoking, cardiometabolic disease, socioeconomic factors, inflammatory dysregulation and health behaviors. A systematic review examining confounding specifically found substantial heterogeneity in covariate selection and adjustment, with approximately half of included observational studies failing to address confounding adequately [28]. Shared genetic susceptibility complicates interpretation further. APOE4, the principal genetic risk allele for sporadic AD, has been examined in relation to periodontal disease through overlapping inflammatory, lipid-metabolic and vascular pathways, though the evidence does not establish a causal link between the two disorders [29].

Reverse causation offers an equally important alternative explanation. In a population-based propensity-matched cohort, individuals with dementia subsequently showed increased risk of developing periodontitis (adjusted HR 1.92, 95% CI 1.77–2.08), with a comparable association in the AD subgroup (HR 1.67, 95% CI 1.24–2.23) [30]. Cognitive impairment may worsen periodontal status through declining oral hygiene, reduced dental attendance, altered nutrition, medication effects and increasing dependence on caregivers. The relationship may therefore be bidirectional rather than a simple sequence running from periodontal disease to AD [11].

Genetic causal-inference evidence reinforces the distinction between preclinical mechanism and demonstrated human causation. A comprehensive bidirectional Mendelian randomization analysis found no substantial evidence that genetically predicted periodontitis causes cognitive impairment or brain atrophy [31]. A 15.6-year prospective cohort likewise found no significant association between baseline periodontitis and incident dementia or mild cognitive impairment, despite potentially relevant associations involving tooth retention and inflammatory or microbial markers [32]. The Bradford Hill considerations therefore yield a mixed picture: temporality, consistency, biological plausibility, coherence and a modest severity gradient receive some support, whereas strength, specificity and human experimental evidence remain limited [33]. Current evidence supports periodontitis as a biologically plausible and potentially modifiable correlate or risk indicator for cognitive decline, but does not establish it as a direct independent cause of AD [34]. Resolving the question will require prospective studies with standardized periodontal and neurological phenotyping, repeated AD-specific biomarkers, rigorous control of shared risk factors and randomized periodontal interventions incorporating long-term cognitive outcomes.

Study	Design	Outcome Measured	Main Result	Interpretation
Asher, et al., [26]	SR/MA, 47 longitudinal studies	Cognitive decline; dementia	OR 1.23 (decline); HR 1.21 (dementia); low-quality evidence	Positive but weak
Larvin, et al., [27]	MA, 39 observational studies	Cognitive decline; dementia/AD	RR 1.33 (decline); RR 1.22 (dementia/AD); severity gradient	Positive, shallow gradient
Carballo, et al., [7]	Prospective cohort	Cognitive decline + blood AD biomarkers	Periodontitis associated with decline and progression	Positive
Holmer, et al., [2]	Swedish nationwide cohort	Incident dementia	No significant association after adjustment	Null
Farsi, et al., [32]	15.6-year prospective cohort	Incident dementia / MCI	No significant association with baseline periodontitis	Null
Deng, et al., [31]	Bidirectional Mendelian randomization	Cognitive impairment; brain atrophy	No genetic causal association	Null (no causation)
Ma, et al., [30]	Propensity-matched cohort	Periodontitis after dementia/AD	HR 1.92 (dementia); HR 1.67 (AD subgroup)	Reverse causation

Table 1: Principal human studies of the periodontitis–cognition relationship, by outcome measured. Outcomes differ across studies (cognitive decline, all-cause dementia, biomarker- or diagnosis-based AD) and are not interchangeable. SR, systematic review; MA, meta-analysis; OR, odds ratio; HR, hazard ratio; RR, relative risk; AD, Alzheimer's disease; MCI, mild cognitive impairment.

