MDPI

Review

Periodontitis and Alzheimer's Disease: Is There a Connection?

William Lundergan *, Kavitha Parthasarathy and Navid Knight

Department of Periodontics, Arthur A. Dugoni School of Dentistry, University of the Pacific, San Francisco, CA 94103, USA
* Correspondence: wlundergan@pacific.edu

Abstract: The oral health/systemic health connection has been an area of research interest that increased dramatically during the 1990s. Periodontal disease has been associated with a number of systemic conditions, including cardiovascular disease, diabetes, pre-term low-birth-weight infants, respiratory conditions, rheumatoid arthritis, cancer, and Alzheimer's disease. Inflammation is the obvious link that connects periodontal disease with these conditions, but is this association casual or causal? We will address the biologic plausibility, evidence from human studies, evidence from animal studies, and therapeutic interventions as we review the current understanding of the link between periodontitis and Alzheimer's disease.

Keywords: Alzheimer's disease; periodontitis; oral health/systemic health connection

1. Introduction

Alzheimer's disease is a progressive form of dementia that primarily affects memory, language, and thinking skills. It is estimated that there are 6.7 million Americans aged sixty-five and older that are living with Alzheimer's disease today, and it is the fifth leading cause of death for this age cohort [1]. Alzheimer's disease is characterized by early-onset and late-onset forms. The early-onset forms are typically linked to dominant genetic mutations, and, although the late-onset form does not seem to be hereditary, evidence supports the existence of genetic as well as behavioral, environmental, and metabolic risk factors [2]. Alzheimer's disease is characterized by the deposition of amyloid-β plaques and tau protein phosphorylation (tangle formation) in the brain tissue that occurs long before the recognized loss of cognitive function. Vascular alterations, mitochondrial dysfunction, oxidative stress, the reduced utilization of brain glucose, and neuroinflammation may play roles in the initiation and progression of the disease [2].

Periodontitis is a chronic inflammatory disease involving the supporting structures of the teeth. Approximately 47% of Americans 30 years of age and over have a form of periodontitis [3]. The disease is associated with a subgingival bacterial dysbiosis in a susceptible host, which results in a hyperinflammatory response characterized by the activation of host-derived proteinases, leading to the loss of supporting bone and attachment around the teeth. The hyperinflammatory response in periodontitis has been associated with increased levels of IL-1β, TNF-α, IL-6, and prostaglandin E2 in addition to matrix metalloproteinases [4,5]. Behavioral, environmental, and genetic risk factors can modify the host response [6]. Periodontal pathogens/microbial tooth deposits, tobacco smoking, and diabetes are the accepted risk factors for periodontitis, which is recognized as the major cause of tooth loss in individuals over the age of thirty.

The oral health/systemic health connection has been an area of research interest that increased dramatically during the 1990s and continues today [7]. Periodontal disease has been associated with a number of systemic conditions, including cardiovascular disease, diabetes, pre-term low-birth-weight infants, respiratory conditions, rheumatoid arthritis, cancer, and Alzheimer's disease [8,9]. Inflammation is the obvious link that connects periodontal disease with these conditions, but is this association casual or causal?

Alzheimer's disease is a complex condition characterized by a number of physiologic and cellular changes in the brain tissues. One hypothesis regarding Alzheimer's disease is that neuroinflammation leads to neurodegeneration with the loss of cognitive function. Microglia cells are common innate immune cells found in the central nervous system. They are thought to play a vital role in maintaining immune homeostasis in the brain. The presence of immune-activated microglial cells that produce exaggerated levels of pro-inflammatory mediators is a characteristic of Alzheimer's disease [10]. These pro-inflammatory mediators are thought to increase amyloid-β production and can lead to neurotoxic changes [11]. Is it possible that periodontal pathogens, or the pro-inflammatory cytokines that the host produces in response to an oral infection, can reach the brain and enhance this neuro-inflammatory process? In this review, we will address the current understanding of the link between periodontitis and Alzheimer's disease.

The PubMed database was searched without additional filters from the year 2000 to 31 July 2023, using the search term "periodontitis and Alzheimer's disease". Review articles were included in the search, which generated 432 articles. The articles were screened by reading the title and the abstract, searching for articles that addressed the association between periodontitis and Alzheimer's disease; the biologic plausibility of such an association; and therapeutic interventions for periodontitis that altered cognitive outcomes. Additional articles were identified by cross-referencing these articles. Following a full-text reading of the identified articles, we included 67 articles in this review.

2. Biologic Plausibility

There are over seven hundred species of oral bacteria, and studies have shown that these bacteria can enter the bloodstream following many dental procedures, including tooth extraction, scaling, and root planing, periodontal probing, and restorative dental procedures. In fact, these bacteria can enter the bloodstream after chewing food and brushing teeth, particularly in patients with periodontitis, and the bacteremia can last from a few minutes to over 30 min [12]. Furthermore, studies have demonstrated that oral bacteria can be isolated from carotid artery atheromas [13]. If these bacteria, their virulence factors, or locally produced cytokines can enter the brain via the bloodstream or neural pathways, they might stimulate microglia cells to produce pro-inflammatory mediators, leading to increased amyloid-β production and neurodegeneration.

Porphyromonas gingivalis is a periodontal pathogen associated with Socransky's Red Complex [14]. It is a late colonizing, Gram-negative, anaerobic bacterium that produces virulence factors known as gingipains. It has been demonstrated that the outer membrane vesicles of *P. gingivalis* can encapsulate virulence factors and be shed to enter host cells [15]. These outer membrane vesicles can cross biologic barriers and eventually reach the brain. Helicobacter pylori is a common gut pathogen for which it has been demonstrated that these outer membrane vesicles are taken up by astrocytes, leading to amyloid-β pathology and dementia [16]. *P. gingivalis* DNA, lipopolysaccharide, and gingipains have been detected in the brain tissue of humans with Alzheimer's disease [17,18].

Other periodontal pathogens have been demonstrated in various tissues of the brain, including red complex organisms such as *T. denticola* and *T. forsythia* [19]. Additionally, antibodies against *P. gingivalis*, *T. denticola*, *A. actinomycetemcomitans*, *F. nucleatum*, and *P. intermedia*, all known periodontal pathogens, have been identified in the brains of subjects with and without Alzheimer's disease [19]. These antibody levels are increased when the subjects have both Alzheimer's disease and periodontitis. Riviere et al. also demonstrated that *Treponema* species can enter the brain and that brains affected by Alzheimer's disease were more likely to have them than control brains [20]. *Treponema* was detected in the trigeminal ganglia of both Alzheimer's disease and control specimens, suggesting that *Treponema* species may infect the brain via branches of the trigeminal nerve.

