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Association of periodontitis with cognitive decline and its progression: Contribution of blood-based biomarkers of Alzheimer's disease to this relationship

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Abstract

Aim: To assess whether periodontitis is associated with cognitive decline and its progression as well as with certain blood-based markers of Alzheimer's disease.

Materials and Methods: Data from a 2-year follow-up prospective cohort study ($n = 101$) was analysed. Participants with a previous history of hypertension and aged ≥60 years were included in the analysis. All of them received a full-mouth periodontal examination and cognitive function assessments (Addenbrooke's Cognitive Examination (ACE) and Mini-Mental State Examination [MMSE]). Plasma levels of amyloid beta $(A\beta)_{1\text{-}40}$, $A\beta_{1\text{-}42}$, phosphorylated and total Tau (p-Tau and t-Tau) were determined at baseline, 12 and 24 months.

Tomás Sobrino and Yago Leira contributed equally as joint senior authors.

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Results: Periodontitis was associated with poor cognitive performance (MMSE: $\beta = -1.5$ [0.6]) and progression of cognitive impairment (hazard ratio [HR] = 1.8; 95% confidence interval: 1.0–3.1). Subjects with periodontitis showed greater baseline levels of p-Tau (1.6 [0.7] vs. 1.2 [0.2] pg/mL, $p < .001$) and $A\beta_{1\text{-}40}$ (242.1 [77.3] vs. 208.2 [73.8] pg/mL, $p = .036$) compared with those without periodontitis. Concentrations of the latter protein also increased over time only in the periodontitis group ($p = .005$).

Conclusions: Periodontitis is associated with cognitive decline and its progression in elderly patients with a previous history of hypertension. Overexpression of p-Tau and $A\beta_{1\text{-}40}$ may play a role in this association.

KEYWORDS

amyloid beta peptides, biomarkers, dementia, periodontitis, Tau protein

Clinical Relevance

Scientific rationale for study: The contribution of periodontitis to cognitive impairment and its progression has been described in the literature. However, the potential contribution of well-known plasma biomarkers of Alzheimer's disease to this link is missing.

Principal findings: Periodontitis is associated with cognitive decline and its progression in elderly individuals with a previous history of hypertension. p-Tau and $A\beta_{1\text{-}40}$ may play a key role in this relationship.

Practical implications: Our study highlights the need for periodontal care in elderly subjects suffering from common chronic conditions such as hypertension to reduce the risk of cognitive dysfunction.

1 | INTRODUCTION

Dementia is a common public health problem and is characterized by a decline in multiple cognitive domains sufficiently severe to affect social or occupational function. It is estimated that approximately 55 million people worldwide have dementia, and this number is expected to increase to 78 million by 2030 (Gauthier et al., 2021). It has a substantial impact on the patient's quality of life, as it is considered as one of the most disabling neurological conditions in the world (Feigin et al., 2019). Although Alzheimer's disease (AD) is the most common cause of dementia in the elderly, followed by vascular dementia (VD), it is suggested that both aetiologies are indeed related and that most patients have a mixed dementia (Arvanitakis et al., 2019). AD is characterized pathologically by brain atrophy, accumulation of amyloid beta (Aβ) peptides in the brain parenchyma (senile plaques) and blood vessels (amyloid angiopathy) as well as aggregation of the microtubule-stabilizing protein Tau (neurofibrillary tangles [NFTs]) (Huang & Mucke, 2012). Vascular-mediated cognitive impairment/dementia results from either localized larger cerebrovascular territory injury (ischaemic or haemorrhagic in nature) or cumulative cerebral small vessel disease such as lacunar infarcts and microbleeds (Bir et al., 2021).

In the last decade, growing evidence of modifiable risk factors for dementia has emerged. One of these factors is hypertension, a well-known vascular disorder that has been shown to increase the risk of dementia (Ou et al., 2020). Hypertension is a major risk factor for cerebrovascular disease and thereby for VD. Traditionally, AD has been thought to be a primary neurodegenerative condition and not of vascular origin. However, several studies support the view that vascular factors and disorders such as hypertension may be involved in AD, which may be considered as a *vasocognopathy* where the cause points towards impaired cerebral perfusion (de La Torre, 2004). With regard to the mechanisms underlying the association between high blood pressure (BP) and dementia, it is speculated that cerebrovascular dysfunction and damage produced by midlife hypertension impairs the vascular clearance of brain Aβ, resulting in amyloid accumulation in cerebral blood vessels and cognitive decline (Iadecola, 2014). Hence, subjects with high BP might be considered as a high-risk population to suffer cognitive decline.

Periodontitis, a highly prevalent chronic, oral, immune-mediated inflammatory infectious disease characterized by hard and soft periodontal tissue destruction, increases the risk of cognitive decline in the elderly (Iwasaki et al., 2016; Kaye et al., 2010; Nilsson et al., 2018). The potential contribution of periodontitis to certain AD-like features, such as neuroinflammation, cerebral Aβ deposits, elevated brain phosphorylated Tau (p-Tau) levels, neurodegeneration as well as cognitive impairment and behavioural/functional changes, has been described (Díaz-Zúñiga et al., 2020; Dominy et al., 2019; Ilievski et al., 2018). Similarly, periodontitis has been associated with hypertension, being one of the main mechanisms of the increased systemic pro-inflammatory state posed by this oral disease that could partially contribute to a rise in BP (Muñoz Aguilera et al., 2021). Therefore, it is reasonable to hypothesize that the presence of periodontitis could be associated with cognitive decline and its progression in a population at high risk of dementia (due to ageing combined with hypertension) and that Tau protein and Aβ peptides might play a significant role in this relationship.

The aim of the present study was to investigate the contribution of periodontitis to cognitive decline and its progression in older individuals

with a history of hypertension. The longitudinal changes over 2 years of follow-up in certain circulating biomarkers of AD were also explored.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The present study is a secondary analysis using data from the SANTIAGO study, which is a prospective cohort study with a mean follow-up of 2 years carried out between 2015 and 2019 in Galicia (Spain) (López-Dequidt, 2019). Originally, in the SANTIAGO study, elderly subjects of both genders with a diagnosis of hypertension (at least 5 years of disease evolution) aged ≥60 years were recruited from two primary care centres in A Estrada and Porto do Son and referred for a detailed cognitive, neuroimaging and periodontal examination to the University Clinical Hospital of Santiago de Compostela ($n = 101$). The primary aim of the SANTIAGO study was to investigate the longitudinal association between cerebral microangiopathy phenotypes and cognitive decline in a high-vascular-risk population (i.e., elderly hypertensive subjects). Arterial hypertension was defined as BP ≥ 140/90 mmHg in two determinations or taking antihypertensive medication. The following exclusion criteria were applied in the SANTIAGO study: (a) <10 teeth present (periodontal examination unreliable) (Vázquez-Reza et al., 2023); (b) previous history of cerebrovascular disease, cardiovascular disease, dementia, malignancy or other severe medical condition; (c) periodontal treatment in the last year; (d) active infectious/inflammatory diseases (e.g., HIV, hepatitis, chronic bronchitis, inflammatory bowel disease, rheumatoid arthritis, allergies or asthma); (e) treatment with systemic antibiotics, corticosteroids and/or immunosuppressive agents within 3 months prior to periodontal examination and (f) not able to give consent.