Bradford Hill Consideration	Evidence in the Periodontitis–AD Literature	Assessment
Temporality	Some cohorts show periodontitis preceding decline; two large cohorts show no association	Partial, inconsistent
Strength	Pooled estimates near RR/OR 1.2–1.3	Weak
Consistency	Several positive cohorts, but large cohorts and Mendelian randomization null	Mixed
Biological gradient	Shallow severity gradient (RR 1.14 moderate to 1.25 severe)	Weak support
Plausibility	Multiple mechanistic routes (BBB, cytokines, outer membrane vesicles)	Supported (mostly preclinical)

Coherence	Consistent with neuroinflammation models of AD	Supported
Experiment	Preclinical models only; no adequately powered human RCT	Not demonstrated in humans
Specificity	Shared risk factors; multiple outcomes and exposures	Not supported
Reverse causation	Dementia increases subsequent periodontitis risk	Actively supported

Table 2: Assessment of the periodontitis–Alzheimer's disease relationship against the Bradford Hill considerations. No single consideration is met decisively for human causation; plausibility and coherence are the best supported, while strength, specificity and human experimental evidence are not. AD, Alzheimer's disease; BBB, blood–brain barrier; RR, relative risk; OR, odds ratio; RCT, randomized controlled trial.

Can Periodontal Therapy Be Neuroprotective? Current Clinical Evidence

If periodontitis contributes to neuroinflammatory burden, controlling it should, in principle, reduce that burden. Whether treating it alters neurological outcomes is a separate question and current evidence answers it only partially [33,36]. Non-surgical periodontal therapy remains the foundation of management. Scaling and root planing reduces local infection, pathogenic bacterial load and inflammatory mediator production by mechanically disrupting and removing subgingival deposits that oral hygiene alone cannot reach [34]. Ultrasonic instrumentation, antiseptic adjuncts such as chlorhexidine and locally delivered minocycline and host-modulation therapy extend this approach [34]. Host-modulation therapy occupies a particular place because it targets the host response rather than the biofilm; sub-antimicrobial-dose doxycycline inhibits matrix metalloproteinase activity and limits collagen degradation within the periodontium without exerting antimicrobial selection pressure [36,53]. The rationale for expecting systemic benefit rests on inflammatory-marker behavior. Elevated IL-1β, IL-6 and plasma C-reactive protein have been associated with risk and progression in AD, acting as circulating signals that can amplify neuroinflammation and cellular injury [34]. Work linking circulating inflammatory markers to longitudinal changes in brain structure and function among older adults proposes a relationship between peripheral inflammatory status and brain health that develops over time [35]. If chronic peripheral inflammation accelerates age-related change in neural networks, then reducing it becomes a plausible though as yet unproven neuroprotective strategy [36]. Periodontitis has also been associated with more rapid cognitive deterioration in patients already diagnosed with dementia or AD which strengthens the case for treating it as a matter of routine geriatric care [7].

Some evidence suggests that treating periodontitis improves oral-health indicators, quality of life and cognitive measures and may influence AD-related brain atrophy [36]. These findings are encouraging, but they should be interpreted with restraint. The available intervention studies are generally small, heterogeneous in periodontal and cognitive outcome measures, short in follow-up relative to the timescale over which AD develops and rarely blinded. No adequately powered long-term randomized controlled trial has yet demonstrated that periodontal therapy alters the trajectory of cognitive decline and until such evidence exists, claims of neuroprotection remain premature [36]. The practical position is therefore straightforward: periodontal therapy is indicated on its own merits in older adults, it reduces systemic inflammatory burden and it improves quality of life in a population where that matters considerably. Whether it also delays neurodegeneration is a hypothesis worth testing properly, not a conclusion the current evidence supports [34,53].

Future Perspectives: Precision Periodontology, Multi-Omics and Neuroprotective Oral Medicine