Herpes simplex virus type 1 (HSV-1) has been associated with periodontitis [21] and brains affected by Alzheimer's disease [22]. HSV-1 is known to reside in a latent state in the trigeminal ganglia and can be reactivated periodically. There is considerable

evidence supporting the molecular mechanisms for HSV-1 pathogenesis in Alzheimer's disease, including the induction of neuroinflammation, oxidative stress, and mitochondrial dysfunction [23]. HSV-1 and bacterial periodontal pathogens may interact synergistically to exacerbate the cognitive decline seen in Alzheimer's disease. Considering that *Treponema* has been shown to enter the trigeminal ganglia, perhaps bacterial periodontal pathogens or their virulence factors can activate a latent HSV-1 infection.

3. Human Association Studies

A common cause of tooth loss for adults over the age of thirty is periodontitis. If periodontitis is associated with Alzheimer's disease, tooth loss might be expected to be associated with Alzheimer's disease as well. The Nun study demonstrated that having few teeth is associated with an increased risk for developing dementia [24]. However, this study did not find a significant association between dementia and periodontal disease, as assessed with radiographic evidence of alveolar bone loss. The authors noted the limitations of the radiographic bone loss assessment, observing that it does not represent a comprehensive periodontal evaluation, and may underrepresent the true periodontal disease burden. Other prospective cohort studies that have addressed the association between tooth loss and dementia have shown conflicting results [25–28].

A prospective cohort study evaluated 596 community-dwelling men between 28 and 70 years of age at baseline [27]. The subjects were participants in the VA Dental Longitudinal Study and were followed for up to 32 years. A cognitive assessment was completed using the Mini-Mental State Examination and a spatial copying task. An oral health assessment was conducted about every 3 years and included the periodontal pocket depth and a radiographic assessment of alveolar bone loss. The study found that periodontal disease progression predicted subsequent cognitive decline. These results suggest that peripheral inflammation can contribute to cognitive impairment and that oral health may be a modifiable risk factor for dementia.

A case–control study evaluated 409 (180 cases to 229 controls) dentate participants [28]. Case subjects were recruited from the neurology departments of two hospitals in Granada, Spain, while the controls were recruited from among non-dental patients treated in a primary care center. The controls did not have subjective memory loss complaints and had scores greater than thirty in the photo-test cognitive exam. The authors found a statistically significant association between clinical attachment loss (CAL) and cognitive impairment after controlling for age, sex, education level, oral hygiene habits, and hyperlipidemia.

Sixty non-smoking subjects with a mean age of 77.7 years and mild to moderate dementia were evaluated for periodontitis by a dental hygienist using the CDC/AAP criteria. The cognitive state was evaluated using the Alzheimer's Disease Assessment Scale and the Mini-Mental State Examination. Fifty-two subjects completed the follow-up evaluation at 6 months. The presence of periodontitis was associated with a six-fold increase in the rate of cognitive decline over the six-month period [29]. The authors concluded that this periodontitis-associated cognitive decline may be mediated through systemic inflammation.

A 2017 study hypothesized that poor periodontal health may be linked with cognitive impairment and dementia via the exacerbation of systemic inflammation [30]. A periodontal examination (probing depth, CAL, bleeding on probing, and plaque index) and a Mini-Mental State Examination were completed for 128 participants. The cytokine levels produced by unstimulated and LPS-stimulated peripheral blood leucocytes isolated from the 128 subjects were also measured. The results showed that periodontal disease combined with cognitive impairment and dementia led to a higher level of systemic inflammation than either condition alone. The authors suggested that the presence of an additional source of cytokines, such as periodontal disease, might exacerbate systemic inflammation, leading to further neurodegeneration. The authors felt it was reasonable to assume that periodontal disease is a modifiable risk factor for cognitive impairment and dementia.

Using the National Health Insurance Research Database in Taiwan, a retrospective population-based cohort study involving 6056 individuals aged 65 years and older (median age 72.4) sought to determine whether periodontitis is a modifiable risk factor for dementia [31]. The experimental group included 3028 subjects with periodontitis who were age-matched and sex-matched with 3028 control subjects without periodontitis. The incidence of newly diagnosed dementia in the periodontitis and control groups was the primary outcome, and dementia was defined by ICD-9-CM codes. The hazard ratios showed that participants with periodontitis had a significantly greater risk of developing dementia than the control subjects. The authors concluded that the treatment of periodontal disease might be a modifiable risk factor for dementia and urged clinicians to develop new preventive and therapeutic strategies for dementia.

A Swedish case–control study selected 154 case subjects (memory clinic patients) and 76 controls from the Swedish Population Register with no experienced memory loss and a score of 28 or greater on the Mini-Mental State Examination [32]. All participants received clinical and radiographic oral examinations, which included probing depth, bleeding on probing, suppuration, tooth mobility, and furcation involvement, and they were followed over a three-year period. The results suggested that marginal periodontitis is associated with early cognitive impairment and Alzheimer's disease. The authors recognized that their results did not preclude non-causal explanations and recommended more longitudinal studies to enhance causal inference.

Using data from the Tosa Longitudinal Aging Study, a five-year longitudinal cohort study evaluated 179 community-dwelling men and women with an average age of just over 80 [33]. A baseline periodontal exam was conducted, which assessed six sites per tooth. The periodontal inflamed surface area was estimated using gingival recession, periodontal probing depth, and bleeding on probing data. The study participants were classified as having "severe" periodontitis or "not severe." Cognitive examinations (Mini-Mental State Examination) were conducted in 2011, 2012, 2013, and 2015. The results indicated that severe periodontitis and periodontal inflammation were associated with mild cognitive impairment in this cohort. A strength of this study is that it evaluated six-sites per tooth for the full mouth and included periodontal inflamed surface area calculations, which is a measure of inflammatory burden.

In a cross-sectional study, forty young adults with a mean age of thirty-four were evaluated for cognitive dysfunction [34]. From radiographic images, ten subjects were diagnosed with aggressive periodontitis, twenty were diagnosed with mild to moderate chronic periodontitis, and ten were diagnosed with no periodontitis. The Rey Auditory Verbal Learning Test, Montreal Cognitive Assessment test, Mini-Mental State Examination, and Prague tests were used to assess cognitive function. The aggressive periodontitis group had lower delayed recall scores and showed reduced learning performance, suggesting that the association between periodontitis and Alzheimer's disease may not be limited to the elderly.

Searching for biomarkers for Alzheimer's disease, a study evaluated the oral microbiomes of 26 patients with Alzheimer's disease and 26 cognitively intact control subjects [35]. The periodontal examination included the probing depth, CAL, and bleeding on probing at six sites per tooth. The diagnosis was based on the 2017 Classification of Periodontal and Peri-Implant Diseases and Conditions Workshop. The samples were collected from saliva and gingival crevicular fluid for microbial analysis. The periodontal health of patients with Alzheimer's disease was worse than that of the cognitively intact participants but without statistical significance. There was a significant difference in the periodontal microbiome between the patients with Alzheimer's disease and the controls, and the periodontal microbiome was sensitive to cognition changes. *Porphyromonas gingivalis* in gingival crevicular fluid was associated with Alzheimer's disease.

