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An Investigation of the Association Between Periodontal Disease and the Risk of Alzheimer's Disease: A Retrospective, Population-Based, Matched Cohort Study in Greek Adults

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Abstract

Background/Aim: Previous studies have reported biological associations between periodontal disease and several malignancies, including cardiovascular disease, diabetes mellitus, rheumatoid arthritis, pulmonary diseases such as chronic obstructive pulmonary disease, and several types of cancer. This study aimed to investigate the potential association between periodontal disease indices and the risk of Alzheimer's Disease.

Materials and Methods: In the current case-control study, 41 patients with Alzheimer's Disease and 123 matched healthy controls were recruited from one dental and two medical private practices. Participants completed a standardized health questionnaire and underwent an oral clinical examination. Periodontal status was evaluated using Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Gingival Index (GI), and Bleeding on Probing (BOP). Univariate and multivariable logistic regression analyses were performed, adjusting for potential confounders.

Results: Male gender (p=0.060, OR=1.688), traumatic brain injury (p=0.07, OR= 2.912), increased Probing Pocket Depth (PPD) (p=0.060, OR = 1.473), and Bleeding on Probing (BOP) (p=0.009, OR = 3.034) were significantly associated with an elevated risk of Alzheimer's Disease, after adjustment for smoking status, educational level, and socio-economic status.

Conclusions: Male gender, a traumatic brain injury history, deeper periodontal pockets, and bleeding on probing were positively associated with the risk of developing Alzheimer's Disease.

Keywords: Periodontal Disease; Alzheimer's Disease; Risk Factors; Adults

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Introduction

Alzheimer's Disease (AD), the most common cause of dementia worldwide, is a progressive neurodegenerative disorder characterized by a gradual decline in cognitive, functional, and behavioral abilities [1].

The global burden of AD is increasing rapidly as a consequence of population aging and rising life expectancy. Epidemiological studies estimate that approximately one in 85 individuals worldwide may develop AD by 2050 [2]. In the United States, the number of adults aged 65 years and older living with AD is expected to increase from approximately 5.8 million in 2020 to 13.8-14 million by 2060 [3, 4]. Disease prevalence rises markedly with advancing age, reaching nearly 33% among individuals older than 85 years [4]. Gender-related differences have also been consistently reported, with females exhibiting a higher global prevalence and age-standardized mortality rate than males, corresponding to an approximately 1.17-fold greater disease burden [5].

AD is broadly classified into two major forms, familial early-onset AD and sporadic late-onset AD. Familial AD accounts for approximately 1-2% of all cases and is inherited in an autosomal

dominant manner, typically presenting with early disease onset and rapid clinical progression [6]. This form is strongly associated with mutations in the genes encoding Presenilin 1 (PSEN1), Presenilin 2 (PSEN2), and Amyloid-β Precursor Protein (AβPP). These mutations alter AβPP processing, resulting in excessive production and deposition of Amyloid-β (Aβ) peptides and subsequent early cognitive impairment [7]. In contrast, sporadic late-onset AD accounts for approximately 98% of cases and represents a multifactorial disorder with a complex and incompletely understood etiology [8].

Despite differences in genetic background and age of onset, both forms share common neuropathological hallmarks [9]. The pathogenesis of sporadic AD is thought to involve interactions among genetic susceptibility, aging-related mechanisms, oxidative DNA damage, vascular dysfunction, environmental exposures, chronic systemic inflammation, and other age-associated factors [7, 10]. Age remains the strongest risk factor for sporadic AD, particularly after 60-65 years of age [11]. Among the identified genetic susceptibility factors, the Apolipoprotein Eε4 (ApoEε4) allele is considered the most significant genetic determinant of disease risk [12]. In addition, Genome-Wide Association Studies (GWAS) have identified more than 20 susceptibility loci associated with AD, underscoring the substantial contribution of genetic factors to disease development [13-15]. Beyond genetic predisposition, numerous modifiable risk factors have been linked to AD onset and progression. Epidemiological studies suggest that low educational attainment, smoking, physical inactivity, depression, midlife obesity, hypertension, and type 2 Diabetes Mellitus (DM) may collectively account for approximately 54% of AD risk [16, 17]. Additional life-style and environmental factors associated with increased risk include dyslipidemia, Cardiovascular Disease (CVD), traumatic brain injury, hyperhomocysteinemia, hearing impairment, chronic stress, sleep disturbances, air pollution exposure, oral diseases, the use of anticholinergic medications [18, 19], while Vitamin D deficiency has also been proposed as a potential contributor to disease susceptibility [20]. The growing recognition of these potentially modifiable determinants highlights the importance of preventive strategies aimed at improving vascular health, promotin healthy lifestyles, and reducing chronic inflammation to delay or mitigate disease onset and progression. Nevertheless, despite substantial advances in research, the precise mechanisms underlying AD pathogenesis remain incompletely understood [10].

Increasing evidence suggests that systemic inflammation may play a critical role in AD development by influencing inflammatory processes within the Central Nervous System (CNS) [21, 22]. Conditions characterized by persistent inflammation, including CVD, DM, renal dysfunction, and Periodontal Disease (PD), may alter CNS immune homeostasis and contribute to neuro-degenerative processes [2, 23-26]. These observations support the concept that inflammatory signals originating from peripheral tissues are able to influence brain function through complex neuroimmune interactions. Moreover, systemic inflammation plays a pivotal role in the pathogenesis of AD by modulating neuro-inflammatory cascades within the CNS [21, 22].