The SANTIAGO study was conducted in accordance with the World Medical Association Declaration of Helsinki (2013) and approved by the Ethics Committee of the Servizo Galego de Saúde (protocol #2016/399). Written informed consent was obtained from all included participants. Moreover, the present study was performed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al., 2008).

2.2 | BP assessment

Ambulatory BP monitoring over 24 h was performed in all participants. The mean 24-h systolic blood pressure and diastolic blood pressure values were recorded using a calibrated and validated SpaceLabs 90207 device (SpaceLabs Inc., USA). The number and type of antihypertensive medications and BP control were also recorded.

2.3 | Cognitive function assessment

Cognitive function was evaluated at three time points (baseline, 12 and 24 months) using the Spanish version of the Addenbrooke's Cognitive Examination (ACE) (García-Caballero et al., 2006) and the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). The maximum score of the ACE is 100 points, of which 30 points correspond to the MMSE included in seven domains (orientation to time [5 points], orientation to place [5 points], three word registration [3 points], attention and calculation [5 points], three-word recall [3 points], language [8 points] and visual construction [1 point]). ACE is distributed over six cognitive domains: orientation (10 points), attention (8 points), memory (35 points), verbal fluency (14 points), language (28 points) and visuospatial skills (5 points). Cognitive decline was defined as an ACE score ≤68/74 points (taking into account education level: low vs. medium/high) or MMSE score ≤24 points. Progressive cognitive decline was defined as a reduction over the follow-up in ACE or MMSE scores of ≥3 points.

2.4 | Periodontal examination

The periodontal examination has been described in detail elsewhere (Leira, Rodríguez-Yáñez, et al., 2019). The periodontal calibration was performed by a single calibrated periodontist (YL). The calibration was completed before the start of the study at the Periodontology Unit of the Faculty of Odontology (University of Santiago de Compostela) using 10 non-study patients suffering from moderate or severe periodontitis. Intra-examiner reliability was assessed by the intra-class correlation coefficients (for pocket depth [PD] and attachment loss [AL]), which were >0.75 for both parameters, thereby demonstrating a good degree of reliability in the measurements (Leira, Rodríguez-Yáñez, et al., 2019). In the present study, the following periodontal parameters were evaluated in all teeth (except third molars): (a) PD, measured from the free gingival margin to the bottom of the sulcus or pocket; (b) AL, measured from the cemento-enamel junction to the bottom of the sulcus or pocket and (c) the number of teeth present (excluding third molars and retained roots). All measurements were recorded at six sites per tooth (mesio-buccal, disto-buccal, mid-buccal, mesio-lingual, disto-lingual and mid-lingual), using a sterile mouth mirror and with a calibrated University of North Carolina periodontal probe (UNC 15; Hu-Friedy, Chicago, IL, USA).

The presence of periodontitis was defined according to the Centers for Disease Control and Prevention–American Academy of Periodontology consensus for epidemiologic studies. Accordingly, a periodontitis case was defined as one showing at least two interproximal sites with AL ≥ 3 mm and at least two interproximal sites with PD ≥ 4 mm (not on the same tooth) or one site with PD ≥ 5 mm (Eke et al., 2012).

2.5 | Other covariates

Socio-demographic data recorded and used in the present analysis included age, gender and educational level (low was defined as those participants who dropped out of school before age 14). Body weight was measured to the nearest 1 kg, and height was recorded to the nearest centimetre. Body mass index was calculated with the formula: weight (kg)/height $(m)^2$. Vascular risk factors that have been associated with increased risk of dementia were also recorded: previous

history of smoking (current smoker or former smoker with less than 1 year), alcohol consumption (>300 g of alcohol/week), history of diabetes (glycated haemoglobin [HbA1c] ≥6.5%, glycaemia ≥200 mg/dL in symptomatic patients, baseline glycaemia ≥126 mg/dL in two determinations or glycaemia after oral glucose tolerance test ≥200 mg/dL or under anti-diabetic medication) and dyslipidaemia (total cholesterol >250 mg/dL or low-density lipoprotein [LDL] cholesterol >130 mg/dL or under lipid-lowering medication).

2.6 | Laboratory analysis

Fasting blood samples were obtained in the morning at the same time as the periodontal assessment and interview. Briefly, 2 mL of venous blood was collected from the antecubital fossa by venepuncture using a 20-gauge needle with a 2-mL syringe. Blood samples were allowed to clot at room temperature, and after 1 h, serum was separated by centrifugation (15 min at 3000*g* at 4°C); then 0.5 mL of extracted serum was immediately transferred to 1.5-mL aliquots. Each aliquot was stored at −80°C until required for analysis. For plasma samples, the same procedure was used with the difference that no clotting needed to be done and EDTA vacutainers were used to collect blood. Standard biochemical parameters were determined at baseline from serum samples, which included levels of lipid fractions (total cholesterol [mg/dL], high-density lipoprotein [HDL, mg/dL] and LDL [mg/dL]), HbA1c (%) and inflammatory markers such as fibrinogen (mg/dL), erythrocyte sedimentation rate (mm/h) and leukocytes ($\times 10^9$/L). In addition, plasma biomarkers of AD were determined at three time points (baseline, 12 and 24 months) including $A\beta_{1\text{-}40}$ (pg/mL), $A\beta_{1\text{-}42}$ (pg/mL), $A\beta_{42:40}$ (pg/mL), p-Tau_{181} (pg/mL) and total Tau (t-Tau) (pg/mL) by an automated chemiluminescent enzyme immunoassay technique (Lumipulse G600II, Fujirebio). Functional sensitivity for plasma $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$ and p-Tau_{181} was 0.44, 0.43 and 0.261 pg/mL, respectively. The values for coefficient of variation were between 2.6% and 4.6% for plasma $A\beta_{1\text{-}40}$, between 4.0% and 5.6% for plasma $A\beta_{1\text{-}42}$ and between 2.3% and 3.9% for plasma p-Tau_{181}.

All determinations were performed in an independent laboratory blinded to clinical data (standard biochemistry at Central Laboratory of the Clinical University Hospital of Santiago de Compostela and neurodegeneration biomarkers at Clinical Neurosciences Research Laboratory of the same hospital). Clinical investigators were unaware of the laboratory results until the end of the study.

2.7 | Statistical analysis

The Kolmogorov–Smirnov test was applied to check for normality. Data are reported as mean values ± standard deviation if the variable is normally distributed, and as median (P25, P75) in case of non-normal distribution. Categorical variables are expressed as percentages (%). The statistical tests used to compare data were the independent *t*-test, Mann–Whitney test and χ^2 test. Intra- and inter-group comparisons between periodontitis and non-periodontitis groups were performed by analysis of variance for repeated measures. Logistic and linear regression models were created to test the associations between periodontitis and its clinical parameters with cognitive function and biomarkers of AD. Multivariate Cox proportional hazards regression analyses were used to determine the risk of progression in cognitive decline in periodontitis and non-periodontitis cohorts. All regression models were adjusted for potential confounders identified during univariate analyses. All statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and R software version 4.0.5 (Lucent Technologies, NJ, USA). The level of statistical significance was set at $p < .05$.