4. Animal Studies

Animal models have been used extensively to help study the pathologic processes associated with Alzheimer's disease. Some of these studies have suggested that the activation of the complement cascade, an important part of the innate immune response, contributes to the neuroinflammatory process that has been linked to Alzheimer's disease. The absence of C1q, the protein that initiates the classical complement cascade, has been shown to lead to less neuropathology in transgenic mice at an age when fibrillar amyloid plaque is present [36]. C5a is a product of the activation of the complement cascade. Treatment with a C5a receptor antagonist decreases pathology and enhances the behavioral performance in murine models of Alzheimer's disease [37]. Using mouse models, it was demonstrated that microglia and complement can mediate early synapse loss in Alzheimer's disease [38]. These authors showed that the inhibition of C1q, C3, or CR3 (microglial complement receptor) reduced the number of phagocytic microglia as well as the extent of early synapse loss. It has also been demonstrated, using an Alzheimer's disease mouse model, that periodontal infection aggravates C1q-mediated microglial activation and synapse pruning [39].

ApoE$^-$/$^-$ mice were infected with *P. gingivalis*, *Treponema denticola*, *Tannerella forsythia*, and *Fusobacterium nucleatum* [40]. The ApoE$^-$/$^-$ mouse is an apolipoprotein knockout mouse, which is characterized by a delayed lipoprotein clearance and is a widely used model for studying atherosclerosis [41]. Nine of twelve mouse brains contained *P. gingivalis* DNA after 24 weeks, demonstrating that *P. gingivalis* can access the ApoE$^-$/$^-$ mouse brain from an oral infection. Complement activation with neuronal injury was also demonstrated. In another study, oral infection in transgenic mice with *P. gingivalis* impaired cognitive function, increased the deposition of amyloid-β plaques in both the hippocampus and cortex, and resulted in alveolar bone loss [42]. Bahar et al. investigated the effect of *P. gingivalis* oral infection on the development of Alzheimer's disease pathophysiology in obese and diabetic mice [43]. Infected mouse brain tissue showed neuroinflammation in the form of reactive microglia and an increased mRNA abundance of several pro-inflammatory mediators, indicating hyperactivation. Another study used amyloid-β protein precursor/presenilin transgenic mice that were injected with *P. gingivalis* lipopolysaccharide and had gingival sulcus ligation of the maxillary second molar [44]. The release of pro-inflammatory cytokines and alveolar bone loss were increased in the experimental group over the control. The mice in the experimental group experienced cognitive impairment and a significant reduction in neurons. These mice also exhibited glial cell activation and increased amyloid-β levels compared to the control mice.

Canine cognitive dysfunction has been used as an animal model for human Alzheimer's disease. A blinded, case–control, prospective investigation compared visual assessments of periodontal status in twenty-one dogs with their cognitive scores [45]. Eleven dogs had a history of cognitive impairment, and ten dogs had no history of cognitive decline. The results showed a significant association between periodontal status and cognitive scores. No association was identified for age and periodontal status or for age and cognitive score.

Animal experiments have shown an association between tooth loss and cognitive impairment [46–50]. Que et al. found that tooth loss induces memory impairment and neuronal cell loss in a mouse model [47]. Luo et al. demonstrated, in rats, that tooth loss results in cognitive impairment through decreased cerebral blood flow and increased glutamate [48]. Goto et al. reported that tooth loss in a mouse model leads to the neurodegeneration of trigeminal mesencephalic neurons and the progression of Alzheimer's disease [46]. Using a mouse model for Alzheimer' disease (App knock in mice), Taslima et al. showed that tooth loss induced microglia activation, which led to the upregulation of mRNA expression levels of the neuroinflammation cytokines TNF-α, IL-6, and IL-1β in the hippocampus [49]. Using a novel object recognition test and a passive avoidance test, they demonstrated that tooth loss induced memory impairment. These authors concluded that oral care is especially important and may reduce the risk of cognitive dysfunction. In another publication [50], Taslima and colleagues demonstrated that tooth loss in wild-type mice induced memory impairment (object recognition test) by decreasing neuronal activity

and synaptic density in the hippocampus. They also demonstrated that tooth loss was associated with increased levels of protein kinase JNK and heat shock protein 90 (proteins activated by chronic stress), which activated glial cells in the hippocampus.

Sakamoto et al. showed that occlusal rehabilitation, after long term tooth loss in rats, resulted in improved spatial memory and increased neuron density in the hippocampus versus the unrestored tooth loss group [51]. The loss of occlusal support is thought to lead to cognitive impairment via the following mechanisms: masticatory dysfunction leading to reduced cerebral blood flow, the reduced stimulation of peripheral receptors, alterations to neural pathways, and neurodegeneration; tooth loss aggravating existing neurodegenerative changes; and long-term inflammatory stress leading to CNS damage [52].

5. Therapeutic Intervention

The apparent association between periodontal disease and Alzheimer's disease raises the following questions: Are patients with Alzheimer's disease at a higher risk for developing periodontitis? Does therapeutic intervention for periodontitis slow the progression of Alzheimer's disease? Can markers for periodontitis predict future cognitive impairment?

A retrospective longitudinal cohort study of 8640 patients who had dementia aimed to determine the risk of developing periodontitis [53]. The findings showed that dementia and Alzheimer's disease were associated with an increased risk of periodontitis, independent of systemic confounding factors. The risk of developing periodontitis was age-dependent. Periodontitis severity increased in patients who developed dementia earlier in life, suggesting a cumulative effect.

The relationship between periodontal therapy and pre-clinical Alzheimer's disease was investigated [54]. This was a cohort study involving 177 periodontally treated and 409 untreated subjects with a median observation period of 7.3 years. The study found that periodontal treatment had a favorable effect on Alzheimer's disease-related brain atrophy, as determined by magnetic resonance imaging. The effects of oral health intervention on the oral flora and cognitive function were studied in sixty-six patients with mild Alzheimer's disease over a 24-week period [55]. The oral health intervention included structured visits three times per week; facilitated self-care three times per week after dinner; and weekly self-management training. Oral self-care included swabbing the oral cavity with 0.2% of chlorhexidiene gluconate and brushing for one minute followed by rinsing with water. Self-management training followed the principle of the self-determination theory [56]. The authors reported favorable alterations of the oral microbiota in the patients receiving the oral health intervention and a slowing of the cognitive decline. These studies support the need for close oral health monitoring in patients with cognitive impairment. Frequent periodontal debridement by a dental clinician in conjunction with oral health intervention programs for regular dental plaque control may have the dual benefit of controlling periodontal disease and slowing the progression of cognitive impairment.

