Received: 18 April 2022 | Revised: 9 January 2023 | Accepted: 11 January 2023

DOI: 10.1111/jcpe.13779

ORIGINAL ARTICLE

Journal of Clinical Periodontology WILEY

Periodontitis and low cognitive performance: A population-based study

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Abstract

Aim: To study the epidemiological association between periodontitis and low cognitive performance among older adults, within a representative sample of the U.S. population.

Materials and Methods: Data from 2086 older adults (≥60 years old), representative of 77.1 million people, were retrieved from the NHANES 2011-2014 database. Periodontitis cases were identified and classified according to the AAP/CDC criteria (mild, moderate, and severe). Cognitive function was assessed through the Consortium to Establish a Registry for Alzheimer's disease (CERAD), the animal fluency test (AFT), the digit symbol substitution test (DSST), and the global cognition score. The lowest non-survey weighted quartile for each cognitive test was defined as low cognitive performance. Simple and multiple regression analyses were performed.

Results: Moderate and severe periodontitis were significantly associated with a low DSST performance (OR = 1.66 and OR = 2.97, respectively). Each millimetre increase in mean CAL was associated with a lower AFT (OR = 1.44), DSST (OR = 1.86), and global cognition (OR = 1.50) performance.

Conclusions: The findings of the present study suggest the existence of an independent association between periodontitis and low cognitive performance among older adults (≥60 years old).

KEYWORDS

Alzheimer's disease, cognitive decline, cognitive impairment, neurocognitive disorders, periodontal diseases

Clinical Relevance

Scientific rationale for study: Although epidemiological studies have reported an association between periodontitis and low cognitive performance, there are no studies on nationally representative samples of high-risk subjects (≥60 years old) using full-mouth periodontal examination data.

Principal findings: Periodontitis was significantly associated with low cognitive performance, specifically in verbal fluency and speed, sustained attention, and working memory.
Practical implications: Given its modifiable nature, the successful management of periodontitis could be a target for the prevention of neurodegenerative disorders.

1 | INTRODUCTION

Alzheimer's disease (AD) and other types of dementia represent a global public health concern, with more than 50 million people currently affected globally (Wu et al., 2017). With an ageing world population, the number of people living with some form of cognitive impairment is expected to rise dramatically (Winblad et al., 2016; Nichols et al., 2019). Considering the current lack of effective treatments, the identification of modifiable risk factors for cognitive decline will be important so that effective preventive measures can be developed (Livingston et al., 2020).

Periodontitis represents one of the most common noncommunicable diseases (NCDs) of humankind, affecting almost half of the adult world population (GBD 2019 Diseases and Injuries Collaborators, 2020; Morales et al., 2021; Stødle et al., 2021). The disease process exerts detrimental effects on both tooth-supporting structures and general health. Indeed, periodontitis has been independently associated with several systemic diseases and mortality through direct and indirect pathways (Genco & Sanz, 2020; Romandini et al., 2021; Antonoglou et al., 2022; Baima et al., 2022), involving bacterial translocation to different target organs and an increase in low-grade systemic inflammation (Romandini et al., 2018; Schenkein et al., 2020). Consequently, as a result of these mechanisms, a possible association with cognitive impairment has been also hypothesized (Hajishengallis & Chavakis, 2021; Harding & Singhrao, 2022).

DNA or virulence factors from periodontal pathogens, such as lipopolysaccharide (LPS) and gingipains, have been detected in the cerebrospinal fluid and brain autopsy specimens of patients with AD (Beydoun et al., 2020; Kantarci et al., 2020). Furthermore, the chronic systemic inflammatory state elicited by periodontitis can plausibly favour the degenerative brain processes via inflammaging and immunosenescence (Baima et al., 2021; Cullen et al., 2021; Jungbauer et al., 2022). Periodontitis may also increase the risk for other NCDs, including diabetes and cardiovascular diseases (particularly hypertension and stroke) (D'Aiuto et al., 2018; Czesnikiewicz-Guzik et al., 2019; Sanz et al., 2020). These NCDs may then act as mediators in the causal pathway between periodontitis and reduced cognitive performance.

Previous epidemiological studies have reported an association between periodontitis and low cognitive performance (Nilsson et al., 2018; Sung et al., 2019; Demmer et al., 2020). However, to date, there are no studies based on nationally representative samples using a full-mouth periodontal examination protocol and focused on high-risk subjects (≥ 60 years), which may expose the available evidence to the risk of both selection and information bias (Alshihayb et al., 2022).

Therefore, the primary aim of this epidemiological investigation was to study the association between periodontitis and low cognitive performance in subjects aged ≥60 years using the National Health and Nutrition Examination Survey (NHANES) 2011-2014. The secondary aim was to assess the potential mediating role of comorbidities (e.g., hypertension) and systemic inflammation in explaining this association.