3 | RESULTS

3.1 | Main characteristics of study population according to periodontal status

The prevalence of periodontitis was 62.4%. Baseline characteristics of participants stratified by periodontal status are shown in Table 1. Periodontitis participants showed increased concentrations of serum HDL in comparison with non-periodontitis individuals. There were more current smokers in the periodontitis group than in the periodontally healthy group. Furthermore, 22.1% of participants had cognitive decline, of which 85.7% were diagnosed with periodontitis compared with 14.3% who had a healthy periodontium ($p = .006$). As expected, the periodontal status of participants was worse in terms of higher PD and AL in participants with periodontitis compared with subjects with a healthy periodontium. No statistically significant differences were observed for the rest of socio-demographic, clinical or biochemical variables as well as in vascular risk factors. No differences were noted for anti-hypertensive medication (Table 1). All participants were under anti-hypertensive treatment for at least 5 years. More than half of individuals in each group were taking more than one anti-hypertensive drug (perio: 66.7% vs. non-perio: 60.5%, $p = .177$). The mean number of anti-hypertensives consumed did not differ between groups (1.9 [0.8] vs. 1.8 [0.9], $p = .435$). The percentage of individuals showing well-controlled BP was similar in the periodontitis and non-periodontitis groups (46.0% vs. 39.5%, $p = .655$).

3.2 | Cross-sectional association between periodontitis and its clinical parameters with cognitive function

Overall, participants with periodontitis showed worse cognitive performance than periodontally healthy subjects at baseline (Figure 1). Particularly, lower MSME scores were found in the periodontitis participants in comparison to subjects without periodontitis (Figure 1b). However, no statistically significant differences were found for ACE (Figure 1a).

Linear regression analysis revealed that periodontitis (categorical variable) was associated with poor MMSE scores (Table 2). Clinical periodontal parameters were only associated with lower

TABLE 1 Chief characteristics of study population ($n = 101$).

Variable	Periodontitis ($n = 63$)	No periodontitis ($n = 38$)	p-Value
Socio-demographic variables			
Age (years)	71.6 (5.4)	70.0 (4.7)	.120
Females, *n* (%)	41 (65.1)	19 (50.0)	.149
Low education level, *n* (%)	39 (61.9)	22 (57.9)	.306
Clinical variables			
SBP (mmHg)	122.3 (11.3)	124.1 (12.0)	.545
DBP (mmHg)	69.5 (7.6)	72.0 (9.6)	.227
BMI (kg/m^2)	30.1 (4.5)	31.2 (5.0)	.243
Anti-hypertensive drugs, *n* (%)			
ACE inhibitors	15 (23.8)	7 (18.4)	.525
ARBs	41 (65.1)	26 (68.4)	.486
Calcium channel blockers	28 (44.5)	12 (31.6)	.362
Beta-blockers	5 (7.9)	7 (18.4)	.131
Diuretics	32 (50.8)	13 (34.2)	.184
Vascular risk factors			
Current smokers, *n* (%)	17 (27.0)	3 (7.9)	.022
Alcohol consumption, *n* (%)	4 (6.3)	6 (84.2)	.124
Diabetes, *n* (%)	22 (34.9)	15 (39.5)	.674
Dyslipidaemia, *n* (%)	47 (74.6)	28 (73.7)	.918
Biochemical parameters			
HbA1c (%)	6.8 (1.5)	6.6 (1.2)	.510
Leukocytes ($\times 10^9$/L)	7.9 (2.2)	7.4 (1.9)	.275
Total cholesterol (mg/dL)	196.2 (40.5)	192.9 (37.8)	.684
HDL (mg/dL)	62.2 (19.5)	54.2 (15.3)	**.039**
LDL (mg/dL)	111.4 (36.1)	114.3 (32.9)	.690
Fibrinogen (mg/dL)	424.7 (90.4)	437.9 (66.5)	.448
ESR (mm/h)	15 (7.0, 35.0)	12.0 (7.0, 25.5)	.404
Clinical periodontal parameters			
PD (mm)	3.7 (1.0)	2.8 (0.8)	**<.001**
AL (mm)	4.1 (1.1)	3.2 (1.2)	**.001**
Number of teeth present	21.5 (3.7)	22.8 (4.2)	.109

Note: Bold denotes $p < .05$.
Abbreviations: ACE, angiotensin-converting enzyme; AL, attachment loss; ARB, angiotensin II receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PD, pocket depth; SBP, systolic blood pressure.

MSME scores. Logistic regression analysis using data from the SANTIAGO study confirmed that subjects with increased PD were almost two times more likely to have cognitive decline (odds ratio $[OR]_{adjusted} = 1.9$; 95% confidence interval [CI]: 1.1–3.0, $p = .025$).

3.3 | Association between periodontitis and its clinical parameters with blood-based biomarkers of AD

Results showed that subjects with periodontitis had increased peripheral levels of $A\beta_{1\text{-}40}$ (mean difference = 33.9 [16.0] pg/mL, $p = .036$) and p-Tau (mean difference = 0.4 [0.1], $p < .001$) compared with periodontally healthy individuals (Figure 2a,d). No statistically significant differences were found for $A\beta_{1\text{-}42}$, $A\beta_{42:40}$ and t-Tau (Figure 2b,c,e).

Linear regression models showed that periodontitis was associated with elevated concentrations of plasma p-Tau (β $coefficient_{adjusted} = 0.3$ [0.1], $p = .016$) (Table 3). No other relevant associations were seen for the rest of the biomarkers.

When the levels of biomarkers of neurodegeneration were compared between groups during the 2-year follow-up period, a statistically significant progressive increase was observed for $A\beta_{1\text{-}40}$, which was more evident in the periodontitis group (Table 4; Figure 2a). No other differences were found for the rest of biomarkers at any of the time points.

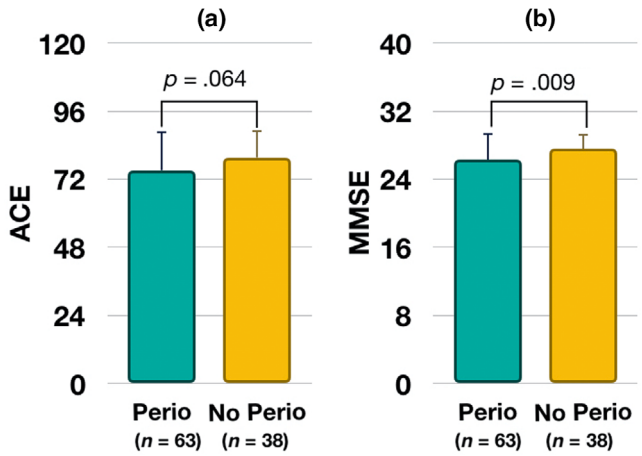

FIGURE 1 Cognitive test performance of study population at baseline: (a) Addenbrooke's Cognitive Examination (ACE); (b) Mini-Mental State Examination (MMSE).