Several studies have explored the use of disease-modifying therapeutic agents in the treatment of Alzheimer's disease targeting amyloid-β plaque, tau aggregation, neuroinflammation, mitochondrial dysfunction, oxidative stress, and infection [57,58]. A 2019 study, using a mouse model, showed that *P. gingivalis* and gingipains may play roles in Alzheimer's disease pathogenesis [16]. The authors showed that the oral administration of a gingipain inhibitor decreased the quantities of *P. gingivalis* in the brain, decreased the amyloid-β response to *P. gingivalis*, decreased tumor necrosis factor alpha, and blocked gingipain-induced neurodegeneration. However, the results of a Phase 3 trial in humans using COR 388 (gingipain inhibitor) failed to provide a significant cognitive benefit [59].

A potentially promising avenue for therapeutic intervention is associated with the NLRP3 inflammasome, which is associated with both periodontitis and Alzheimer's disease. NLRP3 can facilitate osteoclast activity in periodontitis [60] and has been associated with neuronal cell death in Alzheimer's disease [61]. The development of safe and effective NLRP3 inflammasome inhibitors could prove to be promising for the treatment of both diseases.

Since the evidence supports an association between periodontal disease and Alzheimer's disease, markers for periodontal disease, in conjunction with other biomarkers, may have some value in predicting the development of dementia. Using NHANES III data and subjects 60 years and older for whom cognition and IgG antibodies for periodontal pathogens were measured, the ability of IgG antibodies to predict cognitive impairment was assessed [62]. IgG antibodies against periodontal microbes were associated with lower cognition among free-living adults who were previously undiagnosed with cognitive impairment. The authors concluded that combining periodontal microbe IgG antibody data with current algorithms may improve risk prediction for dementia and Alzheimer's disease.

6. Discussion

In 1965, Sir Austin Bradford Hill introduced the Bradford Hill Criteria for establishing causation from epidemiologic association data [63]. He proposed nine guidelines to be considered, which are the strength of the association, consistency, specificity, temporality, biological gradient, biological plausibility, coherence, experiment, and analogy. These criteria were intended to function as flexible guidelines to help epidemiologists establish causation from association studies. Advances in genetics, molecular biology, and statistics require that our criteria for assessing causal inference must also change [64]. It has been suggested that the criteria for establishing causation in epidemiologic studies associating periodontitis with systemic inflammatory conditions should consider the biologic plausibility, the strength of the association, and the outcome of intervention trials [65,66]. In this review, we presented studies that have addressed these three considerations.
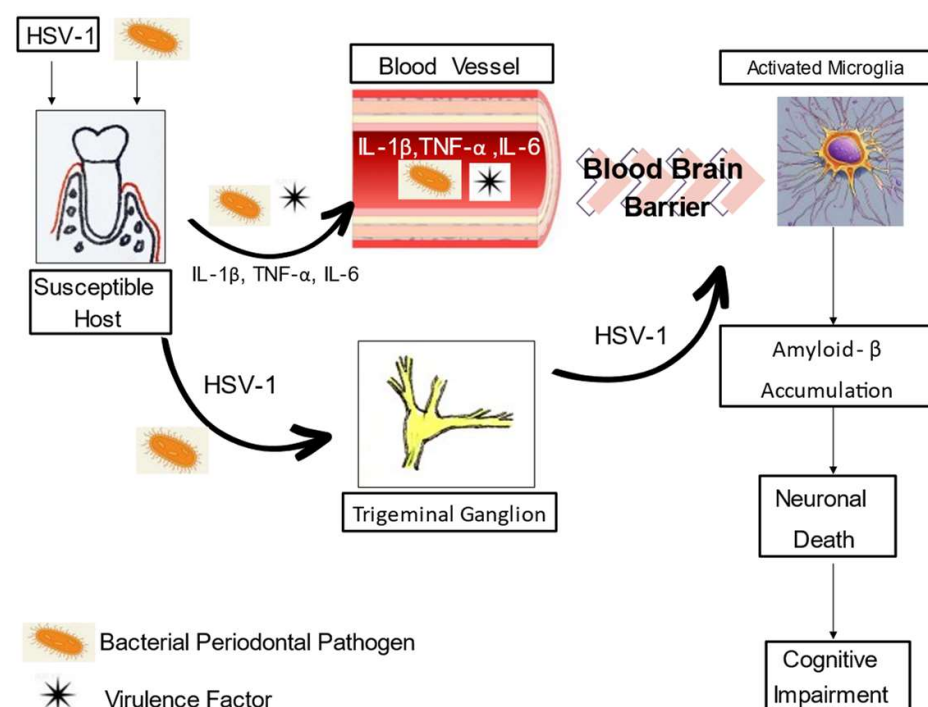
The current evidence supports the biologic plausibility of a cause-and-effect relationship between periodontitis and Alzheimer's disease. Table 1 shows the key studies cited in this review which support the direct association between periodontitis and Alzheimer's disease, and Table 2 shows studies that support the biologic plausibility of a possible cause-and-effect relationship. It seems likely that periodontal pathogens and/or their virulence factors could enter the brain tissues or exert an affect across the blood–brain barrier via vascular or neurological routes and stimulate a neuroinflammatory response that might lead to neurodegeneration and subsequent dementia (Figure 1).

Table 1. Key studies cited in this review supporting an association between periodontitis and Alzheimer's disease.

Author	Year Published	Type of Study	Outcome
Kaye et al. [27]	2010	Prospective cohort study	Periodontal disease related to cognitive decline
Gil-Montoya et al. [28]	2015	Case-control study	Periodontitis appears to be associated with cognitive impairment
Ide et al. [29]	2016	Cohort study	Periodontitis associated with six-fold increase in rate of cognitive decline
Lee et al. [31]	2017	Cohort study	Periodontitis is associated with greater risk of developing dementia
Holmer et al. [32]	2018	Case-control study	Suggests marginal periodontitis is associated with early cognitive impairment
Iwasaki et al. [33]	2019	Cohort study	Severe periodontitis and periodontal inflammation associated with mild cognitive impairment
Ishida et al. [42]	2017	Transgenic mouse model	Cognitive function was significantly impaired in periodontitis-induced mice
Qian et al. [44]	2021	Mouse model	Periodontitis exacerbated learning and memory impairment in mice
Dewey et al. [45]	2021	Dog study	Periodontal disease is associated with cognitive dysfunction
Schwahn et al. [54]	2022	Trial emulation	Periodontal treatment had a favorable effect on brain atrophy
Chen et al. [55]	2022	Randomized controlled trial	Oral health intervention slowed cognitive decline

Table 2. Key studies cited in this review supporting the biologic plausibility of a cause-and-effect relationship between periodontitis and Alzheimer's disease.