Microbial pathogens have emerged as potential contributors of AD pathogenesis [27]. Notable emphasis is placed on periodontal pathogens associated with periodontitis, a prevalent worldwide chronic inflammatory disease affecting the supporting periodontal tissues [28-32]. Advanced periodontitis is characterized by persistent inflammation of the gingiva, periodontal ligament, and alveolar bone, culminating in progressive tissue destruction, tooth mobility, and eventual tooth loss if unresolved [33]. According to the World Health Organization (WHO), severe periodontitis affects approximately 19% of the global adult population, representing over one billion individuals [34]. Cumulatively, PD affects 45-50% of the global population, with prevalence and severity escalating as a function of age [35]. Epidemiological cohorts demonstrate a distinct age-dependent tend prevalence rises from approximately 5% at 35 years of age to nearly 50% by 45 years, exceeding 60% in older cohorts [36]. Crucially, advancing age represents a primary shared risk factor for both AD and PD, as older populations exhibit heightened susceptibility to chronic inflammatory and degenerative states, indicating that aging-related biological mechanisms underpin the progression of both disorders [37].

Periodontitis is epidemiologically and mechanistically linked to diverse systemic pathologies. These include DM [38], atherosclerosis, CVD [20, 35, 39], gastro-intestinal disorders [40], respiratory tract infections such as pneumonia [41], adverse pregnancy outcomes [42], oral and various extraoral malignancies [43, 44], as well as neurodegenerative disorders such as Parkinson's disease [45] and AD [28-32, 46-48].

The oral cavity harbors a complex, dynamic microbial ecosystem essential for maintaining localized and systemic homeostasis [49]. Under physiological conditions, the oral microbiota maintains a symbiotic equilibrium that regulates host immunity, exerts colonization resistance against pathogens, and preserves metabolic homeostasis [50]. However, poor oral hygiene, sustained inflammation, or systemic disease can precipitate oral dysbiosis. This shift induces a pathogenic transition within the subgingival niche, where impaired host defenses facilitate the overgrowth and persistence of virulent species, notably *Porphyromonas gingivalis, Treponema denticola*, and *Fusobacterium nucleatum* [51, 52]. Among these dysbotic species, P. gingivalis acts as a keystone pathogen in chronic periodontitis [53-55]. Its virulence is mediated by an array of factors, including Lipopolysaccharide (LPS), capsular polysaccharides, and gingipains [56]. Gingipains, a specialized family of cysteine proteases, serve as major determinants of P. gingivalis pathogenicity, facilitating bacterial survival, tissue invasion, immune evasion, and biofilm colonization [56]. Furthermore, these enzymes degrade extracellular matrix components, particularly collagen, which impairs tissue repair and perpetuates chronic local inflammation [57]. During advanced disease stages, periodontal infection compromises vascular integrity, enabling the translocation of oral pathogens and their respective virulence factors into the systemic circulation [57]. Transient bacteremia occurs frequently during oral hygiene practices or invasive dental interventions, providing a direct pathway for the systemic dissemination of microorganisms and their metabolic byproducts [58].

Concurrently, chronic periodontitis elevates serum concentrations of inflammatory biomarkers, including C-Reactive Protein (CRP) [59] and pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1beta (IL-1β) [60], demonstrating that localized periodontal inflammation exerts a systemic immunological toll.

Through this hematogenous dissemination, *P. gingivalis* and its structural components reach distant organs to exacerbate peripheral inflammatory and degenerative pathologies, including atherosclerosis, rheumatoid arthritis, non-alcoholic steatohepatitis, and squamous cell carcinoma [61-63]. Crucially, *P. gingivalis* and its associated virulence factors have been detected directly within the brain parenchyma of

AD patients, providing definitive evidence for an oral-brain axis [26, 46, 48, 64-66]. Correspondingly, genomic DNA derived from *P. gingivalis* is present in AD brain tissue, while experimental oral infection in animal models confirms bacterial colonization of the CNS accompanied by the accelerated production and accumulation of Amyloid-beta (Aβ) peptides [53]. Compounding this direct microbial invasion, the oral microbiome contributes significantly to the initiation and acceleration of neuroinflammatory cascades [67]. Chronic peripheral conditions like PD sustain systemic immune activation, which subsequently promotes microglial activation within the CNS [68-71]. As the resident innate immune cells of the brain, microglia serve as central mediators of neuroinflammation, a process widely recognized as a principal driver of neurodegeneration [72, 73]. Consequently, peripheral inflammation alters the host systemic milieu, modulating CNS immune responsiveness and inducing neurodegenerative alterations.