TABLE 2 Association between periodontitis and its clinical parameters with cognitive performance.

	ACE	MMSE
Periodontitis	−2.5 (2.6)	−1.5 (0.6)*
PD	−2.1 (1.2)	−0.6 (0.3)*
AL	−1.5 (1.0)	−0.3 (0.2)

Note: β coefficients (SE) adjusted for age, gender, smoking habit and high-density lipoprotein.
Abbreviations: AL, attachment loss; ACE, Addenbrooke's Cognitive Examination; MMSE, Mini-Mental State Examination; PD, pocket depth.
*$p < .05$.

3.4 | Association between periodontitis and progression of cognitive decline

Over the 2-year follow-up period, participants with periodontitis showed progressive poorer cognitive performance in ACE and MMSE scores (both $p < .001$). This decline in the scores was observed at both 12 and 24 months when compared with baseline for both cognitive tests (Table 4). When the groups were compared at each time point, statistically significant differences were found only at 12 months for the ACE.

Progression in cognitive impairment was seen in 16.9% of the participants, of whom 83.3% had periodontitis compared with 16.7% without periodontitis ($p = .049$). Cox proportional hazards regression analysis showed that the presence of periodontitis at baseline was associated with increased risk of progression in cognitive decline (hazard ratio $[HR]_{adjusted} = 1.9$; 95% CI: 1.1–3.3, $p = .027$) (Figure 3).

4 | DISCUSSION

Results from this study confirmed that periodontitis increases the risk of cognitive decline and its progression in a population at high risk of developing dementia. Moreover, for the first time we showed that periodontitis was associated with increased peripheral levels of p-Tau and $A\beta_{1\text{-}40}$.

In the last decade, several population-based studies have suggested a relationship between periodontitis and poor cognitive function (Kamer et al., 2012; Shin et al., 2016; Sung et al., 2019). Results from our analysis using data from a cohort of elderly hypertensive subjects confirmed that participants with periodontitis were more

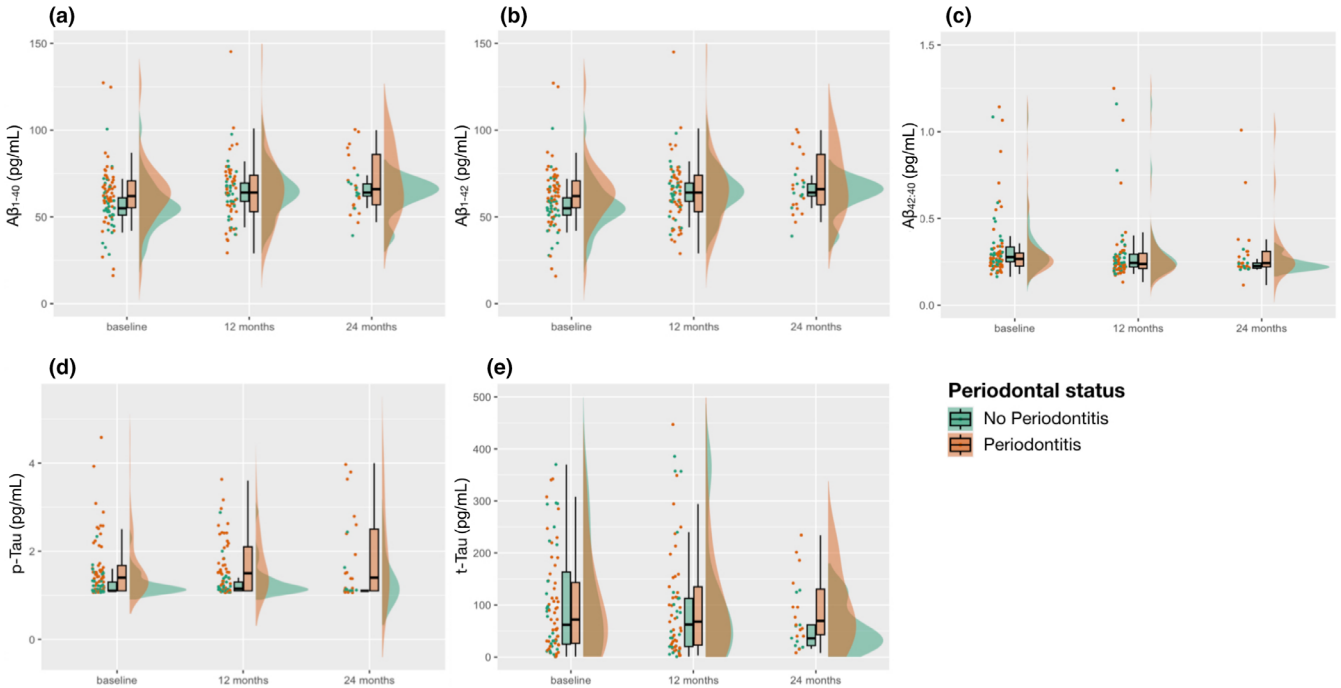

FIGURE 2 Plasma levels of Alzheimer's disease biomarkers at each time point (baseline, 12 and 24 months): (a) amyloid beta $(A\beta)_{1\text{-}40}$ (pg/mL); (b) $A\beta_{1\text{-}42}$ (pg/mL); (c) $A\beta_{42:40}$ (pg/mL); (d) phosphorylated Tau (p-Tau) (pg/mL) and (e) total Tau (t-Tau) (pg/mL).

TABLE 3 Cross-sectional association between periodontitis and its clinical parameters with levels of biomarkers of Alzheimer's disease.

	Periodontitis	*p*-Value	PD	*p*-Value	AL	*p*-Value
$A\beta_{1\text{-}40}$ (pg/mL)	32.3 (17.6)	.071	−4.9 (8.2)	.555	−5.9 (7.0)	.397
$A\beta_{1\text{-}42}$ (pg/mL)	−22.8 (19.8)	.253	−0.1 (9.1)	.990	−2.3 (7.8)	.766
$A\beta_{42:40}$ (pg/mL)	−0.1 (0.1)	.145	−0.0 (0.0)	.871	−0.0 (0.0)	.721
p-Tau (pg/mL)	0.3 (0.1)	**.016**	0.1 (0.1)	.073	0.0 (0.0)	.344
t-Tau (pg/mL)	−99.3 (130.9)	.450	−22.1 (60.3)	.715	−9.9 (51.2)	.847

Note: β coefficients (SE) adjusted for age, gender, smoking habit and high-density lipoprotein. Bold denotes $p < .05$.
Abbreviations: AL, attachment loss; $A\beta_{1\text{-}40}$, amyloid beta 1–40; $A\beta_{1\text{-}42}$, amyloid beta 1–42; $A\beta_{42:40}$, ratio amyloid beta 1–42/1–40; PD, pocket depth; p-Tau, phosphorylated Tau; t-Tau, total Tau.