Author	Year Published	Type of Study	Outcome
Forner et al. [12]	2006	Clinical trial	Suggests increased risk for bacteremia in periodontitis patients after chewing and tooth brushing
Haraszthy et al. [13]	2000	PCR assays of endarterectomy specimens	Periodontal pathogens are found in atherosclerotic plaques
Poole et al. [17]	2013	Brain histology	Lipopolysaccharide from periodontal bacteria can access Alzheimer's disease brain
Dominy et al. [18]	2019	PCR and immunohistochemical assays	Demonstrated *P. gingivalis* and gingipains in brain tissues and CSF of Alzheimer's patients
Riviere et al. [20]	2002	PCR and monoclonal antibody tests of brain tissue	Oral *Treponema* demonstrated in Alzheimer's disease brain tissues
Jamieson et al. [22]	1991	PCR assays of brain tissue	Latent herpes virus found in normal and Alzheimer's disease brains
Guo et al. [35]	2023	PCR assays of saliva and gingival crevicular fluid samples	Microbiome community was altered in Alzheimer's disease patients and the periodontal microbiome was sensitive to cognition changes
Hong et al. [38]	2016	Mouse model	Complement and microglia mediate synaptic loss in Alzheimer's disease
Hao et al. [39]	2022	Mouse model	*Porphyromonas gingivalis* induced brain overactivation of complement is critical for periodontitis associated acceleration of Alzheimer's disease
Poole et al. [40]	2015	Mouse model	*Porphyromonas gingivalis* was able to access mice brains and contribute to the activation of the complement cascade

Figure 1. Biologic plausibility: the presence of subgingival periodontal pathogens can lead to periodontitis in a susceptible host. This can result in systemic inflammation as pathogenic bacteria, their virulence factors, and pro-inflammatory mediators enter the vasculature. Systemic inflammation can exert an effect across the blood–brain barrier, activating microglia. Activated microglia can result in amyloid-β accumulation, neuronal death, and cognitive impairment. Bacterial pathogens and HSV-1 may also enter the trigeminal ganglion and act alone or synergistically to activate microglia.

The data from human studies generally support the hypothesis that there is an association between periodontitis and dementia and support a possible neuroinflammatory mechanism for the progression of Alzheimer's disease. The evidence suggests that *Porphyromonas gingivalis* and its virulence factors may play a role in the pathogenesis. Some evidence supports that HSV-1 may also play a role, acting synergistically with *Porphyromonas gingivalis*. Evidence from human studies supporting an association between tooth loss and dementia is more conflicting. This may be because tooth loss can be associated with caries, fractures, root resorption, iatrogenic factors, and the treatment of tooth malposition in addition to periodontitis.

The animal-based data seem to support an association between tooth loss and Alzheimer's disease better than the human evidence. Taslima et al. [50] recently showed that tooth loss in wild-type mice is associated with increased levels of proteins activated by chronic stress, which activated microglial cells. Sakamoto et al. [51] demonstrated that occlusal rehabilitation in rats improved spatial memory and increased neuron density. Tooth loss in humans is often followed by occlusal rehabilitation with fixed bridges, implants, and dentures, avoiding chronic stress. Perhaps this is another reason why human tooth loss data are not as convincingly associated with dementia as animal-based data. Like the human-based data, the evidence from animal studies supports the hypothesis that there is an association between periodontitis and Alzheimer's disease. The animal-based data also support a neuroinflammatory component to the Alzheimer's disease mechanism.

Papapanou wrote about the lessons learned from epidemiological data supporting an association between periodontitis and atherosclerosis and periodontitis and adverse pregnancy outcomes [65]. He pointed out the need for the use of consistent measures of periodontitis; the need for a consistent case definition for periodontitis; and the need to adjust for confounding factors that are known to affect the outcome. Of course, these principles are of equal importance for epidemiologic studies evaluating the association between periodontitis and Alzheimer's disease. The American Academy of Periodontology and the European Federation of Periodontology addressed the need for a case definition for periodontitis at the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. The case definition for periodontitis is [67] "interdental CAL detectable at ≥2 non-adjacent teeth, or buccal or oral CAL ≥ 3 mm with pocketing ≥ 3 mm detectable at ≥2 teeth but the observed CAL cannot be ascribed to non-periodontitis-related cause." Future studies evaluating the association between periodontitis and Alzheimer's disease need to use this case definition to establish consistency and should, to the extent possible, control for confounding variables.

Late-onset Alzheimer's disease is a complex disease process that may involve genetic, inflammatory, metabolic, and vascular conditions. With such a complex pathogenesis, it will not be easy to establish a clear cause-and-effect relationship between periodontal disease and Alzheimer's disease. Current studies cannot rule out the possibility of a hyper-inflammatory phenotype that makes individuals more susceptible to both periodontitis and Alzheimer's disease. In addition to using the accepted case definition for periodontitis and controlling for confounding variables, more prospective longitudinal studies that evaluate periodontal health at six sites per tooth, consider the inflammatory burden, and analyze the microbiota are needed.

There is currently limited evidence that therapeutic intervention for periodontitis is going to significantly alter Alzheimer's disease outcomes. Randomized controlled clinical trials evaluating intervention therapies for periodontitis in patients with Alzheimer's disease with mild cognitive impairment need to be conducted to determine the effect on the progression of dementia. Furthermore, early detection and treatment may be beneficial for slowing disease progression. Perhaps, once the signs and symptoms of Alzheimer's disease manifest themselves, it may be too late for periodontal interventions to have a significant impact on the progression of dementia. If this is the case, a focus on the prevention of periodontitis for individuals that have known risks for developing Alzheimer's disease may prove beneficial. Additional randomly controlled studies need to be conducted evaluating

the value of periodontal biomarkers for identifying individuals who are at risk for late onset Alzheimer's disease. An analysis of the blood microbiome for periodontal pathogens or immunoglobulins targeting these organisms may prove useful in this regard.