2 | MATERIALS AND METHODS

This cross-sectional study is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (von Elm et al., 2007; Vandenbroucke et al., 2014).

2.1 | Study sample: NHANES 2011-2014

Data for the present study were drawn from the 2011–2014 cycles of the NHANES. NHANES is a nationwide cross-sectional survey conducted by the Centers for Disease Control and Prevention (CDC). Each cycle consists of a stratified multi-stage probability sample representative of the civilian, non-institutionalized U.S. population. For each cycle, questionnaires were administered in the participants' homes followed by a standardized examination performed in a specially equipped mobile examination centre (MEC). Detailed information regarding the contents of the survey and the sampling methods is provided elsewhere (Dye et al., 2019). The NHANES cycles were ethically approved by the CDC's National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB). All survey participants signed a written consent form.

2.2 | Periodontal assessment

All survey participants aged 30 years or older, with at least one remaining tooth (excluding third molars) and not meeting any of the health exclusion criteria, were eligible for a full-mouth periodontal examination performed by licensed dentists using a colour-coded periodontal probe (PCP2, HuFriedy). The position of the gingival margin and probing pocket depth (PPD) were measured at six sites/tooth (excluding third molars). Clinical attachment level (CAL) was subsequently calculated from these measurements. The examiners were trained and calibrated before the beginning of the surveys and then periodically 2–3 times a year. Further details on the periodontal examination process are reported elsewhere (Dye et al., 2019).

For this study, only participants aged >60 years with a complete periodontal examination were eligible. Moderate and severe periodontitis cases were defined using the CDC/AAP criteria (Eke et al., 2012). The presence of ≥2 interproximal sites with CAL ≥4 mm (not on the same tooth) or ≥2 interproximal sites with PPD ≥5 mm defined moderate periodontitis. Severe periodontitis was defined as the presence of ≥2 interproximal sites with CAL ≥6 mm (not on the same tooth) and ≥1 interproximal site with PPD ≥5 mm. Mean PPD and mean CAL were also calculated for each study participant.

2.3 | Cognitive functioning assessment

Only survey participants aged 60 years or more were eligible for the cognitive functioning assessment. Cognitive function was evaluated through the Word Learning and recall modules from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-WL), the animal fluency test (AFT), and the digit symbol substitution test (DSST).

The CERAD-WL assesses immediate and delayed learning ability after new verbal information (memory sub-domain) (Morris et al., 1989). This test consists of three consecutive immediate recall learning tests (CERAD-IR) and a delayed word recall test (CERAD-DR). For the learning tests (CERAD-IR), participants were instructed to read aloud 10 unrelated words, one at a time. Immediately following their presentation, participants had to recall as many words as possible, and the number of words recalled represented the score for each trial (0–10). Therefore, the total CERAD-IR score could range between 0 and 30. The delayed word recall test (CERAD-DR), which was scored between 0 and 10, was performed once the two other cognitive exercises (Animal Fluency and DSST) were completed (approximately 8–10 minutes from the start of the word learning trials). The scores obtained in the CERAD-IR and the CERAD-DR were then totalled to calculate an overall CERAD-WL score (Q. Zhang et al., 2022).

The AFT examines categorical verbal fluency, a component of executive function (Strauss et al., 2006). Participants were asked to name as many animals as possible in 1 minute, and the number of named animals represented the AFT score.

The DSST, a performance module from the Wechsler Adult Intelligence Scale (WAIS III), relies on processing speed, sustained attention, and working memory (Ryan & Lopez, 2001). This exercise was conducted using a paper form with a top key containing nine numbers paired with symbols. Participants had 2 minutes to copy the corresponding symbols in the 133 boxes that adjoin the numbers. The total number of correct matches represented the DSST score.

A global cognition score was calculated as the sum of the standardized z-scores of the CERAD-WL, AFT, and DSST tests, as previously reported (Li et al., 2019; Q. Zhang et al., 2022). Further details on cognitive function testing methods are reported elsewhere (National Health and Nutrition Examination Survey, 2011–2012, 2013–2014).

Only participants completing at least one recall of the provided tests were included in the current study. Scores derived from the cognitive tests were regarded as continuous variables (i.e., cognitive functioning) and were also dichotomized, considering the lowest non-survey weighted quartile to define low cognitive performance.

2.4 | Confounders

Age, gender, smoking, family poverty level (FPL), educational level, and alcohol intake were considered as *a priori* confounders. A detailed description of the confounders' assessment methods is reported in Appendix S1.

2.5 | Mediators

Possible mediators included diabetes, hypertension, cardiovascular or cerebrovascular diseases, and biomarkers of systemic inflammation (white blood cells count [WBC] and platelet count). The detailed mediators' assessment methods are reported in Appendix S1.