Multiple pathways link microbial dysbiosis to neurological disease. While extensive literature characterizes the gut-brain axis and the intestinal microbiome's role in regulating cognition and neurodegeneration [74, 75], accumulating epidemiological and experimental evidence increasingly implicates extraintestinal microbial ecosystems, specifically the oral microbiome, in the pathogenesis of neurodegenerative disorders [76]. This emerging framework indicates that oral dysbiosis contributes to neuroinflammation *via* systemic immune activation, microbial translocation, and subsequent neuroinflammatory progression. To date, no prospective or retrospective epidemiological studies in Greece have systematically investigated the association between PD indices and the risk of developing AD. Therefore, the present case-control study was designed to evaluate the potential relationship between clinical periodontal parameters and AD development in a population of Greek adults.

Materials and Methods

Study design and estimation of the study size

A case-control study design was employed, including a total of 164 participants (90 males and 74 females), aged 55-86 years. The study population comprised 41 patients diagnosed with AD and 123 systemically healthy controls. Sample size estimation was assessed according to EPI-TOOLS guidelines (https://epitools.ausvet.com.au) [77], based on AD prevalence, assuming a 95% confidence interval and 80% statistical power. Participants were recruited from two medical clinics and one private dental practice between May 2024 and March 2026. All individuals underwent comprehensive oral and dental clinical examinations and completed a structured standardized medical and dental questionnaire. Periodontal status was assessed according to World Health Organization (WHO) recommendations for age-specific periodontal evaluation [78].

Eligibility criteria for cases and controls

Eligible CM patients and healthy controls had not received periodontal treatment, either conservative or surgical, within the preceding six months. Furthermore, participants had not received systemic glucocorticoids, immunosuppressive therapy, or systemic antibiotic treatment during the correspondent period. Inclusion criteria also required the presence of more than 15 natural teeth and a diagnosis of periodontitis ranging from stage I to IV [79].

Exclusion criteria included systemic conditions potentially affecting oral and periodontal health, such as rheumatoid arthritis, acute lung diseases immuno-suppressed patients and malignancies, due to their potential confounding effects on periodontal outcomes [80].

Participants were recruited from similar social and professional environments, resided within the same metropolitan area, and attended the selected medical and dental practices for routine healthcare follow-up. To minimize genetic clustering, members of the same family were excluded. To reduce selection bias, healthy controls were frequency-matched to CM cases according to age, gender, and smoking status, which are recognized risk factors for periodontitis and potential covariates in statistical analyses [81, 82].

Patients with advanced AD were excluded from the study, as it is evident that such patients often neglect or are unable to adequately maintain their oral health. Therefore, their inclusion could have resulted in biased associations.

Diagnosis of AD

The clinical diagnosis of AD is based on the medical history, comprehensive clinical and neurological examination, neurocognitive and Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), to evaluate cognitive impairment and exclude other causes of dementia. However, the definitive diagnosis of AD is established through biomarkers as they can detect the underlying pathological processes long before severe dementia appears. In cerebrospinal fluid that is obtained through a lumbar puncture, the following biomarkers are exaimed, Beta-Amyloid 42 (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau). Blood biomarkers include p-tau217, p-tau181, NfL (Neurofilament Light chain), and Aβ42/Aβ40 ratio. Theoretically an histopathological diagnosis of AD can be made in a living patient, but this is not performed as a routine clinical practice because it requires obtaining brain tissue (brain biopsy), which is invasive and carries risks. Histopathological examination can demonstrate the characteristic findings of the disease, amyloid plaques (β-amyloid plaques), neurofibrillary tangles composed of tau protein, and neuronal loss and brain atrophy [83-86].

In addition, patients with a diagnosed AD who were receiving pharmacological treatment (such as anti-amyloid antibodies [87], Cholinesterase inhibitors [88], and NMDA receptor antagonists [89] were also excluded from the study, as certain pharmacological agents may adversely affect the periodontal tissues and the oral mucosa [90].

The selection of patients for the study was based on individuals with the earliest possible diagnosis of AD. For this reason, the sample size was relatively small. In both forms of the disease, the primary clinical manifestation was memory impairment. The majority of cases involved individuals aged 60 years and older (sporadic [late-onset] AD), whereas a smaller proportion involved younger individuals aged 30-60 years (familial [early-onset] AD). In the sporadic form, the problem of differential diagnosis existed because, in older age groups, memory impairments may be attributed to advanced age rather than to the onset of the disease [91].

Collection of demographic and clinical variables

Prior to periodontal examination, all participants completed a standardized modified medical questionnaire [80]. Potential confounding variables recorded for adjustment included age, gender, smoking status, educational level, Socioeconomic Status (SES), medical history, current medication use, and the presence of chronic systemic conditions. Age was categorized into four groups: < 60, 61-70, 71-80, and ≥81 years. SES was classified according to monthly

income as ≤1,000 € or >1,000 €. Educational level was categorized as elementary education or university/college graduation.

Smoking status was classified as follows: never smokers: individuals who had smoked <100 cigarettes during their lifetime; former smokers: individuals who had smoked ≥100 cigarettes during their lifetime but were not current smokers; current smokers: individuals who had smoked ≥ 100 cigarettes during their lifetime and reported current daily or occasional smoking.

Intra-Examiner reliability

To evaluate intra-examiner reliability, 33 participants (20% of the total sample) were randomly selected for re-examination by the same calibrated dentist three weeks after the initial assessment. No statistically significant differences were identified between the two examinations, demonstrating excellent reproducibility (Cohen's κ=0.96). No oral hygiene instructions were provided during the interval between examinations.