Current periodontal assessment contributes little to the diagnosis of AD and is constrained by operator dependence and the need for comprehensive clinical evaluation [37,38]. This limitation has driven interest in less invasive, more precise approaches-biomarkers, multi-omics profiling and artificial-intelligence-assisted analysis, with the longer-term aim of individualized care [39]. Saliva has attracted attention as an accessible, minimally invasive source of candidate biomarkers for neurodegenerative disease, though clinical implementation will require standardized collection and analytical protocols and validation in larger cohorts [39]. Elevated salivary total tau has been reported in AD and correlated with established cerebrospinal-fluid tau biomarkers, with moderate discriminatory performance between AD and cognitively unimpaired individuals (AUC 0.78) [40]. Gingival crevicular fluid is a second candidate compartment: metabolomic profiling of this fluid in AD and amnestic mild cognitive impairment, integrated with subgingival microbiome analysis, has identified correlations between microbial and metabolic signatures, though longitudinal validation in larger, better-matched cohorts remains outstanding [37]. Oral microbiome profiling may similarly support future research, since oral dysbiosis has been observed with increasing consistency in AD, although substantial species-level heterogeneity and methodological limitations persist [41,42].

Proteomic profiling offers a broader molecular view of cellular responses to periodontal bacterial components. A study of *P. gingivalis*-LPS exposure in neuronal and microglial models identified extensive changes in protein expression and pathway activity, but it did not identify proteomic biomarkers specific to AD patients [43]. Exosomal microRNAs have also been investigated as diagnostic candidates; a systematic review and meta-analysis reported promising diagnostic performance but substantial methodological heterogeneity and limited population diversity, indicating that larger prospective multicenter studies and standardized laboratory procedures are prerequisites for clinical translation [44]. Artificial intelligence may help integrate complex systemic and oral data into more individualized risk assessment: machine-learning models built on electronic dental records can support earlier prediction of periodontitis [45,46], help quantify the relative contribution of behavioral, systemic and clinical factors [47], and, combined with transcriptomic and epigenetic data, identify candidate biomarkers [48], provided that standardization, interpretability, external validation and real-world testing are addressed [38].

Therapeutically, the field appears to be moving beyond non-specific bacterial reduction toward targeted modulation of microbial virulence, host inflammation and dysbiosis. Gingipain inhibitors illustrate pathogen-directed therapy, although clinical translation remains constrained by safety concerns, the discontinuation of the gingipain inhibitor COR-388 following hepatotoxicity being the clearest example [49]. Immunomodulatory strategies may complement conventional therapy by restoring periodontal immune homeostasis [50]. Microbiome-based interventions aim to restore ecological balance rather than eliminate bacteria indiscriminately and probiotics, prebiotics and bacteriocins offer additional ways to modify oral microbial communities, though microbiome-targeted therapy remains in its early stages and requires long-term clinical investigation [51,10,52]. Emerging host-response technologies, including localized delivery of engineered microbial therapeutics, are largely preclinical and await clinical evaluation [53].

Conclusion

Several research priorities follow from the evidence reviewed here. Large prospective cohorts with standardized periodontal case definitions and repeated AD-specific biomarker measurement are needed to establish temporality more securely. Randomized clinical trials of periodontal therapy with long-term cognitive endpoints represent the decisive experimental test and have not yet been conducted at adequate scale or duration. Mechanistic studies in humans, rather than in animal models, are required to determine whether the pathways demonstrated experimentally operate in patients. Standardized diagnostic criteria across both disciplines would substantially improve comparability between studies. On the central question, the honest position is that periodontitis should be regarded as a biologically plausible and potentially modifiable risk indicator for cognitive decline rather than an established cause of Alzheimer's disease. That framing is not a reason for clinical inaction. Periodontal disease is treatable, its treatment is justified independently and the population in whom cognitive decline occurs is precisely the population in whom oral health is most often neglected. Meaningful progress will depend on collaboration between dentistry, neurology and geriatric medicine-disciplines that currently investigate these conditions largely in isolation and whose integration would reshape preventive care for older adults regardless of how the causal question is finally settled.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Acknowledgement

The authors have no acknowledgments to declare.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement
Not applicable.

Authors' Contributions
All authors contributed equally to this paper.