2.6 | Statistical analyses

All statistical analyses were performed with the statistical software STATA BE (version 17.1, StataCorp LP, Texas, USA), setting the level of significance at 5%. Analyses for complex samples were applied to allow the generalization of the results to the entire non-institutionalized U.S. population.

Continuous variables were described as means (linearized standard errors [SE]), while categorical variables were expressed as proportions (SE).

Simple and multiple logistic/linear regression models were formulated to evaluate the crude and adjusted estimates of the association between moderate and severe periodontitis (vs. no or mild periodontitis), mean PPD, and mean CAL, with low cognitive performance (lowest non-survey weighted quartile) and cognitive functioning (continuous variable) in the global cognition, CERAD, AFT, and DSST scores. In addition, a priori sub-group analyses by gender were also reported.

Finally, a mediation analysis was performed to study the role of each potential mediator in explaining the statistically significant estimates resulting from the multiple logistic regression models. In this analysis, the percentage (%) of excess risk explained was calculated using the following formula: [(OR (final multiple model)−OR (final multiple model + mediator))/(OR (final multiple model)−1)]. This value refers to the extent to which each potential mediator could explain the association estimates found (Han et al., 2016; Romandini et al., 2017; Marruganti et al., 2023).

3 | RESULTS

Out of the 19,931 subjects included in the NHANES 2011–2014 database, 3632 were aged >60 years and were potentially eligible for cognitive functioning assessment. From these, 1546 subjects were

excluded because they were edentulous, did not complete at least one recall of the cognitive tests, or did not have a complete periodontal examination. Consequently, the present study included 2086 participants, representing a weighted population of approximately 77.1 million civilian non-institutionalized U.S. adults aged >60 years old.

3.1 | Study population

The weighted mean age of the analysed sample was 68.6 (0.25) years, with a higher proportion of female participants (weighted 53.3%). While most of the included subjects were non-smokers (weighted 90.3%), more than half of the selected population was either hypertensive (weighted 22.1%) or borderline hypertensive (weighted 50.5%) (Tables S1 and S2). In addition, the weighted prevalence of periodontitis was 51.9% (mild: 1.4%; moderate: 41.9%; severe: 8.6%), while the weighted prevalence of low cognitive performance was 14.9% for the global cognition score, 16.0% for CERAD-IR, 19.5% for CERAD-DR, 18.0% for CERAD-WL, 14.6% for AFT, and 13.1% for DSST (Table 1).

3.2 | Moderate/severe periodontitis and low cognitive performance

Results from the logistic regression analyses on the association between moderate/severe periodontitis and low cognitive performance are reported in Table 2.

In the crude analyses, moderate periodontitis was significantly associated with increased odds of low cognitive performance in all tests. However, when adjusting for confounders, moderate periodontitis was only significantly associated with a low DSST performance (OR = 1.66; 95% CI: 1.10–2.52). In the adjusted sub-group analyses by gender, moderate periodontitis was significantly associated with low performance in AFT (OR = 1.47; 95% CI: 1.01–2.14) and DSST (OR = 1.81; 95% CI: 1.20–2.72) tests in females only.

Severe periodontitis was significantly associated in the crude models with increased odds of low performance in global cognition, CERAD-IR and CERAD-WL, AFT, and DSST, but not CERAD-DR scores. After adjusting for confounders, severe periodontitis was associated with higher odds of low DSST performance (OR = 2.97; 95% CI: 1.56–5.65), but was not significantly associated with global cognition and CERAD scores. In the adjusted sub-group analyses, this association remained significant in both genders. Additionally, severe periodontitis was associated with low performance in the global cognition score in females only (OR = 2.91; 95% CI: 1.32–6.40).

The results were consistent when analysing the continuous cognitive function scores (Figure 1; Table S3).

3.3 | Mean PPD/CAL and low cognitive performance

Results from the logistic regression analyses on the association between mean PPD/mean CAL and low cognitive performance are reported in Table 3.

In the crude analyses, mean PPD was significantly associated with increased odds of low performance in the global cognition, CERAD-IR, CERAD-WL, AFT, and DSST scores. However, when adjusting for confounders, mean PPD was significantly associated only with low performance in global cognition (OR = 1.83; 95% CI: 1.11–3.01) and DSST scores (OR = 2.91; 95% CI: 1.88–4.51). Furthermore, in the adjusted sub-group analyses, the association with low DSST performance remained significant in both genders, while the association with global cognition score was significant in females only (OR = 2.85; 95% CI: 1.56–5.21).