7. Conclusions

Numerous human and animal studies point to an association between periodontal disease and Alzheimer's disease. It seems clear that periodontal pathogens and/or their virulence factors can enter the brain via vascular or neural pathways. It also seems clear that these pathogens can stimulate a neuroinflammatory response that could lead to neurodegeneration and subsequent cognitive impairment. It is likely that the pathogenic microbiota, their virulence factors, and the inflammatory response they generate all play roles in the etiology of Alzheimer's disease. Limited evidence has suggested that combining periodontal care with lifestyle changes and pharmacologic therapy may slow Alzheimer's disease progression. Markers for periodontitis, in conjunction with other biomarkers, may prove useful in identifying individuals who are at risk for developing cognitive impairment.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. *Alzheimer's Dement.* **2023**, *19*, 1598–1695. [CrossRef] [PubMed]
2. Rostagno, A.A. Pathogenesis of Alzheimer's Disease. *Int. J. Mol. Sci.* **2023**, *24*, 107. [CrossRef] [PubMed]
3. Eke, P.I.; Dye, B.A.; Wei, L.; Slade, G.D.; Thorton-Evans, G.O.; Borgnakke, W.S.; Taylor, G.W.; Page, R.C.; Beck, J.D.; Genco, R.J. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *J. Periodontol.* **2015**, *86*, 611–622. [CrossRef] [PubMed]
4. Page, R.C. The role of inflammatory mediators in the pathogenesis of periodontal disease. *J. Periodont. Res.* **1991**, *26*, 230–242. [CrossRef] [PubMed]
5. Graves, D.T. The potential role of chemokines and inflammatory cytokines in periodontal disease progression. *Clin. Infect. Dis.* **1999**, *28*, 482–490. [CrossRef]
6. Kornman, K.S.; Page, R.C.; Tonetti, M.S. The host response to the microbial challenge in periodontitis: Assembling the players. *Periodontology* **2000**, *14*, 33–53. [CrossRef] [PubMed]
7. Beck, J.D.; Papapanou, P.N.; Phillips, K.H.; Offenbacher, S. Periodontal Medicine: 100 Years of Progress. *J. Dent. Res.* **2019**, *98*, 1053–1062. [CrossRef] [PubMed]
8. Bui, Q.F.; Almeida-da-Silva, C.L.C.; Huynh, B.; Trinh, A.; Liu, J.; Woodward, J.; Asadi, H.; Ojcius, D.M. Association between periodontal pathogens and systemic disease. *Biomed. J.* **2019**, *42*, 27–35. [CrossRef]
9. Zhang, Z.; Liu, D.; Liu, S.; Zhang, S.; Pan, Y. The role of *Porphyromonas gingivalis* outer membrane vesicles in periodontal disease and related systemic diseases. *Front. Cell. Infect. Microbiol.* **2021**, *10*, 585917. [CrossRef]
10. Kamer, A.R.; Craig, R.G.; Dasanayake, A.P.; Brys, M.; Glodzik-Sobanska, L.; de Leon, M.J. Inflammation and Alzheimer's disease: Possible role of periodontal diseases. *Alzheimer's Dement.* **2008**, *4*, 242–250. [CrossRef]
11. Ahmed, M.H.; Fatima, M.; Mondal, A.C. Influence of microglia and astrocyte activation in the neuroinflammatory pathogenesis of Alzheimer's disease: Rational insights for the therapeutic approaches. *J. Clin. Neurosci.* **2019**, *59*, 6–11. [CrossRef] [PubMed]
12. Forner, L.; Larsen, T.; Kilian, M.; Holmstrup, P. Incidence of bacteremia after chewing, tooth brushing, and scaling in individuals with periodontal inflammation. *J. Clin. Periodontol.* **2006**, *33*, 401–407. [CrossRef] [PubMed]
13. Haraszthy, V.I.; Zambon, J.J.; Trevisan, M.; Zeid, M.; Genco, R.J. Identification of periodontal pathogens in atheromatous plaques. *J. Periodontol.* **2000**, *71*, 1554–1560. [CrossRef] [PubMed]
14. Socransky, S.S.; Haffajee, A.D.; Cugini, M.A.; Smith, C.; Kent, R.L., Jr. Microbial complexes in subgingival plaque. *J. Clin. Periodontol.* **1998**, *25*, 134–144. [CrossRef] [PubMed]

15. Nara, P.L.; Sindelar, D.; Penn, M.S.; Potempa, J.; Griffin, W.; Sue, T. *Porphyromonas gingivalis* outer membrane vesicles as the major driver of and explanation for neuropathogenesis, the chlorine hypothesis, iron dyshomeostasis, and salivary lactoferrin in Alzheimer's disease. *J. Alzheimer's Dis.* **2021**, *82*, 1417–1450. [CrossRef] [PubMed]

16. Xie, J.; Cools, L.; Van Imschoot, G.; Van Wonterghem, E.; Pauwels, M.J.; Vlaeminck, I.; De Witte, C.; Andaloussi, S.E.; Wierda, K.; De Groef, L.; et al. *Helicobacter pylori* derived outer membrane vesicles contribute to Alzheimer's disease pathogenesis via C3-C3aR signaling. *J. Extacell Vesicles* **2023**, *12*, 12306. [CrossRef] [PubMed]

17. Poole, S.; Singhrao, S.K.; Kesavalu, L.; Curtis, M.A.; Crean, S. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. *J. Alzheimer's Dis.* **2013**, *6*, 665–677. [CrossRef]

18. Dominy, S.S.; Lynch, C.; Ermini, F.; Benedyk, M.; Marczyk, A.; Konradi, A.; Haditsch, U.; Raha, D.; Griffin, C.; Holsinger, L.J.; et al. *Porphyromonas gingivalis* in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Sci. Adv.* **2019**, *5*, eaau3333. [CrossRef]

19. Parra-Torres, V.; Melgar-Rodríguez, S.; Muñoz-Manríquez, C.; Sanhueza, B.; Cafferata, E.A.; Paula-Lima, A.C.; Díaz-Zúñiga, J. Periodontal bacteria in the brain—Implication for Alzheimer's disease: A systematic review. *Oral Dis.* **2023**, *29*, 21–28. [CrossRef]

20. Riviere, G.R.; Riviere, K.H.; Smith, K.S. Molecular and immunological evidence of oral *Treponema* in the human brain and their association with Alzheimer's disease. *Oral Microbiol. Immunol.* **2002**, *17*, 113–118. [CrossRef]

21. Chen, C.; Feng, P.; Slots, J. Herpesvirus-bacteria synergistic interaction in periodontitis. *Periodontol. 2000* **2020**, *82*, 42–64. [CrossRef] [PubMed]

22. Jamieson, G.A.; Maitland, N.J.; Wilcock, G.K.; Craske, J.; Itzhaki, R.F. Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. *J. Med. Virol.* **1991**, *33*, 224–227. [CrossRef] [PubMed]

23. Harris, S.A.; Harris, E.A. Molecular mechanisms for herpes simplex virus type 1 pathogenesis in Alzheimer's disease. *Front. Aging Neurosci.* **2018**, *10*, 48. [CrossRef] [PubMed]

24. Stein, P.S.; Desrosiers, M.; Donegan, S.J.; Yepes, J.F.; Kryscio, R.J. Tooth loss, dementia and neuropathology in the Nun Study. *J. Am. Dent. Assoc.* **2007**, *138*, 1314–1322. [CrossRef]

25. 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. Alzheimer's Dis.* **2015**, *44*, 777–786. [CrossRef]

26. 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*, 100–105. [CrossRef] [PubMed]