Periodontal examination

Periodontal examinations were performed at the dental practice using a Williams periodontal probe with controlled probing force (0.2 N; DB764R, Aesculap AG & Co. KG), a dental mirror, tissue forceps, and a standard dental light source. Third molars and residual roots were excluded from the assessment.

Clinical periodontal parameters included Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Gingival Index (GI), and Bleeding on Probing (BOP). Measurements were obtained at four sites per tooth (mesiobuccal, distobuccal, mesiolingual, and distolingual) in all quadrants. The highest recorded value for each index was documented to the nearest 1.0 mm and subsequently dichotomized for statistical analysis.

PPD was categorized as stage I/II (maximum probing depth ≤4.0 mm with mostly horizontal bone loss, and maximum probing depth ≤5.0 mm with the same bone loss, respectively), and stage III/IV (in addition to stage II: probing depth ≥6.0 mm with vertical bone loss ≥3.0 mm and furcation involvement Class II or III and moderate ridge defect, and in addition to stage III: need for complex rehabilitation due to: masticatory dysfunction, secondary occlusal trauma-tooth mobility degree ≥ 2-and severe ridge defect, bite collapse, drifting, flaring, and less than 20 remaining teeth-10 opposing pairs, respectively) [92]. Concurrently, CAL was classified as stage I/II (interdental CAL at site of greatest loss, 1-2.0 mm, and 3-4.0mm, respectively), and stage III/IV (interdental CAL at site of greatest loss, ≥5.0 mm with tooth loss ≤4 teeth, and ≥5.0mm with tooth loss with tooth loss ≥5.0 teeth, respectively) [92].

Gingival inflammation severity was assessed using the Gingival Index (GI) of Löe and Silness [93] and dichotomized as: score 0: healthy gingiva or mild inflammation (GI scores 0-1); score 1: moderate to severe inflammation (GI scores 2-3).

BOP presence/absence was classified as- score 0: BOP absence, and -score 1: BOP presence and regarded positive if it observed within 15 seconds of probing.

Ethical considerations

Under Greek regulations, formal ethical approval is generally required for prospective interventional studies and clinical trials conducted under the supervision of national health authorities. As the present investigation was designed as a retrospective case control study, formal review and approval by the relevant regulatory authorities were not required.

All participants were informed regarding the objectives and procedures of the study and provided written informed consent prior to enrolment.

Assessment of covariates

Socio-demographic variables, and potential AD risk factors included as covariates in the statistical analysis. Other potential risk factors include CVDs [94], hyperlipidemia [95], DM [96], and traumatic brain injury [97].

Results

The mean age of the study sample was 53±4.5 years. The main clinical types concerned the sporadic [late-onset] AD (92.8%), and the familial [early-onset] AD (7.2%).

Table 1 displays the outcomes after application of Univariate analysis, and showed that previous Traumatic Brain Injury (p=0.007), deeper Periodontal Pockets (PPD) (p=0.087), and Bleeding on Probing (BOP) (p=0.022) were statistically significantly associated with risk for AD development. Table 1 also shows Unadjusted OR's and 95% CI for each variable analyzed. After application of the first step (step 1a - Enter method) of the logistic regression model it was found that Traumatic Brain Injury history (p=0.008) and Bleeding on Probing (p=0.016) were significantly associated with risk of AD appearance (Table 2). Table 2 also demonstrates Adjusted OR's and 95%CI for each index examined. The final step (step 10a -Wald method) of the model showed (Table 2) that male gender (p=0.060), Traumatic Brain Injury (p=0.007), deeper periodontal pockets (p=0.060), and Bleeding on Probing (p=0.009), were statistically significantly associated with risk for developing CM, after adjusting for known confounders.

Discussion

Over the past few decades, an extensive body of literature has linked PD, encompassing both gingivitis and, more notably, chronic periodontitis, to a diverse spectrum of systemic pathologies and disorders [98]. Following adjustment for confounding variables in the present study, male gender, a history of Traumatic Brain Injury (TBI), and specific clinical periodontal parameters, such as PPD and BOP, emerged as statistically significant risk factors for the development of AD. Conversely, traditional epidemiological covariates, including advanced age, SES, and educational attainment, exhibited no statistically significant association with AD risk in our cohort. This latter finding contrasts with several recent epidemiological reports, which have demonstrated that advanced age [3, 11], female gender, higher SES, lower educational status, tobacco smoking [98, 99], CVD, prior TBI [100, 101], DM, and hyperlipidemia [18, 19, 102-104] are associated with an increased incidence of AD.

PPD serves as a validated objective metric for assessing the severity and current inflammatory status of periodontal tissues [105]. Our findings demonstrated a statistically significant positive association between elevated PPD values and an increased risk of incident AD. This aligns with data from multiple cohort and case-control studies, which reported that deeper clinical probing depths associate with poorer cognitive performance [31, 106-113]. Nonetheless, given the observational design of the majority of these studies, the precise directionality and pathophysiological causality of this link remain to be definitively elucidated.

Table 1: Univariate analysis of cases and controls regarding each independent variable examined.