TABLE 1 Prevalence of low cognitive performance: overall and according to periodontal status and gender

	Overall[a]	No/mild periodontitis[b]	Moderate periodontitis[c]	Severe periodontitis[d]	Males[e]	Females[f]
Global cognition score <−1.55, % (SE)	14.9 (0.01)	10.5 (0.01)	18.0 (0.01)	24.9 (0.01)	16.9 (0.02)	13.1 (0.01)
CERAD-IR <16, % (SE)	16.0 (0.01)	12.9 (0.02)	18.8 (0.02)	20.3 (0.02)	18.7 (0.02)	13.6 (0.02)
CERAD-DR <5, % (SE)	19.5 (0.02)	16.6 (0.02)	22.7 (0.02)	19.9 (0.02)	23.2 (0.02)	16.2 (0.02)
CERAD-WL <21, % (SE)	18.0 (0.01)	14.5 (0.02)	21.2 (0.01)	22.7 (0.02)	21.4 (0.02)	15.1 (0.01)
AFT <13, % (SE)	14.6 (0.01)	11.1 (0.01)	17.4 (0.01)	21.5 (0.01)	13.7 (0.01)	15.4 (0.01)
DSST <36, % (SE)	13.1 (0.01)	7.2 (0.01)	17.1 (0.02)	27.7 (0.02)	13.8 (0.01)	12.5 (0.01)

Abbreviations: AFT, animal fluency test; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease Delayed Recall; CERAD-IR, Consortium to Establish a Registry for Alzheimer's Disease Immediate Recall; CERAD-WL, Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest; DSST, digit symbol substitution test; SE, standard error.

[a]Overall: *N* = 2086; weighted *N* in millions = 77,123,337.

[b]No/mild periodontitis: *N* = 817; weighted *N* in millions = 38,2.

[c]Moderate periodontitis: *N* = 989; weighted *N* in millions = 32,3.

[d]Severe Periodontitis: *N* = 280; weighted *N* in millions = 6,6.

[e]Males: *N* = 1034; weighted *N* in millions = 36,1.

[f]Females: *N* = 1052; weighted *N* in millions = 41,1.

TABLE 2 Simple and multiple logistic regression analyses for the association between moderate and severe periodontitis with low cognitive performance, overall and by gender

	Moderate periodontitis[a] – OR (95% CI)			Severe periodontitis[a] – OR (95% CI)		
	Overall	**Males**	**Females**	**Overall**	**Males**	**Females**
Global cognition score <−1.55						
Crude	*1.85 (1.42–2.49)***	*1.49 (1.03–2.16)**	*2.22 (1.54–3.22)****	*2.84 (1.76–4.59)****	*2.15 (1.02–4.55)**	*3.70 (1.80–7.59)***
Adjusted[b]	1.12 (0.78–1.63)	0.89 (0.52–1.51)	1.40 (0.93–2.11)	1.74 (0.92–3.30)	1.28 (0.47–3.44)	*2.91 (1.32–6.40)***
CERAD-IR <16						
Crude	*1.56 (1.21–2.00)***	1.26 (0.79–2.00)	*1.79 (1.29–2.48)***	*1.71 (1.05–2.81)**	1.37 (0.68–2.76)	1.84 (0.69–4.85)
Adjusted[b]	0.90 (0.62–1.30)	0.78 (0.43–1.35)	1.05 (0.71–1.57)	0.81 (0.41–1.60)	0.65 (0.30–1.41)	1.06 (0.32–3.49)
CERAD-DR <5						
Crude	*1.47 (1.06–2.04)**	1.21 (0.69–2.14)	*1.65 (1.20–2.26)****	1.24 (0.76–2.02)	0.96 (0.42–2.18)	1.36 (0.53–3.47)
Adjusted[b]	0.98 (0.64–1.47)	0.89 (0.45–1.73)	1.06 (0.80–1.40)	0.86 (0.43–1.71)	0.70 (0.30–1.65)	1.18 (0.43–3.27)
CERAD-WL <21						
Crude	*1.59 (1.22–2.08)***	1.14 (0.76–1.73)	*2.08 (1.54–2.80)****	*1.73 (1.06–2.83)**	1.27 (0.63–2.56)	2.00 (0.82–4.90)
Adjusted[b]	0.93 (0.62–1.39)	0.69 (0.39–1.22)	1.24 (0.87–1.77)	0.77 (0.39–1.51)	0.58 (0.27–1.26)	1.15 (0.40–3.32)
AFT <13						
Crude	*1.70 (1.33–2.18)****	1.40 (0.88–2.24)	*2.05 (1.42–2.95)****	*2.20 (1.40–5.18)***	1.49 (0.74–2.99)	*4.92 (3.25–7.45)****
Adjusted[b]	1.21 (0.88–1.68)	0.90 (0.50–1.63)	*1.47 (1.01–2.14)**	1.67 (0.91–3.08)	1.91 (0.82–4.46)	1.12 (0.43–2.91)
DSST <36						
Crude	*2.66 (1.84–3.84)****	*2.46 (1.44–4.20)***	*2.88 (1.97–4.22)****	*4.92 (3.25–7.45)****	*4.96 (2.69–9.12)****	*4.91 (2.67–9.02)****
Adjusted[b]	*1.66 (1.10–2.52)**	1.46 (0.65–3.27)	*1.81 (1.20–2.72)****	*2.97 (1.56–5.65)***	*3.20 (1.10–9.29)**	*2.36 (1.14–4.91)**