27. Kaye, E.K.; Valencia, A.; Baba, N.; Spiro III, A.; Dietrich, T.; Garcia, R.I. Tooth loss and periodontal disease predict poor cognitive function in older men. *J. Am. Geriatr. Soc.* **2010**, *58*, 713–718. [CrossRef]

28. Gil-Montoya, J.A.; Sanchez-Lara, I.; Carnero-Pardo, C.; Fornieles, F.; Montes, J.; Vilchez, R.; Burgos, J.S.; Gonzalez-Moles, M.A.; Barrios, R.; Bravo, M. Is periodontitis a risk factor for cognitive impairment and dementia? A case-control study. *J. Periodontal.* **2015**, *86*, 244–253. [CrossRef]

29. Ide, M.; Harris, M.; Stevens, A.; Sussams, R.; Hopkins, V.; Culliford, D.; Fuller, J.; Ibbett, P.; Raybould, R.; Thomas, R.; et al. Periodontitis and cognitive decline in Alzheimer's disease. *PLoS ONE* **2016**, *11*, e0151081. [CrossRef]

30. Sochocka, M.; Sobczyński, M.; Sender-Janeczek, A.; Zwolińska, K.; Blachowicz, O.; Tomczyk, T.; Ziętek, M.; Leszek, J. Association between periodontal health status and cognitive abilities. The role of cytokine profile and systemic inflammation. *Curr. Alzheimer Res.* **2017**, *14*, 978–990. [CrossRef]

31. Lee, Y.-T.; Lee, H.-C.; Hu, C.-J.; Huang, L.-K.; Chao, S.-P.; Lin, C.-P.; Su, E.C.-Y.; Lee, Y.-C.; Chen, C.-C. Periodontitis as a modifiable risk factor for dementia: A nationwide population-based cohort study. *J. Am. Geriatr. Soc.* **2017**, *65*, 301–305. [CrossRef] [PubMed]

32. Holmer, J.; Eriksdotter, M.; Schultzberg, M.; Pussinen, P.J.; Buhlin, K. Association between periodontitis and risk of Alzheimer's disease, mild cognitive impairment and subjective cognitive decline: A case-control study. *J. Clin. Periodontol.* **2018**, *45*, 1287–1298. [CrossRef] [PubMed]

33. Iwasaki, M.; Kimura, Y.; Ogawa, H.; Yamaga, T.; Ansai, T.; Wada, T.; Sakamoto, R.; Ishimoto, Y.; Fujisawa, M.; Okumiya, K.; et al. Periodontitis, periodontal inflammation, and mild cognitive impairment: A 5-year cohort study. *J. Periodont. Res.* **2019**, *54*, 233–240. [CrossRef]

34. Hategan, S.I.; Kamer, S.A.; Craig, R.G.; Sinescu, C.; de Leon, M.J.; Jianu, D.C.; Marian, C.; Bora, B.I.; Dan, T.-F.; Birdac, C.D.; et al. Cognitive dysfunction in young subjects with periodontal disease. *Neurol. Sci.* **2021**, *42*, 4511–4519. [CrossRef]

35. Guo, H.; Li, B.; Yao, H.; Liu, D.; Chen, R.; Zhou, S.; Ji, Y.; Zeng, L.; Du, M. Profiling the oral microbiomes in patients with Alzheimer's disease. *Oral Dis.* **2023**, *29*, 1341–1355. [CrossRef]

36. Fonseca, M.I.; Zhou, J.; Botto, M.; Tenner, A.J. Absence of C1q leads to less neuropathology in transgenic mouse models of Alzheimer's disease. *J. Neurosci.* **2004**, *24*, 6457–6465. [CrossRef]

37. Fonseca, M.I.; Ager, R.R.; Chu, S.-H.; Yazan, O.; Sanderson, S.D.; LaFerla, F.M.; Taylor, S.M.; Woodruff, T.M.; Tenner, A.J. Treatment with a C5aR antagonist decreases pathology and enhances behavioral performance in murine models of Alzheimer's disease. *J. Immunol.* **2009**, *183*, 1375–1383. [CrossRef]

38. Hong, S.; Beja-Glasser, V.F.; Nfonoyim, B.M.; Frouin, A.; Li, S.; Ramakrishnan, S.; Merry, K.M.; Shi, Q.; Rosenthal, A.; Barres, B.A.; et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* **2016**, *352*, 712–716. [CrossRef]

39. Hao, X.; Li, Z.; Li, W.; Katz, J.; Michalek, S.M.; Barnum, S.R.; Pozzo-Miller, L.; Saito, T.; Saido, T.C.; Wang, Q.; et al. Periodontal infection aggravates C1q-mediated microglial activation and synapse pruning in Alzheimer's mice. *Front. Immunol.* **2022**, *13*, 816640. [CrossRef]

40. Poole, S.; Singhrao, S.K.; Chukkapalli, S.; Rivera, M.; Velsko, I.; Kesavalu, L.; Crean, S. Active invasion of *Porphyromonas gingivalis* and infection-induced complement activation in ApoE$^{-/-}$ mice brains. *J. Alzheimer's Dis.* **2015**, *43*, 67–80. [CrossRef]

41. Lo Sasso, G.; Schlage, W.K.; Boué, S.; Veljkovic, E.; Peitsch, M.C.; Hoeng, J. The Apoe$^{-/-}$ mouse model: A suitable model to study cardiovascular and respiratory diseases in the context of cigarette smoke exposure and harm reduction. *J. Transl. Med.* **2016**, *14*, 146. [CrossRef] [PubMed]

42. Ishida, N.; Ishihara, Y.; Ishida, K.; Tada, H.; Funaki-Kato, Y.; Hagiwara, M.; Ferdous, T.; Abdullah, M.; Mitani, A.; Michikawa, M.; et al. Periodontitis induced by bacterial infection exacerbates features of Alzheimer's disease in transgenic mice. *Aging Mech. Dis.* **2017**, *3*, 15. [CrossRef] [PubMed]

43. Bahar, B.; Kanagasingam, S.; Tambuwala, M.M.; Aljabali, A.A.A.; Dillon, S.A.; Doaei, S.; Welbury, R.; Chukkapalli, S.S.; Singhrao, S.K. *Porphyromonas gingivalis* (W83) infection induces Alzheimer's disease-like pathophysiology in obese and diabetic mice. *J. Alzheimer's Dis.* **2021**, *82*, 1259–1275. [CrossRef] [PubMed]

44. Qian, X.; Zhang, S.; Duan, L.; Yang, F.; Zhang, K.; Yan, F.; Ge, S. Periodontitis deteriorates cognitive function and impairs neurons and glia in a mouse model of Alzheimer's disease. *J. Alzheimer's Dis.* **2021**, *79*, 1785–1800. [CrossRef] [PubMed]