References

1. 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):144-56.
2. Holmer J, Eriksdotter M, Häbel H, Hed Myrberg I, Jonsson A, Pussinen PJ, et al., Periodontal conditions and incident dementia: a nationwide Swedish cohort study. J Periodontol. 2022;93(9):1378-86.
3. Li R, Wang J, Xiong W, Luo Y, Feng H, Zhou H, et al. The oral-brain axis: can periodontal pathogens trigger the onset and progression of Alzheimer's disease? Front Microbiol. 2024;15:1358179.
4. Li X, Kiprowska M, Kansara T, Kansara P, Li P. Neuroinflammation: a distal consequence of periodontitis. J Dent Res. 2022;101(12):1441-9.
5. Lei S, Li J, Yu J, Li F, Pan Y, Chen X, et al. Porphyromonas gingivalis bacteremia increases the permeability of the blood-brain barrier via the Mfsd2a/Caveolin-1 mediated transcytosis pathway. Int J Oral Sci. 2023;15(1):3.
6. Salhi L, Al Taep Y, Salmon E, Van Hede D, Lambert F. How periodontitis or periodontal bacteria can influence Alzheimer's disease features? A systematic review of pre-clinical studies. J Alzheimers Dis. 2023;96(3):979-1010.
7. Carballo A, López-Dequidt I, Custodia A, Botelho J, Aramburu-Núñez M, Machado V, et al.,Association of periodontitis with cognitive decline and its progression: contribution of blood-based biomarkers of Alzheimer's disease to this relationship. J Clin Periodontol. 2023;50(11):1444-54.
8. Jin W, Tang L, Yang J, Hu X, Guo W, Ai H, et al. The oral-X axis: from periodontal dysbiosis to systemic disease. Front Immunol. 2026;17:1806445.
9. Visentin D, Gobin I, Maglica Ž. Periodontal pathogens and their links to neuroinflammation and neurodegeneration. Microorganisms. 2023;11(7):1832.
10. Rozenblum G, Ait-Aissa K, Zahran G, Alipour M, Sahyoun AM, Munkhsaikhan U,, et al., Unraveling the oral microbiome's role in Alzheimer's disease: from pathophysiology to therapeutic potential. Alzheimers Dement. 2025;21(12).
11. Zhang W, Li S, Cui Y, Lun Y, Liu H, Li M. The interface of oral and brain health: current insights into the bidirectional relationship between Alzheimer's disease and periodontitis. CNS Neurosci Ther. 2026;32(1).
12. Ma X, Shin YJ, Yoo JW, Park HS, Kim DH. Extracellular vesicles derived from Porphyromonas gingivalis induce trigeminal nerve-mediated cognitive impairment. J Adv Res. 2023;54:293-303.
13. Weber C, Dilthey A, Finzer P. The role of microbiome-host interactions in the development of Alzheimer's disease. Front Cell Infect Microbiol. 2023;13:1151021.
14. Leira Y, Vivancos J, Diz P, Martín Á, Carasol M, Frank A. The association between periodontitis and cerebrovascular disease and dementia. Scientific report of the working group of the Spanish Society of Periodontology and the Spanish Society of Neurology. Neurologia (Engl Ed). 2024;39(3):302-11.
15. Singh R, Asthana S, Arya A, Kaushik M, Khan M. The oral-brain axis: mechanistic insights linking periodontitis with Alzheimer's and Parkinson's diseases. Cureus. 2026;18(6).
16. Zheng Q, Wang X. Alzheimer's disease: insights into pathology, molecular mechanisms and therapy. Protein Cell. 2025;16(2):83-120.
17. Kim KY, Shin KY, Chang KA. GFAP as a potential biomarker for Alzheimer's disease: a systematic review and meta-analysis. Cells. 2023;12(9):1309.
18. Kindstedt E, Wänman M, Wu WY, Hofer-Mattsson K, Lövgren A, Lundberg P. Systemic cytokine alterations in periodontitis independent of comorbidities: a systematic review and meta-analysis. Aging Dis. 2026. Epub ahead of print.
19. Gan R, Xie H, Zhao Z, Wu X, Wang R, Wu B, et al. Investigation of patterns and associations of neuroinflammation in cognitive impairment. Cereb Cortex. 2025;35(2).
20. Bai R, Guo J, Ye XY, Xie Y, Xie T. Oxidative stress: the core pathogenesis and mechanism of Alzheimer's disease. Ageing Res Rev. 2022;77:101619.

21. Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox Biol. 2018;14:450-64.
22. Ionescu-Tucker A, Cotman CW. Emerging roles of oxidative stress in brain aging and Alzheimer's disease. Neurobiol Aging. 2021;107:86-95.
23. Papadakis KA, Doufexi AE, Kalamaki MS, Bourazanas E, Lymperaki E. The role of oxidative stress in the relationship between periodontitis and Alzheimer's disease: a review of the literature. J Pers Med. 2025;15(8):384.
24. Plachokova AS, Gjaltema J, Hagens ERC, Hashemi Z, Knüppe TBA, Kootstra TJM, et al. Periodontitis: a plausible modifiable risk factor for neurodegenerative diseases? A comprehensive review. Int J Mol Sci. 2024;25(8):4504.
25. Villar A, Paladini S, Cossatis J. Periodontal disease and Alzheimer's: insights from a systematic literature network analysis. J Prev Alzheimers Dis. 2024;11(4):1148-65.
26. 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):2695-709.
27. Larvin H, Gao C, Kang J, Aggarwal VR, Pavitt S, Wu J. The impact of study factors in the association of periodontal disease and cognitive disorders: systematic review and meta-analysis. Age Ageing. 2023;52(2).
28. Nascimento GG, Leite FRM, Mesquita CM, Vidigal MTC, Borges GH, Paranhos LR. Confounding in observational studies evaluating the association between Alzheimer's disease and periodontal disease: a systematic review. Heliyon. 2023;9(4).
29. Arévalo-Caro C, Arce Retana M, Losada Amaya S, Arboleda H, Gallart-Palau X, Serra A. APOE4, Alzheimer's and periodontal disease: a scoping review. Ageing Res Rev. 2025;105:102649.
30. Ma KS, Hasturk H, Carreras I, Dedeoglu A, Veeravalli JJ, Huang JY, et al. Dementia and the risk of periodontitis: a population-based cohort study. J Dent Res. 2022;101(3):270-7.
31. Deng Z, Li J, Zhang Y, Zhang Y. No genetic causal associations between periodontitis and brain atrophy or cognitive impairment: evidence from a comprehensive bidirectional Mendelian randomization study. BMC Oral Health. 2024;24(1):571.
32. Farsi DN, Abadalkareem R, Linden GJ, McKay GJ, McEvoy CT, McAlinden M, et al. Periodontitis and incident cognitive decline and dementia: a 15-year prospective cohort study of older men residing in Northern Ireland. J Alzheimers Dis. 2025;109(2):980-95.
33. Cichońska D, Mazuś M, Kusiak A. Recent aspects of periodontitis and Alzheimer's disease: a narrative review. Int J Mol Sci. 2024;25(5):2612.
34. Bijoch J, Jędrasiak K. Red complex pathogens, periodontal dysbiosis and periodontal therapy in Alzheimer's disease and dementia. J Clin Med. 2026;15(13):5296.
35. Warren KN, Beason-Held LL, Carlson O, Egan JM, An Y, Doshi J, et al. Elevated markers of inflammation are associated with longitudinal changes in brain function in older adults. J Gerontol A Biol Sci Med Sci. 2018;73(6):770-8.
36. Zhang M, Mi N, Ying Z, Lin X, Jin Y. Advances in the prevention and treatment of Alzheimer's disease based on oral bacteria. Front Psychiatry. 2023;14:1291455.
37. Qiu C, Zhou W, Shen H, Wang J, Tang R, Wang T, et al. Profiles of subgingival microbiomes and gingival crevicular metabolic signatures in patients with amnestic mild cognitive impairment and Alzheimer's disease. Alzheimers Res Ther. 2024;16(1):41.
38. Yadavalli P, Reddy SSP, Kesavalu L. Artificial intelligence in periodontics and peri-implant medicine: from diagnosis to precision care. Front Dent Med. 2026;7:1816844.
39. Jiao LL, Dong HL, Liu MM, Wu PL, Cao Y, Zhang Y, et al. The potential roles of salivary biomarkers in neurodegenerative diseases. Neurobiol Dis. 2024;193:106442.
40. Bamford AR, Logan C, Do QT, Nguyen K, McMillan LC, Yassa MA, et al. Salivary total tau: a clinically practical measure of tau neuropathology in Alzheimer's disease. J Neurol. 2026;273(2):149.
41. Weber C, Wind D, Petzsch P, Supprian T, Dilthey A, Christl J, et al. Dysbiotic shift in the oral microbiota of patients with Alzheimer's disease compared to their healthy life partners: a combinatorial approach and a paired study design. Alzheimers Res Ther. 2026;18(1):23.
42. Seyedmoalemi MA, Saied-Moallemi Z. Association between periodontitis and Alzheimer's disease: a narrative review. IBRO Neurosci Rep. 2025;18:360-5.
43. Verma A, Azhar G, Patyal P, Zhang W, Zhang X, Wei JY. Proteomic analysis of *P. gingivalis*-lipopolysaccharide induced neuroinflammation in SH-SY5Y and HMC3 cells. Geroscience. 2024;46(5):4315-32.
44. Liu S, Zhao M, Yang X, Liu Y, Xu H, Yan H, et al. Exosomal microRNA biomarkers in Alzheimer's disease: systematic review