Abbreviations: AFT, animal fluency test; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease Delayed Recall; CERAD-IR, Consortium to Establish a Registry for Alzheimer's Disease Immediate Recall; CERAD-WL, Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest; CI, confidence interval; DSST, digit symbol substitution test; OR, odds ratio.

[a]Versus no/mild periodontitis.

[b]Adjusted for age, gender, smoking, family poverty level, education, and alcohol intake.

Significance levels for the estimates in italics.

*$p < .05$; **$p < .01$; ***$p < .001$.

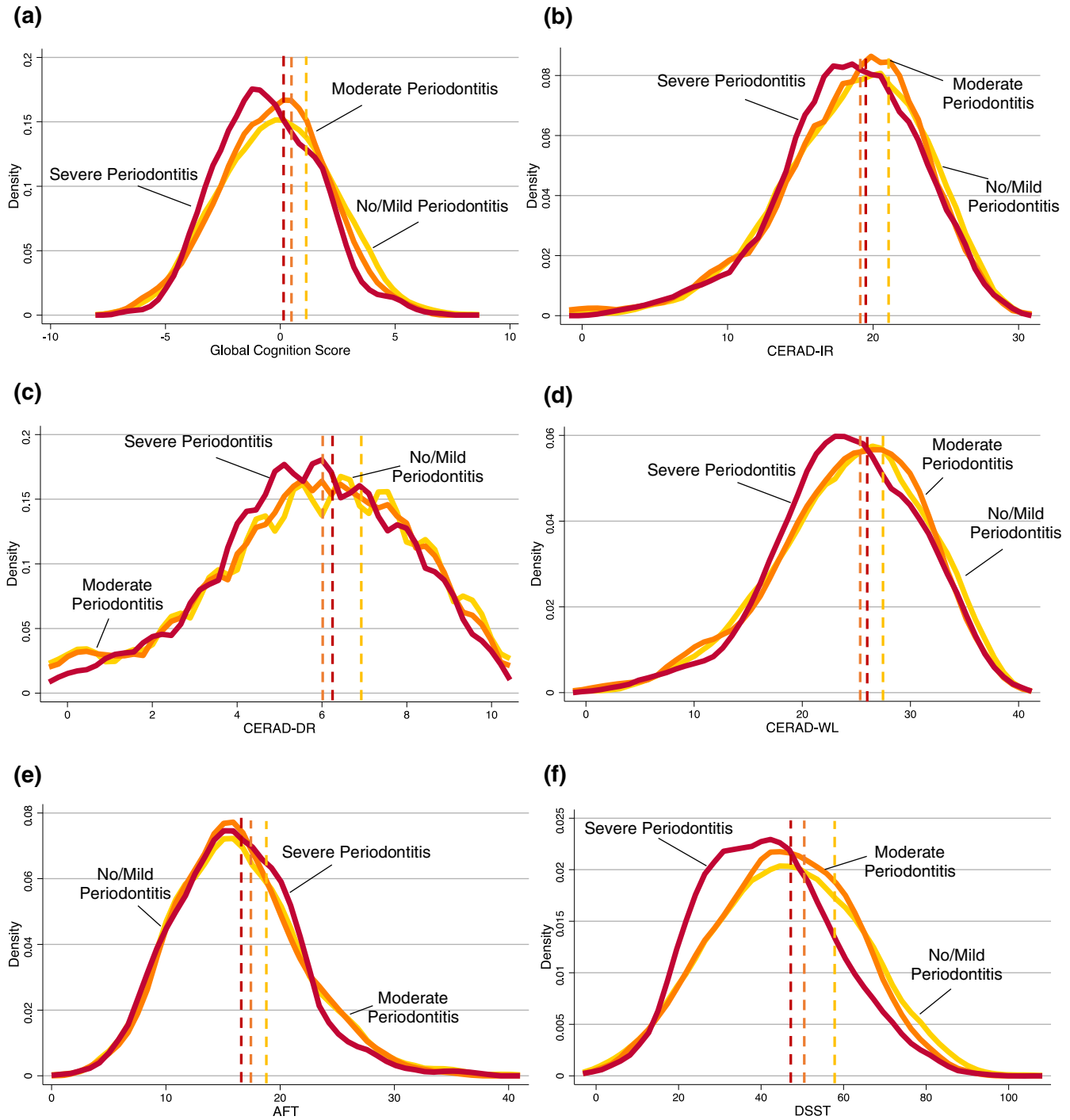

FIGURE 1 Distribution of cognitive test scores by periodontitis severity (no/mild vs. moderate vs. severe periodontitis): (a) global cognition; (b) CERAD-IR; (c) CERAD-DR; (d) CERAD-WL; (e) AFT; (f) DSST. The vertical dashed lines indicate the mean value of each cognitive test score by sub-group of periodontitis severity. AFT, animal fluency test; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease Delayed Recall; CERAD-IR, Consortium to Establish a Registry for Alzheimer's Disease Immediate Recall; CERAD-WL, Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest; DSST, digit symbol substitution test