45. Dewey, C.W.; Rishniw, M. Periodontal disease is associated with cognitive dysfunction in aging dogs: A blinded prospective comparison of visual periodontal and cognitive questionnaire scores. *Open Vet. J.* **2021**, *11*, 210–216. [CrossRef] [PubMed]

46. Goto, T.; Kuramoto, E.; Dhar, A.; Wang, R.P.-H.; Seki, H.; Iwai, H.; Yamanaka, A.; Matsumoto, S.-E.; Hara, H.; Michikawa, M.; et al. Neurodegeneration of trigeminal mesencephalic neurons by the tooth loss triggers the progression of Alzheimer's disease in 3 x Tg-AD model mice. *J. Alzheimer's Dis.* **2020**, *76*, 1443–1459. [CrossRef] [PubMed]

47. Oue, H.; Miyamoto, Y.; Okada, S.; Koretake, K.; Jung, C.-G.; Michikawa, M.; Akagawa, Y. Tooth loss induces memory impairment and neuronal cell loss in APP transgenic mice. *Behav. Brain Res.* **2013**, *252*, 318–325. [CrossRef]

48. Luo, B.; Pang, Q.; Jiang, Q. Tooth loss causes spatial cognitive impairment in rats through decreased cerebral blood flow and increased glutamate. *Arch. Oral Bio.* **2019**, *102*, 225–230. [CrossRef]

49. Taslima, F.; Jung, C.-G.; Zhou, C.; Abdelhamid, M.; Abdullah, M.; Goto, T.; Saito, T.; Saido, T.C.; Michikawa, M. Tooth loss induces memory impairment and gliosis in *App* knock-in mouse models of Alzheimer's disease. *J. Alzheimer's Dis.* **2021**, *80*, 1687–1704. [CrossRef]

50. Taslima, F.; Abdelhamid, M.; Zhou, C.; Chen, Y.; Jung, C.-G.; Michikawa, M. Tooth loss induces memory impairment and glial activation in young wild-type mice. *J. Alzheimer's Dis. Rep.* **2022**, *6*, 663–675. [CrossRef]

51. Sakamoto, S.; Hara, T.; Kurozumi, A.; Oka, M.; Kuroda-Ishimine, C.; Araki, D.; Iida, S.; Minagi, S. Effect of occlusal rehabilitation on spatial memory and hippocampal neurons after long-term loss of molars in rats. *J. Oral Rehab.* **2014**, *41*, 715–722. [CrossRef] [PubMed]

52. 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. [CrossRef] [PubMed]

53. Ma, K.S.; Hasturk, H.; Carreras, I.; Dedeoglu, A.; Veeravalli, J.J.; Huang, J.Y.; Kantarci, A.; Wei, J.C. Dementia and the risk for periodontitis: A population-based cohort study. *J. Dent. Res.* **2022**, *101*, 270–277. [CrossRef] [PubMed]

54. Schwahn, C.; Frenzel, S.; Holtfreter, B.; Van der Auwera, S.; Pink, C.; Bülow, R.; Friedrich, N.; Völzke, H.; Biffar, R.; Kocher, T.; et al. Effect of periodontal treatment on preclinical Alzheimer's disease—Results of a trial emulation approach. *Alzheimer's Dement.* **2022**, *18*, 127–141. [CrossRef]

55. Chen, L.; Cao, H.; Wu, X.; Xu, X.; Ji, X.; Wang, B.; Zhang, P.; Li, H. Effects of oral health intervention strategies on cognition and microbiota alterations in patients with mild Alzheimer's disease: A randomized controlled trial. *Geriatr. Nurs.* **2022**, *48*, 103–110. [CrossRef] [PubMed]

56. Rees, J.; Tuijt, R.; Burton, A.; Walters, K.; Cooper, C. Supporting self-care of long-term conditions in people with dementia: A systematic review. *Int. J. Nurs. Stud.* **2021**, *116*, 103432. [CrossRef] [PubMed]

57. Sharma, C.; Kim, S.; Nam, Y.; Jung, U.J.; Kim, S.R. Mitochondrial dysfunction as a driver of cognitive impairment in Alzheimer's disease. *Int. J. Mol. Sci.* **2021**, *22*, 4850. [CrossRef]

58. Scheltens, P.; De Strooper, B.; Kivipelto, M.; Holstege, H.; Chételat, G.; Teunissen, C.E.; Cummings, J.; van der Flier, W.M. Alzheimer's disease. *Lancet* **2021**, *397*, 1577–1590. [CrossRef]

59. Available online: https://clinicaltrials.gov/study/NCT03823404 (accessed on 17 July 2023).

60. Zhao, Y.; Quan, Y.; Lei, T.; Fan, L.; GE, X.; Hu, S. The role of inflammasome NLRP3 in the development and therapy of periodontitis. *Int. J. Me. Sci.* **2022**, *19*, 1603–1614. [CrossRef]

61. Van Zellar, M.; Dias, D.; Sebastio, A.M.; Valente, C.A. NLRP3 Inflammasome: A starring role in amyloid-β- and tau-driven pathological events in Alzheimer's disease. *J. Alzheimer's Dis.* **2021**, *83*, 939–961. [CrossRef]

62. Merchant, A.T.; Yi, F.; Vidanapathirana, N.P.; Lohman, M.; Zhang, J.; Newman-Norlund, R.D.; Fridriksson, J. Antibodies against periodontal microorganisms and cognition in older adults. *JDR Clin. Trans. Res.* **2023**, *8*, 148–157. [CrossRef] [PubMed]

63. Hill, B.A. The environment and disease: Association or causation? *JR Soc. Med.* **2015**, *108*, 32–37. [CrossRef] [PubMed]

64. Fedak, K.M.; Bernal, A.; Capshaw, Z.A.; Gross, S. Applying the Bradford Hill criteria in the 21st century: How data integration has changed causal inference in molecular epidemiology. *Emerg. Themes Epidemiol.* **2015**, *12*, 14. [CrossRef] [PubMed]

65. Papapanou, P.N. Systemic effects of periodontitis: Lessons learned from research on atherosclerotic vascular disease and adverse pregnancy outcomes. *Int. Dent. J.* **2015**, *65*, 283–291. [CrossRef] [PubMed]

66. Ryder, M.I.; Xenoudi, P. Alzheimer disease and the periodontal patient: New insights, connections and therapies. *Periodontol. 2000* **2021**, *87*, 32–42. [CrossRef]

67. Papapanou, P.N.; Sanz, M.; Buduneli, N.; Dietrich, T.; Feres, M.; Fine, D.H.; Flemmig, T.F.; Garcia, R.; Giannobile, W.V.; Graziani, F.; et al. Periodontitis: Consensus report of workgroup 2 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. *J. Periodontol.* **2018**, *89* (Suppl. S1), S173–S182. [CrossRef]