Variables	Cases	Controls	*p*-value	Odds Ratio and 95% Confidence Interval
Gender				
Males	26 (63.4)	64 (52.0)	0.138	1.598 (0.772-3.307)
Females	15 (36.6)	59 (48.0)		
Age (years)				
≤ 60	9 (22.0)	16 (13.0)		
61-70	13 (31.7)	31 (25.2)		
71-80	10 (24.4)	48 (39.0)	0.265	_____
≥ 81	9 (22.0)	28 (22.8)		
Socio-economic status				
Low	22 (53.7)	70 (56.9)	0.427	0.877 (0.431-1.783)
High	19 (46.3)	53 (43.1)		
Education level				
Low	25 (61.0)	65 (52.8)	0.235	1.394 (0.678-2.866)
High	16 (39.0)	58 (47.2)		
Smoking				
Never smokers	18 (43.9)	57 (46.3)	0.465	0.906 (0.445-1.846)
Previous/current smokers	23 (56.1)	66 (53.7)		
CVDs				
Absence	26 (63.4)	74 (60.2)	0.429	1.148 (0.553-2.384)
Presence	15 (36.6)	49 (39.8)		
Hyperlipidemia				
<240 mg/dL	21 (51.2)	59 (48.0)	0.428	1.139 (0.562-2.310)
≥240 mg/dL	20 (48.8)	64 (52.0)		
Diabetes Mellitus				
Absence	24 (58.5)	67 (54.5)	0.394	1.180 (0.577-2.413)
Presence	17 (41.5)	56 (45.5)		
Traumatic Brain Injury				
Absence	15 (36.6)	74 (60.2)	**0.007***	0.382 (0.184-0.783)
Presence	26 (63.4)	49 (39.8)		
Probing pocket depth				
≤4.00 mm	18 (43.9)	71 (57.7)	**0.087***	1.745 (0.855-3.559)
≤4.00- ≥6.0 mm	23 (56.1)	52 (42.3)		
Clinical Attachment Loss				
1.00-2.00 mm	14 (34.1)	54 (43.9)	0.180	1.509 (0.722-3.155)
≥ 3.0 mm	27 (65.9)	69 (56.1)		
Gingival Index				
Absence/Mild	17 (41.5)	59 (48.0)	0.294	0.768 (0.376-1.571)
Moderate/Severe	24 (58.5)	64 (52.0)		
Bleeding on Probing				
Absence	12 (29.3)	60 (48.8)	**0.022***	2.302 (1.076-4.921)
Presence	29 (70.7)	63 (51.2)		

*p-value: Statistically significant

The clinical relevance of this record is further supported by a meta-analysis conducted by Qiu *et al*., [114], which revealed that individuals with periodontitis carry a significantly higher risk of developing AD (Relative Risk [RR]=1.22, 95% Confidence Interval [CI]: 1.13-1.33, *P*<0.00001). This risk escalated further in cases of severe periodontitis (RR=1.54, 95% CI: 1.05-2.26, *P*=0.03), whereas moderate periodontitis did not yield a statistically significant risk increase (RR=1.19, 95% CI: 0.98-1.44, *P*=0.07). Furthermore, their pool data indicated that PPD was significantly higher in AD cohorts compared to healthy controls (Mean Difference [MD]=2.58, 95% CI:0.17-4.99, *P*=0.04). Consistent with these data, a separate systematic investigation by Goyal *et al*., [115] documented a positive correlation between increased probing depth and cognitive impairment. In contrast to PPD, CAL constitutes a critical index for evaluating cumulative, long-term periodontal tissue destruction, thus reflecting a retrospective biomarker of past inflammatory episodes. Although both parameters characterize distinct destructive phases of chronic periodontal inflammation [116], our dataset revealed no statistically significant association between CAL and the risk of AD. While previous epidemiological frameworks have suggested that advanced CAL significantly is associated with diminished cognitive functions [106-113], paralleling the trends observed for PPD, evidence remains mixed. For instance, the aforementioned meta-analysis by Qiu *et al*., [114] demonstrated that patients with AD exhibited significantly greater CAL than control groups (MD = 1.27, 95% CI: 0.43-2.10, P = 0.003). Similarly, a recent report by Goyal *et al*., [115] established that CAL positively associated with measurable cognitive decline.

Although the GI quantifies the severity of gingival inflammation and serves as a valuable tool for estimating localized inflammatory load, it is less frequently deployed in largescale epidemiological investigations [105]. In the present study, clinical measures of GI exhibited no statistically significant positive association with AD risk. Conversely, a longitudinal assessment by Mo et al. suggested that chronic gingivitis may significantly elevate the risk of Early-Onset AD (EOAD) [117].

BOP represents another cornerstone of periodontal examination and diagnosis, serving as the most reliable indicator of active PD. Biologically, BOP evaluates the host vascular response, capturing erythema, capillary expansion, and increased blood flow within the inflamed periodontal tissues. Consequently, it is an extensively utilized criterion for diagnosing gingival inflammation [118]. In our cohort, no statistically significant difference in BOP was recorded between patients with AD and healthy controls. It is worth noting, however, that this specific record has been underutilized in previous studies investigating this potential pathogenic link. In contrast to our findings, a prior meta-analysis demonstrated that the percentage of BOP in AD cohorts was significantly elevated compared to healthy control groups (MD=21.11%, 95% CI:18.23%-23.99%, *P*<0.00001) [114].