Mean CAL was significantly associated with increased odds of low performance in all cognitive tests. After adjusting for confounders, mean CAL was significantly associated with low performance in global cognition (OR = 1.50; 95% CI: 1.14–1.98), AFT (OR = 1.44; 95% CI: 1.18–1.77), and DSST (OR = 1.86; 95% CI: 1.44–2.39), but not CERAD, scores. In the sub-group analyses, the estimates for a low DSST performance remained significant in both genders, while the association with global cognition (OR = 2.38, 95% CI: 1.63–3.47) and AFT (OR = 1.77; 95% CI: 1.29–2.45) scores were present only among females. Additionally, the mean CAL was associated

TABLE 3 Simple and multiple logistic regression analyses for the association between mean probing pocket depth (PPD) and mean clinical attachment level (CAL) with low cognitive performance: overall and by gender

	Mean PPD - OR (95% CI)			Mean CAL - OR (95% CI)		
	Overall	Males	Females	Overall	Males	Females
Global cognition score <−1.55						
Crude	*2.31 (1.56–3.43)***	*1.88 (1.13–3.13)**	*2.73 (1.59–4.69)***	*2.04 (1.60–2.60)****	*1.63 (1.28–2.08)****	*3.03 (2.10–4.38)****
Adjusted[a]	*1.83 (1.11–3.01)**	1.31 (0.68–2.50)	*2.85 (1.56–5.21)***	*1.50 (1.14–1.98)***	1.15 (0.87–1.53)	*2.38 (1.63–3.47)****
CERAD-IR <16						
Crude	*1.57 (1.07–2.29)**	1.46 (0.84–2.54)	1.44 (0.75–2.77)	*1.52 (1.27–1.82)****	*1.30 (1.06–1.59)**	*1.82 (1.27–2.62)***
Adjusted[a]	1.17 (0.70–1.96)	0.97 (0.51–1.84)	1.49 (0.74–3.00)	1.05 (0.80–1.38)	0.87 (0.63–1.19)	1.38 (0.90–2.12)
CERAD-DR <5						
Crude	1.33 (0.92–1.92)	1.07 (0.59–1.96)	1.43 (0.94–2.18)	*1.40 (1.11–1.76)***	1.18 (0.85–1.62)	*1.67 (1.26–2.20)***
Adjusted[a]	1.13 (0.69–1.88)	0.96 (0.47–1.93)	1.40 (0.81–2.44)	1.10 (0.83–1.46)	0.97 (0.68–1.38)	1.35 (0.97–1.87)
CERAD-WL <21						
Crude	*1.59 (1.11–2.27)**	1.44 (0.92–2.26)	1.47 (0.85–2.54)	*1.58 (1.30–1.91)****	*1.31 (1.06–1.62)**	*1.97 (1.39–2.78)****
Adjusted[a]	1.19 (0.74–1.93)	1.02 (0.55–1.89)	1.45 (0.83–2.53)	1.09 (0.82–1.46)	0.91 (0.63–1.31)	*1.45 (1.01–2.09)**
AFT <13						
Crude	*1.49 (1.11–1.98)***	*1.67 (1.01–2.76)**	1.44 (0.96–2.16)	*1.75 (1.45–2.11)****	*1.62 (1.29–2.03)****	*2.23 (1.58–3.15)****
Adjusted[a]	1.22 (0.85–1.74)	1.10 (0.62–1.96)	1.34 (0.84–2.13)	*1.44 (1.18–1.77)***	1.24 (0.95–1.62)	*1.77 (1.29–2.45)***
DSST <36						
Crude	*3.85 (2.63–5.64)****	*4.78 (2.87–7.90)****	*3.02 (1.83–5.00)****	*2.58 (2.03–3.28)****	*2.35 (1.79–3.08)****	*3.36 (2.35–4.79)****
Adjusted[a]	*2.91 (1.88–4.51)****	*3.14 (1.46–6.76)***	*2.58 (1.38–4.83)***	*1.86 (1.44–2.39)****	*1.60 (1.11–2.31)**	*2.34 (1.61–3.39)****

Abbreviations: AFT, animal fluency test; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease Delayed Recall; CERAD-IR, Consortium to Establish a Registry for Alzheimer's Disease Immediate Recall; CERAD-WL, Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest; CI, confidence interval; DSST, digit symbol substitution test; OR, odds ratio.