and meta-analysis. Clin Chim Acta. 2026;578:120542.
45. Chung PC, Chan TC. Digital oral health biomarkers for early detection of cognitive decline. BMC Public Health. 2023;23(1):1952.
46. Swinckels L, de Keijzer A, Loos BG, Applegate RJ, Kookal KK, Kalenderian E, et al. A personalized periodontitis risk based on nonimage electronic dental records by machine learning. J Dent. 2025;153:105469.
47. Suh B, Yu H, Cha JK, Choi J, Kim JW. Explainable deep learning approaches for risk screening of periodontitis. J Dent Res. 2025;104(1):45-53.
48. Jin L, Yuan ZZ, Liu Y. Multi-omics integration to identify immune-associated biomarkers and potential therapeutics in periodontitis. Front Med (Lausanne). 2025;12:1640961.
49. Pedrosa ME, Martin V, Fernandes MH, Gomes PS. Gingipain inhibitors as an innovative therapy for periodontal and associated-systemic diseases: a systematic review. Clin Oral Investig. 2025;29(8):418.
50. Zhang Y, Qin X, Yang J, Rogers HM, Baban B, Tian S. Clinical effect of immunomodulatory therapy in periodontitis: a systematic review and meta-analysis. Front Bioeng Biotechnol. 2025;13:1693365.
51. Salah AN, Doghish YA, Abbass SO, Mansour RM, Sayed GA, Elshami NH, et al. Microbiota-based therapies in oral health and disorders. Folia Microbiol (Praha). 2025;70(6):1217-40.
52. Kuraji R, Shiba T, Dong TS, Numabe Y, Kapila YL. Periodontal treatment and microbiome-targeted therapy in management of periodontitis-related nonalcoholic fatty liver disease with oral and gut dysbiosis. World J Gastroenterol. 2023;29(6):967-96.
53. Phanrungsuwan A, Huang J, Dharmaraj N, Cobos Perez A, Veiseh O, Young S, et al. Host modulation therapy in periodontitis: from established therapies to emerging technologies. Front Immunol. 2026;17:1762187.

About the journal

ATHENAEUM SCIENTIFIC PUBLISHERS

Journal of Neuro and Oncology Research is a peer-reviewed, open-access scholarly journal published by Athenaeum Scientific Publishers. The journal publishes original research articles, case reports, reviews, editorials, and commentaries within its defined scope, with the aim of supporting scientific research and clinical knowledge in neuro-oncology.

All manuscripts are evaluated through an independent peer-review process conducted in accordance with the journal's editorial policies and established publication ethics. Editorial decisions are made solely on the basis of academic merit.

Manuscript submission: https://athenaeumpub.com/submit-manuscript/