Regarding disease status, although patients with Chronic Periodontitis (CP) exhibited higher crude Hazard Ratios (HR=1.301, 95% CI: 1.012-1.673, *P*=0.0404) for developing AD than their periodontally healthy counterparts, the fully adjusted model failed to reach statistical significance (adjusted HR [aHR]=1.297, 95% CI: 0.995-1.692, *P*=0.0547). Nevertheless, a significant chronological threshold was observed, as the association between CP and AD became pronounced after 10 years of sustained CP exposure (aHR=1.707, *P*=0.0077) [64].

Accumulating evidence from longitudinal cohorts, case-control frameworks, and meta-analyses has progressively established a robust, dose-dependent relationship between periodontitis and AD pathology [64, 119-121]. Individuals diagnosed with periodontitis consistently displayed an elevated predisposition to AD compared to healthy individuals [122-125]. For instance, a large-scale retrospective cohort study involving 262,349 participants demonstrated that CP was associated with a 5% higher risk of incident AD (aHR=1.05, 95% CI: 1.00-1.11), underlining periodontitis as an independent, modifiable risk factor for dementia regardless of lifestyle behaviors [107]. This progression was further substantiated by a prospective cohort study of 90 AD patients, in which comorbid periodontitis was linked to accelerated cognitive decline [107].

Furthermore, a trial emulation study by Schwahn et al. comparing 177 periodontally treated patients with 409 untreated subjects revealed that periodontal intervention exerted a protective effect against AD-related brain atrophy (adjusted effect: -0.41, 95% CI: -0.70 to -0.12), implying a therapeutic role in mitigating preclinical AD progression [106]. Collectively, these findings illustrate that periodontitis acts as a modifiable risk factor with graded effects on AD susceptibility. Despite these insights, several discrepancies and inconsistent results persist

Table 2: Presentation of association between potentially risk factors and AD according to Enter (first step-1[a]) and Wald (last step 7[a]) method of multivariate logistic regression analysis model.

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP (B)	
								Lower	Upper
Step 1[a]	Gender	,542	,419	1,672	1	,196	1,719	,756	3,908
	Age.group	,408	,209	3,793	1	**,051***	,665	,441	1,003
	Socioecon.stat	,147	,422	,121	1	,728	1,158	,507	2,648
	Educat.lev	-,316	,408	,600	1	,438	,729	,328	1,621
	Smok.stat	,003	,416	,000	1	,995	1,003	,444	2,266
	Cardiovas.dis	,329	,435	,572	1	,449	,719	,306	1,689
	Hyperlipid	,053	,404	,017	1	,895	1,055	,478	2,328
	Diab.mellit	,144	,438	,108	1	,742	1,155	,490	2,723
	Traum.br.inj	1,174	,440	7,099	1	**,008***	3,234	1,364	7,667
	Prob.poc.dep	,551	,465	1,402	1	,236	1,576	,432	1,435
	Clin.att.loss	515	,507	1,032	1	,310	,597	,221	1,614
	Ging.ind	,221	,499	,197	1	,657	1,248	,470	3,316
	Bl.on.prob	1,155	,479	5,825	1	**,016***	3,175	1,243	8,115
	Constant	1,608	,690	5,430	1	,020	,200		
Step 10[a]	Gender	,474	,401	1,543	1	**,060***	1,688	,522	3,016
	Traum.br.inj	1,069	,396	7,269	1	**,007***	2,912	1,339	6,334
	Prob.poc.dep	,749	,398	3,539	1	**,060***	1,473	,417	1,332
	Bl.on.prob	1,110	,424	6,856	1	**,009***	3,034	1,322	6,962
	Constant	2,352	,462	8,565	1	,003	,259		

a. Variable(s) entered on step 1: gender, age.group, socioecon.stat, educat.lev, smok.stat, cardiovas.dis, hyperlipid, diab.mellit, traum.br.inj, prob.poc.dep, clin.att. loss, ging.ind, bl.on.prob.

*p-value: Statistically significant

in the literature [106]. These variations are hypothesized to stem from methodological and confounding factors, such as cohort age heterogeneity, differing follow-up durations, and baseline disparities in oral hygiene status. Consequently, well-designed, prospective, standardized cohort studies, employing rigorous control for these specific confounders and utilizing uniform outcome measures, are critically warranted to reconcile these inconsistencies and validate the precise pathophysiological links.

Patients with sustained exposure to chronic periodontitis for a minimum duration of eight years demonstrate an elevated risk of developing cognitive decline or manifest AD, while notably, alveolar bone loss is associated with a 2.1-fold increase in the risk of incident cognitive impairment [126]. Several of the underlying pathophysiological mechanisms responsible for this link remain poorly understood and warrant deeper academic exploration [126]. Parallel clinical and epidemiological investigations have corroborated these established associations [64, 123, 127-130]. Concurrently, owing to inherent methodological constraints within epidemiological frameworks, specifically regarding residual confounding variables and the potential for reverse causation, definitive evidence establishing a solid causal relationship between PD and AD remains relatively constrained [8].