TABLE 4 Longitudinal changes of biomarkers of Alzheimer's disease and cognitive performance according to periodontal status.

Group	Biomarker	Baseline	12 months	24 months	*p*-Value
Periodontitis	$A\beta_{1\text{-}40}$ (pg/mL)	242.1 (77.3)[a]	272.5 (122.6)	294.4 (141.1)[b,c]	**.005**
No periodontitis		208.2 (73.8)	264.1 (72.9)	266.1 (46.8)	**.043**
Periodontitis	$A\beta_{1\text{-}42}$ (pg/mL)	77.6 (70.2)	85.9 (132.3)	91.1 (66.8)	.053
No periodontitis		93.8 (114.7)	91.6 (87.7)	62.5 (10.4)	.288
Periodontitis	$A\beta_{42:40}$ (pg/mL)	0.4 (0.3)	0.3 (0.4)	0.3 (0.2)	.907
No periodontitis		0.5 (0.4)	0.4 (0.4)	0.2 (0.0)	.092
Periodontitis	p-Tau (pg/mL)	1.6 (0.7)[a]	1.6 (0.6)	1.9 (1.0)	.309
No periodontitis		1.2 (0.2)	1.3 (0.4)	1.3 (0.4)	.994
Periodontitis	t-Tau (pg/mL)	318.2 (546.3)	289.1 (545.9)	504.7 (763.8)	.170
No periodontitis		398.4 (594.0)	378.8 (591.9)	55.3 (43.6)	.620
Group	**Cognitive test**	**Baseline**	**12 months**	**24 months**	***p*-Value**
Periodontitis	ACE	75.2 (13.9)	74.1 (14.2)[a,b]	71.7 (15.1)[b]	**<.001**
No periodontitis		79.7 (9.5)	80.0 (8.8)	80.7 (10.3)	.516
Periodontitis	MMSE	26.3 (3.1)[a]	26.7 (2.6)[b]	25.0 (3.1)[b]	**<.001**
No periodontitis		27.6 (1.7)	27.3 (1.9)	26.7 (2.6)	.253

Note: Bold denotes $p < .05$.
Abbreviations: ACE, Addenbrooke's Cognitive Examination; $A\beta_{1\text{-}40}$, amyloid beta 1–40; $A\beta_{1\text{-}42}$, amyloid beta 1–42; $A\beta_{42:40}$, ratio amyloid beta 1–42/1–40; MMSE, Mini-Mental State Examination; p-Tau, phosphorylated Tau; t-Tau, total Tau.
[a]Statistically significant between-groups difference for the same category (baseline, 12 or 24 months).
[b]Statistically significant within-group difference from the reference category (baseline).
[c]Statistically significant within-group difference from the reference category (12 months).

likely to show worse performance in a number of cognitive tests than those without periodontitis. Indeed, PD, which is a measure of current periodontitis, is positively associated with a poor outcome in MMSE ($\beta = -0.6$, $p < .05$). Accordingly, a cross-sectional relationship was found between periodontitis and cognitive decline (OR = 1.9, $p = .025$). This finding is supported by the positive relationship found between periodontitis and increased plasma levels of p-Tau ($\beta = 0.3$, $p = .026$). On one hand, p-Tau is a key component of NFTs in AD pathology. With the recent advent of blood-based biomarkers related to AD, it is now possible to measure Tau protein in plasma (Ashton et al., 2020). Initially, it was found that p-Tau_{181} was increased in AD patients compared with cognitively normal subjects (Mielke et al., 2018; Tatebe et al., 2017; Yang et al., 2018). Moreover, recent investigations have shown that plasma p-Tau_{181} accurately could identify patients with abnormal Aβ- and Tau-PET scans and distinguish AD dementia from other forms of dementia (Janelidze et al., 2020; Thijssen et al., 2020). In addition, p-Tau_{181} has been described as a predictor of AD progression, showing a high degree of accuracy in non-demented subjects (Janelidze et al., 2020). Based on all these studies, plasma p-Tau_{181} may be considered a useful diagnostic and prognostic biomarker of AD. On the other hand, results from several preclinical investigations have shown detrimental effects of experimental periodontitis (mainly induced by *Porphyromonas gingivalis* infection) on Tau (Díaz-Zúñiga et al., 2020; Ilievski et al., 2018; Tang et al., 2021), thus supporting our findings. For example, oral application of *P. gingivalis* in wild-type C57BL mice promoted the formation of NFTs of p-Tau (ser396) in the hippocampus (Ilievski et al., 2018). Another experiment demonstrated that *P. gingivalis* injected intravenously induced Tau hyperphosphorylation at p-Tau_{181} in the hippocampus by triggering a systemic inflammatory response and neuroinflammation in wild-type Sprague–Dawley rats (Tang et al., 2021). Palatal injections of different serotypes of *P. gingivalis* (K1 and K2) in rats also increased p-Tau levels in

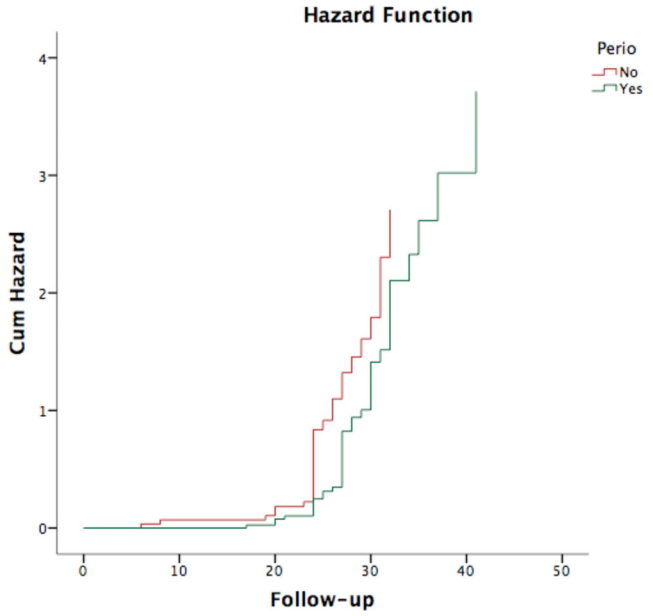

FIGURE 3 Kaplan–Meier model based on the Cox regression analysis with the log-rank Mantel–Cox test ($p = .016$) for the cumulative risk of cognitive decline progression among participants with and without periodontitis at baseline.

the hippocampus (Díaz-Zúñiga et al., 2020). Recently, a landmark study showed that the load of certain subtypes of *P. gingivalis* endotoxins, so-called gingipains (i.e., Kgp and RgpB), correlated with Tau load in AD brains (Dominy et al., 2019). Furthermore, in the hippocampus of AD patients, one of these gingipains (RgpB) was co-localized with Tau tangles (Dominy et al., 2019). In vitro experiments from the same study also showed that gingipains are capable of fragmenting Tau, demonstrating a direct damage to this protein (Dominy et al., 2019). In line with all of these experimental findings, clinical data support an association between serum antibodies against *P. gingivalis* and the cerebrospinal fluid (CSF) t-Tau (Laugisch et al., 2018).