[a]Adjusted for age, gender, smoking, family poverty level, education, and alcohol intake.

Significance levels for the estimates in italics.

*$p < .05$; **$p < .01$; ***$p < .001$.

TABLE 4 Mediation analysis for the association between periodontal variables and low performance in the global cognition, animal fluency test (AFT), and digit symbol substitution tests (DSST)

	Global cognition score <−1.55				AFT <13		DSST <36							
	Mean PPD		Mean CAL		Mean CAL		Moderate periodontitis[a]		Severe periodontitis[a]		Mean PPD		Mean CAL	
	OR (95% CI)	% excess risk explained[b]	OR (95% CI)	% excess risk explained[b]	OR (95% CI)	% excess risk explained[b]	OR (95% CI)	% excess risk explained[b]	OR (95% CI)	% excess risk explained[b]	OR (95% CI)	% excess risk explained[b]	OR (95% CI)	% excess risk explained[b]
Base model (B)	1.83 (1.11–3.01)	—	1.50 (1.14–1.98)	—	1.44 (1.18–1.77)	—	1.66 (1.10–2.51)	—	2.97 (1.56–5.65)	—	2.91 (1.88–4.51)	—	1.86 (1.44–2.39)	—
B + diabetes	1.82 (1.09–3.04)	1.2%	1.49 (1.14–1.96)	2.0%	1.44 (1.17–1.77)	0.0%	1.62 (1.05–2.50)	6.1%	3.03 (1.58–5.80)	0.0%	2.94 (1.88–4.58)	0.0%	1.86 (1.45–2.39)	0.0%
B + hypertension	1.70 (1.01–2.86)	15.7%	1.45 (1.09–1.92)	10.0%	1.42 (1.14–1.76)	4.5%	1.57 (1.10–2.25)	13.6%	2.20 (1.36–3.55)	39.0%	2.42 (1.62–3.62)	25.7%	1.66 (1.30–2.10)	23.3%
B + Cardiovascular or cerebrovascular diseases	1.83 (1.11–3.02)	0.0%	1.50 (1.14–1.98)	0.0%	1.44 (1.18–1.77)	0.0%	1.68 (1.10–2.57)	0.0%	2.99 (1.54–5.80)	0.0%	2.91 (1.85–4.57)	0.0%	1.86 (1.43–2.41)	0.0%
B + White blood cell count	1.82 (1.10–2.99)	1.2%	1.48 (1.12–1.97)	4.0%	1.44 (1.17–1.77)	0.0%	1.71 (1.14–2.56)	0.0%	3.15 (1.68–5.91)	0.0%	2.96 (1.91–4.58)	0.0%	1.86 (1.44–2.41)	0.0%
B + platelet count	1.87 (1.15–3.03)	0.0%	1.48 (1.13–1.95)	4.0%	1.45 (1.18–1.77)	0.0%	1.69 (1.12–2.54)	0.0%	3.08 (1.62–5.83)	0.0%	2.94 (1.92–4.51)	0.0%	1.85 (1.44–2.38)	1.2%

Note: The base model (B) is adjusted for age, gender, smoking, family poverty level, education, and alcohol intake.
Different potential mediators have been added separately to the base model.
Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Versus no/mild periodontitis.
[b]Negative values were considered as 0.00% excess risk explained.

with a low CERAD-WL performance among females (OR = 1.77; 95% CI: 1.29–2.45).

The results were consistent when analysing the continuous cognitive function scores (Table S4).

3.4 | Mediation analysis

Table 4 shows the ORs for the association between periodontal variables and low cognitive performance after adjusting for putative mediators. The magnitude of most ORs was mainly attenuated by hypertension (up to 39% for severe periodontitis/DSST score). This was also observed when considering continuous outcomes of cognitive functioning scores (Table S5).

4 | DISCUSSION

The findings from the present population-based study showed a significant association between periodontitis and low performance in specific cognitive tests. Sub-group analyses indicated a possible effect modification by gender, with stronger estimates observed among females. Mediation analysis suggested that these associations may be partially mediated by hypertension.