PD is increasingly recognized as a chronic low-grade systemic inflammatory condition carrying profound implications for overall systemic health, with documented links to CVD, DM, and, more recently, neurodegenerative pathologies such as AD [131]. Longitudinal epidemiological surveys have consistently reported that individuals diagnosed with PD exhibit a higher prevalence of both AD and mild cognitive impairment [64, 106, 132].

In a large-scale, age- and gender-matched cohort involving 10,115 participants with severe periodontitis and an equal number of periodontally healthy controls, the clinical consequences of oral health status were explicitly clear [133]. Following rigorous multivariable adjustment for sociodemographic attributes, anthropometric parameters, lifestyle factors, and underlying comorbidities, the risk profiles for AD (HR=1.08), Vascular Dementia (VaD; HR=1.24), and Mixed Dementia (MD; HR=1.16) were found to be significantly elevated among patients suffering from severe periodontitis who retained between 1 and 9 teeth [133]. Consistently, recent clinical literature has demonstrated that periodontitis negatively impacts the onset and/or kinetic progression of multiple dementia subtypes, including AD and VaD [64, 134]. Conversely, alternative investigative frameworks have failed to corroborate these distinct outcomes, reporting an absence of a direct causal progression [135, 136]. Finally, certain cohorts have noted that while PD displays a positive association with AD and overarching dementia phenotypes, the association does not always cross the threshold of statistical significance, with risk estimates for general dementia typically trending lower than those calculated specifically for AD [137].

Although the precise biological mechanisms underlying the implication of oral health or PD in the pathogenesis of AD remain fully elucidated, several interconnected mechanistic hypotheses have been proposed. Mounting evidence increasingly associates periodontitis with Amyloid-β (Aβ) accumulation, accelerated

cognitive decline, all-cause dementia, and incident AD [115, 119, 122, 125, 127, 128, 138-141]. At the microbiological level, periodontal pathogens have been heavily implicated in AD-related cascades. Specifically, *P. gingivalis* has been detected within AD brain tissues and is fundamentally associated with Aβ aggregation, tau hyper-phosphorylation, neuroinflammation, and neuronal apoptosis [53, 54, 142-144]. Furthermore, elevated systemic antibody responses against distinct periodontal pathogens, including *F. nucleatum* and *Prevotella intermedia*, have been robustly linked to long-term cognitive decline [52]. An increased abundance of *P. gingivalis, F. nucleatum, P.intermedia*, and *Veillonella parvula* has also been documented in AD cohorts, further supporting a distinct microbial contribution to the disease phenotype [145, 146].

Periodontitis and AD share overlapping inflammatory and metabolic risk pathways, including advanced aging, DM, CVD, vascular dysfunction, insulin resistance, and chronic systemic inflammation [147-154].

Aging-related phenomena, such as inflammaging, immunosenescence, and oral-systemic dysbiosis, may further amplify these bidirectional interactions between oral and cerebral pathologies. A central mechanistic framework involves the systemic dissemination of periodontal pathogens and their associated inflammatory mediators. Gram-negative anaerobes, predominantly *P. gingivalis, T. denticola, T. forsythia*, and *Aggregatibacter actinomycetemcomitans*, can breach local barriers and enter the systemic circulation as a consequence of periodontal tissue breakdown [53, 155]. These microorganisms and their potent virulence factors may subsequently gain access to the CNS *via* hematogenous spread, infected migrating immune cells, or retrograde neural pathways, such as the trigeminal and olfactory cranial nerves [53, 66, 155-158].

This neuro-invasion is further facilitated by Blood-Brain Barrier (BBB) disruption, which is mediated by circulating inflammatory cytokines and matrix metalloproteinases [156]. Compelling evidence from both experimental models and human post-mortem studies confirms the presence of *P. gingivalis* DNA and Lipopolysaccharides (LPS) in the brain, validating this dissemination route [53, 66]. Once inside the CNS, these microbial constituents activate resident microglia and astrocytes, precipitating an upregulation and sustained secretion of pro-inflammatory cytokines, specifically Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [65, 159]. Consequently, neuroinflammation represents a pivotal axis linking periodontitis to AD progression. Peripheral inflammatory signals amplify central immune responses, promoting sustained microglial activation and contributing to pathological Aβ deposition, tau propagation, and synaptic dysfunction [123, 160]. Microglia, the resident immuno-competent cells of the CNS, maintain homeostatic equilibrium under physiological conditions, however, they adopt a highly neurotoxic, pro-inflammatory phenotype in response to chronic stimuli such as LPS, fibrillar Aβ, and interferon-γ, resulting in the chronic release of IL-1β, IL-6, and TNF-α, and subsequent neurodegeneration [161-164].

Among the studied periodontal pathogens, *P. gingivalis* remains the most extensively evaluated. Its structural and secretory virulence factors, encompassing gingipains, LPS, fimbriae, and Outer Membrane Vesicles (OMVs), can profoundly disrupt BBB integrity, accelerate amyloidogenesis, and induce hyperphosphorylated tau pathology [53, 165-169]. Notably, experimental target inhibition of gingipains has been shown to reduce neuro-inflammatory signalling and attenuate amyloid burden, providing evidence of a causal contribution [53]. Concurrently, *T. denticola* has been isolated from AD brains and demonstrated to induce Aβ accumulation, tau phosphorylation, and neuronal apoptosis in experimental bio-models [158, 170, 171]. Similarly, *F. nucleatum* and *A. actinomycetemcomitans* contribute to neuroinflammatory cascades *via* LPS, and OMV, mediated activation of cerebral glial cells [164, 172-174]. Additional periodontal species, including *T. forsythia*, *Campylobacter rectus*, *P. intermedia*, and *V. parvula*, may further fuel microbial dysbiosis and exert synergistic inflammatory effects, although their precise individual roles remain less characterized.