Findings from our prospective cohort study confirmed that in participants with periodontitis the risk of progression in cognitive decline was almost two times higher than in those without periodontitis (HR = 1.9, $p = .027$). Over the 2 years of follow-up, a statistically significant elevation in circulating $A\beta_{1\text{-}40}$ was observed mainly in the periodontitis group. Therefore, it could be speculated that as cognitive function declines, $A\beta_{1\text{-}40}$ plasma levels increase. On the contrary, no significant changes were noticed for $A\beta_{1\text{-}42}$ or Tau (both phosphorylated and total). Previous reports have suggested that in AD brains, $A\beta_{1\text{-}42}$ is deposited first and constitutes the predominant form in senile plaques, while $A\beta_{1\text{-}40}$ is deposited later in the disease process (Iwatsubo et al., 1995; Younkin, 1995). In a longitudinal, population-based study, higher baseline plasma levels of $A\beta_{1\text{-}40}$ but not $A\beta_{1\text{-}42}$ were associated with an increased risk of dementia (van Oijen et al., 2006). In the early 1990s, de La Torre (2004) proposed that sporadic AD is a vascular disorder rather than a primary neurodegenerative disease, caused mainly by chronic hypoperfusion often seen in vascular risk factors such as hypertension. In vitro and in vivo experiments have suggested direct toxic effects of $A\beta_{1\text{-}40}$ on the blood vessel wall (Niwa, Carlson, et al., 2000; Niwa, Younkin, et al., 2000). Indeed, $A\beta_{1\text{-}40}$ but not $A\beta_{1\text{-}42}$ causes cerebrovascular dysfunction through the production of reactive-oxygen species (Niwa, Carlson, et al., 2000; Niwa, Younkin, et al., 2000). Experimental data from our group showed that *P. gingivalis* lipopolysaccharide-induced periodontitis produced increased circulating levels of $A\beta_{1\text{-}40}$ in systemically healthy Sprague–Dawley rats (Leira, Iglesias-Rey, et al., 2019). These findings were confirmed in a clinical study including otherwise healthy periodontitis cases and controls without periodontitis, where an association was found between periodontitis and increased serum $A\beta_{1\text{-}40}$ (Leira et al., 2020). It has been suggested that hypertension could exacerbate Aβ-induced cerebro-microvascular damage in AD, worsening the disease and accelerating its progression (Yao et al., 2023). Therefore, based on our findings, it could be hypothesized that in patients with vascular risk factors such as hypertension, periodontitis could contribute to reduced Aβ-vascular clearance, thus increasing the risk of developing AD. Further mechanistic studies are needed to confirm our hypothesis.

The present study has a number of limitations worth mentioning. The main shortcoming of our study is the utilization of blood-derived biomarkers of AD instead of routinely used CSF or neuroimaging markers. Although protein collection from blood samples is easier and less invasive compared with that from CSF or by MRI/PET techniques, analysis of brain-derived protein concentrations in blood and interpretation of results are complex processes (Ashton et al., 2020). For instance, some proteins can undergo proteolytic degradation in plasma, and this seems to be the case of non-modified Tau, which is stable in CSF but has a short half-life in blood (Zetterberg, 2017). Moreover, other proteins could be expressed at high concentrations outside the brain by different cells, platelets or other tissues as is the case of Aβ, thereby making it difficult to discern whether its changes in plasma reflect events in the brain or at a systemic level (Ashton et al., 2020; Teunissen et al., 2022). Nevertheless, new-generation immunocapture assays such as the one used in our study can readily and precisely measure plasma levels of neurodegeneration markers such as $p\text{-}Tau_{181}$, which is considered a promising candidate biomarker for AD screening, diagnosis and prognosis (Ashton et al., 2020; Teunissen et al., 2022). Finally, the population selected in the SANTIAGO study may be criticized, as almost half of them had their BP well controlled (43.6%). The reason for this could be that a significant number of subjects from the SANTIAGO study were taking more than one anti-hypertensive at the time of the examination (64.4%). However, the percentage of subjects with well-controlled hypertension did not differ between periodontitis individuals and those without periodontitis (46.0% vs. 39.5%, $p = .655$).

In conclusion, periodontitis is associated with cognitive decline and its progression in elderly hypertensive individuals. p-Tau and $A\beta_{1\text{-}40}$ may be key biomolecules involved in this relationship. Intervention studies are needed to investigate whether periodontal treatment might reduce BP and subsequently the risk of future dementia.

AUTHOR CONTRIBUTIONS

Álvaro Carballo, Iria López-Dequidt, Antía Custodia, Marta Aramburu-Núñez, Alberto Ouro, Daniel Romaus-Sanjurjo, Laura Vázquez-Vázquez and Isabel Jiménez-Martín contributed

substantially to the acquisition of data for the work and revising the work critically for important intellectual content. João Botelho and Vanessa Machado made substantial contributions to the analysis and interpretation of data for the work and revising the work critically for important intellectual content. Juan Manuel Pías-Peleteiro, Pablo Aguiar, Manuel Rodríguez-Yáñez, José Manuel Aldrey, Juan Blanco and José Castillo substantially contributed to the interpretation of data and revising the work critically for important intellectual content. Tomás Sobrino made substantial contribution to the conception or design of the work and revising the work critically for important intellectual content. Yago Leira made substantial contribution to the conception or design of the work, acquisition, analysis and interpretation of data for the work as well as drafting the work and revising it critically for important intellectual content. All authors gave final approval of the version to be published and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

Arvanitakis, Z., Shah, R. C., & Bennett, D. A. (2019). Diagnosis and management of dementia: Review. *JAMA*, *322*(16), 1589–1599. https://doi.org/10.1001/jama.2019.4782

Ashton, N. J., Hye, A., Rajkumar, A. P., Leuzy, A., Snowden, S., Suárez-Calvet, M., Karikari, T. K., Schöll, M., la Joie, R., Rabinovici, G. D., Höglund, K., Ballard, C., Hortobágyi, T., Svenningsson, P., Blennow, K., Zetterberg, H., & Aarsland, D. (2020). An update on blood-based biomarkers for non-Alzheimer neurodegenerative disorders. *Nature Reviews Neurology*, *16*(5), 265–284. https://doi.org/10.1038/s41582-020-0348-0

Bir, S. C., Khan, M. W., Javalkar, V., Toledo, E. G., & Kelley, R. E. (2021). Emerging concepts in vascular dementia: A review. *Journal of Stroke and Cerebrovascular Diseases*, *30*(8), 105864. https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105864

de La Torre, J. C. (2004). Alzheimer's disease is a vasocognopathy: A new term to describe its nature. *Neurological Research*, *26*(5), 517–524. https://doi.org/10.1179/016164104225016254