Recent epidemiological reports have explored the relationship between periodontitis and low cognitive performance. In a longitudinal analysis from a large cohort of U.S. adults aged between 45–64 years, from a study non-representative sample (the Atherosclerosis Risk in Communities study), a significant association was reported between severe periodontitis and incident dementia (Demmer et al., 2020). Furthermore, Sung and colleagues evaluated the association between periodontitis and three validated functional cognitive tests in the NHANES III database. They found a significant adjusted association with the DSST and the serial digit learning tests, but not with the simple reaction time test (SRTT) (Sung et al., 2019). The present study corroborates these findings on high-risk subjects (≥60 years) and additional cognitive functioning domains. Specifically, the association pattern found in this current epidemiological report suggests that the hypothesized deleterious effect of periodontitis on the central nervous system may be more substantial on executive function, attention, and working memory domains (AFT and DSST), instead of learning (CERAD-IR) and retention/recall abilities (CERAD-DR).

Stronger estimates of association were observed among females in the gender sub-group analyses, which may be interpreted within the gender-related epidemiological differences in cognitive decline (Mielke et al., 2014; Gannon et al., 2019). Moreover, specific sex hormones may exert different effects on the periodontal tissues and the cognitive system (Miller & Halpern, 2014; Romandini et al., 2020). Thus, they may act as plausible effect modifiers in the mechanistic pathway between periodontitis and low cognitive performance.

Although the mechanistic pathways for the association between periodontitis and cognitive decline have not been fully elucidated yet, the role of systemic inflammation and vascular reactivity has been widely recognized (van der Flier et al., 2018; Wardlaw et al., 2019). Kantarci and colleagues used a transgenic murine model of Alzheimer's disease to evaluate the effect of experimental periodontitis on neuroinflammatory parameters (Kantarci et al., 2020). Experimental periodontitis negatively impacted the microglia, brain's cytokine profile, deposition of amyloid-beta peptide, and intra-neuronal neurofibrillary tangles of hyperphosphorylated tau protein. Similarly, J. Zhang et al. (2018) provided pre-clinical evidence on the inflammatory pathways linking periodontitis with cognitive decline, assessed through the impaired spatial learning and memory Morris' water maze tests. The findings from the present study provide only minimal support for the role of systemic inflammation as a mediating mechanism for the association between periodontitis and low cognitive performance. Moreover, the role of direct bacterial translocation cannot be dismissed, since DNA from oral pathobionts has been detected in brain samples of deceased patients with Alzheimer's disease (Jungbauer et al., 2022).

The present study identified hypertension as a possible mediator in the association between periodontitis and low cognitive performance. Despite the novelty of this finding, long-term research studies have already demonstrated that experiencing high blood pressure during middle age is a critical factor that can increase the risk of developing dementia (Walker et al., 2019). At the same time, both observational and interventional epidemiological studies have highlighted the possible role of periodontitis as a risk factor for hypertension (Martin-Cabezas et al., 2016; Drummond et al., 2019; Muñoz Aguilera et al., 2020; Sanz et al., 2020).

The results from this study must be interpreted with caution because of its cross-sectional design, which prevents the evaluation of causality and limits the value of the reported mediation analyses. Additional limitations include the possible lack of statistical power for some of the non-significant estimates, the risk of residual confounding, the lack of a clinical examination able to diagnose and further classify cognitive impairment, and the lack of additional information on markers of systemic inflammation (e.g., C-reactive protein and erythrocyte sedimentation rate). Nonetheless, the use of a complete periodontal examination protocol minimized the risk of information bias. Additionally, the external validity of the reported findings is favoured by the employed sampling procedures, which allow their generalizability to the whole non-institutionalized U.S. population.

5 | CONCLUSIONS

This study suggests the presence of an independent association between periodontitis and low cognitive performance, specifically in verbal fluency and speed, sustained attention, and working memory, as measured by the AFT and DSST tests. This association may be partially mediated by the impact of periodontitis on hypertension. Longitudinal cohort studies are needed to verify the role of periodontitis in cognitive impairment. Future research should also include

interventional studies assessing the role of periodontal treatment as a preventive measure for low cognitive performance.

AUTHOR CONTRIBUTIONS

Crystal Marruganti contributed to study design, data analysis, and manuscript drafting. Giacomo Baima contributed to data interpretation and manuscript drafting. Mario Aimetti, Simone Grandini, and Mariano Sanz contributed to data interpretation and critically revised the manuscript. Mario Romandini contributed to study conception and design, data analysis and interpretation, and manuscript drafting. All authors have given their approval of the final manuscript to be published and agree to be held accountable for all aspects of the work.

ACKNOWLEDGEMENTS

The authors are extremely grateful to Dr. Varkha Rattu for her contribution to proofreading the manuscript.

FUNDING INFORMATION

No external funding was received for this study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at: https://www.cdc.gov/nchs/nhanes/index.htm.

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SUPPORTING INFORMATION

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How to cite this article: Marruganti, C., Baima, G., Aimetti, M., Grandini, S., Sanz, M., & Romandini, M. (2023). Periodontitis and low cognitive performance: A population-based study. *Journal of Clinical Periodontology*, *50*(4), 418–429. https://doi.org/10.1111/jcpe.13779