Innate immune activation represents another critical mechanistic bridge. Inflammasomes, particularly the NLRP1 and NLRP3 complexes, are heavily upregulated in AD, driving cytokine maturation, pyroptosis, and progressive neurodegeneration. Periodontal pathogens and their shedding products, including *P. gingivalis* - derived OMVs, prime and activate NLRP3 signalling, thereby amplifying downstream neuroinflammatory cascades and enhancing IL-1β production [53, 174]. Furthermore, classical complement pathway activation, particularly C1q-mediated aberrant synaptic pruning, alongside Cathepsin B-dependent molecular pathways, closely links chronic periodontal infection to amyloidogenesis and accelerated neuronal loss [180, 181].

Genetic susceptibility further modulates these intricate inflammatory and microbial interactions. Apolipoprotein E (APOE), particularly the ε4 allele, stands as the most robust genetic risk factor for late-onset AD, regulating physiological amyloid clearance, tau pathology, lipid metabolism, and central neuroinflammation [72, 177, 178]. Synergistic interactions between the APOE genotype and the periodontal microbiota may drastically heighten individual disease susceptibility [72, 178, 179]. Biologically, gingipains may directly cleave the APOE protein, potentially generating neurotoxic fragments [180, 181]. Experimental models further indicate that APOE deficiency increases host susceptibility to *P. gingivalis* - induced cerebral infection and abnormal complement activation, while advanced age amplifies these deleterious effects via heightened baseline inflammation and diminished neuroprotective capacity [62, 65].

Systemic inflammation and vascular dysfunction provide additional critical links between PD and neurodegeneration. Periodontitis is robustly associated with systemic endothelial dysfunction, vascular wall injury, and impaired cerebral perfusion, all of which compromise cognitive reserve [182]. From a broader perspective, an infectious hypothesis of AD proposes that a polymicrobial burden, comprising oral bacteria, spirochetes, and herpes viruses, collectively drives disease progression [183]. Within this conceptual frame-work, Aβ has been characterized as an antimicrobial peptide, suggesting that its cerebral accumulation may initially represent an innate immune defense mechanism rather than an exclusively pathological aggregation [184]. Nonetheless, chronic systemic inflammation driven by circulating microbial products, such as LPS, inevitably promotes BBB hyper-permeability, chronic immune exhaustion, and amyloidogenic processes [185-187].

Furthermore, the gut microbiome contributes to this systemic network via distant immune modulation, establishing a bidirectional oral-gut-brain axis that influences neurodegenerative risk [188-191]. Concurrently, epigenetic modifications, including altered DNA methylation patterns and histone modifications, represent shared

hallmarks of both periodontitis and AD, suggesting a long-term epigenetic regulation of pro-inflammatory gene expression [192-194].

Despite the compelling epidemiological and mechanistic evidence corroborating an association between periodontitis and AD, definitive causality remains obscured by confounding variables and the confounding effect of reverse causation, given that progressive cognitive decline severely impairs oral hygiene and secondary periodontal status [195]. To address these limitations, Mendelian randomization studies have been increasingly deployed to clarify true causal vectors [196, 197]. In conclusion, current evidence strongly supports a multifactorial association between periodontitis and AD mediated by systemic microbial dissemination, sustained peripheral inflammation, and chronic neuro-immune activation, although the definitive causal pathways remain to be unequivocally established.

Discrepancies between studies could be due to differences in study design, population or periodontal disease measures used. The possible explanation for the conflicting results could be attributed to differences in the study samples in relation to age, gender, SES, educational status concerning smoking habits, and the extent and severity of PD. In most cases the confounding effect of smoking has been taken into account applying multivariate regression models with a non-quantitative smoking variable. In other similar reports the confounding effect of smoking has been removed by excluding smokers. Confounding represents a bias that the investigator hopes to prevent or remove from the effect estimate. In contrast, effect modification is a property of the effect under study. Tobacco and other risk factors, such as age, SES, and educational status can act as confounding factors or effect modifiers [198].

The strengths and limitations of the present study should be carefully considered when interpreting the observed findings. Key strengths include the completeness of follow-up and the use of a well-characterized cohort, which enabled the assessment of both confounding and interaction by established risk factors, thereby minimizing the likelihood of biased associations. Furthermore, PD was defined based on clinical oral examination rather than self-reported data, reducing the risk of exposure misclassification and the potential underestimation of the association under investigation [199, 200].

Nevertheless, certain limitations should be acknowledged. In particular, the possibility of residual confounding cannot be excluded, as risk estimates may still be influenced by unmeasured or unknown confounders.

Conclusions

The current research showed that male gender, a traumatic brain injury history, deeper periodontal pockets, and bleeding on probing were positively associated with the risk of developing Alzheimer's Disease.

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