Díaz-Zúñiga, J., More, J., Melgar-Rodríguez, S., Jiménez-Unión, M., Villalobos-Orchard, F., Muñoz-Manríquez, C., Monasterio, G., Valdés, J. L., Vernal, R., & Paula-Lima, A. (2020). Alzheimer's disease-like pathology triggered by *Porphyromonas gingivalis* in wild type rats is serotype dependent. *Frontiers in Immunology*, *11*, 588036. https://doi.org/10.3389/fimmu.2020.588036

Dominy, S. S., Lynch, C., Ermini, F., Benedyk, M., Marczyk, A., Konradi, A., Nguyen, M., Haditsch, U., Raha, D., Griffin, C., Holsinger, L. J., Arastu-Kapur, S., Kaba, S., Lee, A., Ryder, M. I., Potempa, B., Mydel, P., Hellvard, A., Adamowicz, K., … Potempa, J. (2019). *Porphyromonas gingivalis* in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Science Advances*, *5*(1), eaau3333. https://doi.org/10.1126/sciadv.aau3333

Eke, P. I., Page, R. C., Wei, L., Thornton-Evans, G., & Genco, R. J. (2012). Update of the case definitions for population-based surveillance of periodontitis. *Journal of Periodontology*, *83*(12), 1449–1454. https://doi.org/10.1902/jop.2012.110664

Feigin, V. L., Nichols, E., Alam, T., Bannick, M. S., Beghi, E., Blake, N., Culpepper, W. J., Dorsey, E. R., Elbaz, A., Ellenbogen, R. G., Fisher, J. L., Fitzmaurice, C., Giussani, G., Glennie, L., James, S. L., Johnson, C. O., Kassebaum, N. J., Logroscino, G., Marin, B., … Vos, T. (2019). Global, regional, and national burden of neurological disorders, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*(5), 459–480. https://doi.org/10.1016/S1474-4422(18)30499-X

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

García-Caballero, A., García-Lado, I., González-Hermida, J., Recimil, M. J., Area, R., Manes, F., Lamas, S., & Berrios, G. E. (2006). Validation of the Spanish version of the Addenbrooke's Cognitive Examination in a rural community in Spain. *International Journal of Geriatric Psychiatry*, *21*(3), 239–245. https://doi.org/10.1002/gps.1450

Gauthier, S., Rosa-Neto, P., Morais, J. A., & Webster, C. (2021). *World Alzheimer Report 2021: Journey through the diagnosis of dementia*. Alzheimer's Disease International.

Huang, Y., & Mucke, L. (2012). Alzheimer mechanisms and therapeutic strategies. *Cell*, *148*(6), 1204–1222. https://doi.org/10.1016/j.cell.2012.02.040

Iadecola, C. (2014). Hypertension and dementia. *Hypertension*, *64*(1), 3–5. https://doi.org/10.1161/HYPERTENSIONAHA.114.03040

Ilievski, V., Zuchowska, P. K., Green, S. J., Toth, P. T., Ragozzino, M. E., Le, K., Aljewari, H. W., O'Brien-Simpson, N. M., Reynolds, E. C., & Watanabe, K. (2018). Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. *PLoS One*, *13*(10), e0204941. https://doi.org/10.1371/journal.pone.0204941

Iwasaki, M., Yoshihara, A., Kimura, Y., Sato, M., Wada, T., Sakamoto, R., Ishimoto, Y., Fukutomi, E., Chen, W., Imai, H., Fujisawa, M., Okumiya, K., Taylor, G. W., Ansai, T., Miyazaki, H., & Matsubayashi, K. (2016). Longitudinal relationship of severe periodontitis with cognitive

decline in older Japanese. *Journal of Periodontal Research*, *51*(5), 681–688. https://doi.org/10.1111/jre.12348

Iwatsubo, T., Mann, D. M. A., Odaka, A., Suzuki, N., & Ihara, Y. (1995). Amyloid β protein (Aβ) deposition: Aβ42(43) precedes Aβ40 in Down syndrome. *Annals of Neurology*, *37*(3), 294–299. https://doi.org/10.1002/ana.410370305

Janelidze, S., Mattsson, N., Palmqvist, S., Smith, R., Beach, T. G., Serrano, G. E., Chai, X., Proctor, N. K., Eichenlaub, U., Zetterberg, H., Blennow, K., Reiman, E. M., Stomrud, E., Dage, J. L., & Hansson, O. (2020). Plasma P-tau$_{181}$ in Alzheimer's disease: Relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nature Medicine*, *26*(3), 379–386. https://doi.org/10.1038/s41591-020-0755-1

Kamer, A. R., Morse, D. E., Holm-Pedersen, P., Mortensen, E. L., & Avlund, K. (2012). Periodontal inflammation in relation to cognitive function in an older adult Danish population. *Journal of Alzheimer's Disease*, *28*(3), 613–624. https://doi.org/10.3233/JAD-2011-102004

Kaye, E. K., Valencia, A., Baba, N., Spiro, A., Dietrich, T., & Garcia, R. I. (2010). Tooth loss and periodontal disease predict poor cognitive function in older men. *Journal of the American Geriatrics Society*, *58*(4), 713–718. https://doi.org/10.1111/j.1532-5415.2010.02788.x

Laugisch, O., Johnen, A., Maldonado, A., Ehmke, B., Bürgin, W., Olsen, I., Potempa, J., Sculean, A., Duning, T., & Eick, S. (2018). Periodontal pathogens and associated intrathecal antibodies in early stages of Alzheimer's disease. *Journal of Alzheimer's Disease*, *66*(1), 105–114. https://doi.org/10.3233/JAD-180620

Leira, Y., Carballo, Á., Orlandi, M., Aldrey, J. M., Pías-Peleteiro, J. M., Moreno, F., Vázquez-Vázquez, L., Campos, F., D'Aiuto, F., Castillo, J., Sobrino, T., & Blanco, J. (2020). Periodontitis and systemic markers of neurodegeneration: A case–control study. *Journal of Clinical Periodontology*, *47*, 561–571. https://doi.org/10.1111/jcpe.13267

Leira, Y., Iglesias-Rey, R., Gómez-Lado, N., Aguiar, P., Campos, F., D'Aiuto, F., Castillo, J., Blanco, J., & Sobrino, T. (2019). *Porphyromonas gingivalis* lipopolysaccharide-induced periodontitis and serum amyloid-beta peptides. *Archives of Oral Biology*, *99*, 120–125. https://doi.org/10.1016/j.archoralbio.2019.01.008

Leira, Y., Rodríguez-Yáñez, M., Arias, S., López-Dequidt, I., Campos, F., Sobrino, T., D'Aiuto, F., Castillo, J., & Blanco, J. (2019). Periodontitis as a risk indicator and predictor of poor outcome for lacunar infarct. *Journal of Clinical Periodontology*, *46*(1), 20–30.

López-Dequidt, I. (2019). *Clinical study of cerebral small vessel disease*. [PhD Thesis], University of Santiago de Compostela.

Mielke, M. M., Hagen, C. E., Xu, J., Chai, X., Vemuri, P., Lowe, V. J., Airey, D. C., Knopman, D. S., Roberts, R. O., Machulda, M. M., Jack, C. R., Petersen, R. C., & Dage, J. L. (2018). Plasma phospho-tau$_{181}$ increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. *Alzheimer's & Dementia*, *14*(8), 989–997. https://doi.org/10.1016/j.jalz.2018.02.013

Muñoz Aguilera, E., Leira, Y., Miró Catalina, Q., Orlandi, M., Czesnikiewicz-Guzik, M., Guzik, T. J., Hingorani, A. D., Nart, J., & D'Aiuto, F. (2021). Is systemic inflammation a missing link between periodontitis and hypertension? Results from two large population-based surveys. *Journal of Internal Medicine*, *289*(4), 532–546. https://doi.org/10.1111/joim.13180

Nilsson, H., Sanmartin Berglund, J., & Renvert, S. (2018). Longitudinal evaluation of periodontitis and development of cognitive decline among older adults. *Journal of Clinical Periodontology*, *45*(10), 1142–1149. https://doi.org/10.1111/jcpe.12992

Niwa, K., Carlson, G. A., & Iadecola, C. (2000). Exogenous Aβ1–40 reproduces cerebrovascular alterations resulting from amyloid precursor protein overexpression in mice. *Journal of Cerebral Blood Flow & Metabolism*, *20*(12), 1659–1668. https://doi.org/10.1097/00004647-200012000-00005

Niwa, K., Younkin, L., Ebeling, C., Turner, S. K., Westaway, D., Younkin, S., Ashe, K. H., Carlson, G. A., & Iadecola, C. (2000). Aβ1–40-related reduction in functional hyperemia in mouse neocortex during somatosensory activation. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(17), 9735–9740. https://doi.org/10.1073/pnas.97.17.9735

Ou, Y.-N., Tan, C.-C., Shen, X.-N., Xu, W., Hou, X.-H., Dong, Q., Tan, L., & Yu, J.-T. (2020). Blood pressure and risks of cognitive impairment and dementia. *Hypertension*, *76*(1), 217–225. https://doi.org/10.1161/HYPERTENSIONAHA.120.14993

Shin, H.-S., Shin, M.-S., Ahn, Y.-B., Choi, B.-Y., Nam, J.-H., & Kim, H.-D. (2016). Periodontitis is associated with cognitive impairment in elderly Koreans: Results from the Yangpyeong Cohort Study. *Journal of the American Geriatrics Society*, *64*(1), 162–167. https://doi.org/10.1111/jgs.13781

Sung, C., Huang, R., Cheng, W., Kao, T., & Chen, W. (2019). Association between periodontitis and cognitive impairment: Analysis of national health and nutrition examination survey (NHANES) III. *Journal of Clinical Periodontology*, *46*(8), 790–798. https://doi.org/10.1111/jcpe.13155

Tang, Z., Liang, D., Cheng, M., Su, X., Liu, R., Zhang, Y., & Wu, H. (2021). Effects of *Porphyromonas gingivalis* and its underlying mechanisms on Alzheimer-like tau hyperphosphorylation in Sprague-Dawley rats. *Journal of Molecular Neuroscience*, *71*(1), 89–100. https://doi.org/10.1007/s12031-020-01629-1

Tatebe, H., Kasai, T., Ohmichi, T., Kishi, Y., Kakeya, T., Waragai, M., Kondo, M., Allsop, D., & Tokuda, T. (2017). Quantification of plasma phosphorylated tau to use as a biomarker for brain Alzheimer pathology: Pilot case-control studies including patients with Alzheimer's disease and Down syndrome. *Molecular Neurodegeneration*, *12*(1), 63. https://doi.org/10.1186/s13024-017-0206-8

Teunissen, C. E., Verberk, I. M. W., Thijssen, E. H., Vermunt, L., Hansson, O., Zetterberg, H., van der Flier, W. M., Mielke, M. M., & del Campo, M. (2022). Blood-based biomarkers for Alzheimer's disease: Towards clinical implementation. *The Lancet Neurology*, *21*(1), 66–77. https://doi.org/10.1016/S1474-4422(21)00361-6

Thijssen, E. H., la Joie, R., Wolf, A., Strom, A., Wang, P., Iaccarino, L., Bourakova, V., Cobigo, Y., Heuer, H., Spina, S., VandeVrede, L., Chai, X., Proctor, N. K., Airey, D. C., Shcherbinin, S., Duggan Evans, C., Sims, J. R., Zetterberg, H., Blennow, K., … Boxer, A. L. (2020). Diagnostic value of plasma phosphorylated tau$_{181}$ in Alzheimer's disease and frontotemporal lobar degeneration. *Nature Medicine*, *26*(3), 387–397. https://doi.org/10.1038/s41591-020-0762-2

van Oijen, M., Hofman, A., Soares, H. D., Koudstaal, P. J., & Breteler, M. M. (2006). Plasma Aβ1–40 and Aβ1–42 and the risk of dementia: A prospective case-cohort study. *The Lancet Neurology*, *5*(8), 655–660. https://doi.org/10.1016/S1474-4422(06)70501-4

Vázquez-Reza, M., López-Dequidt, I., Ouro, A., Iglesias-Rey, R., Campos, F., Blanco, J., Rodríguez-Yáñez, M., Castillo, J., Sobrino, T., & Leira, Y. (2023). Periodontitis is associated with subclinical cerebral and carotid atherosclerosis in hypertensive patients: A cross-sectional study. *Clinical Oral Investigations*, *27*, 3489–3498. https://doi.org/10.1007/s00784-023-04958-8

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2008). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Journal of Clinical Epidemiology*, *61*(4), 344–349. https://doi.org/10.1016/j.jclinepi.2007.11.008

Yang, C.-C., Chiu, M.-J., Chen, T.-F., Chang, H.-L., Liu, B.-H., & Yang, S.-Y. (2018). Assay of plasma phosphorylated tau protein (threonine 181) and total tau protein in early-stage Alzheimer's disease. *Journal of Alzheimer's Disease*, *61*(4), 1323–1332. https://doi.org/10.3233/JAD-170810

Yao, Q., Jiang, K., Lin, F., Zhu, T., Khan, N. N., & Jiang, E. (2023). Pathophysiological association of Alzheimer's disease and hypertension: A clinical concern for elderly population. *Clinical Intervention in Aging*, *18*, 713–728. https://doi.org/10.2147/CIA.S400527

Younkin, S. G. (1995). Evidence that Aβ42 is the real culprit in Alzheimer's disease. *Annals of Neurology*, *37*(3), 287–288. https://doi.org/10.1002/ana.410370303

Zetterberg, H. (2017). Review: Tau in biofluids – Relation to pathology, imaging and clinical features. *Neuropathology and Applied Neurobiology*, *43*(3), 194–199. https://doi.org/10.1111/nan.12378

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