Supplementary Material

Cross-Sectional Analysis of Periodontal Disease and Cognitive Impairment Conducted in a Memory Clinic: The Pearl Study

Supplementary Methods

Baseline assessment

All participants underwent a comprehensive geriatric assessment [1] of the following features: 1) demographic characteristics; 2) risk factors; 3) activities of daily living (ADL); 4) global cognitive function, as assessed using the Mini-Mental State Examination (MMSE) [2], Montreal Cognitive Assessment-Japanese version (MoCA-J) [3], and Clinical Dementia Rating (CDR) scales [4]; 5) neuropsychological tests, such as the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) [5], Frontal Assessment Battery (FAB) [6], Raven's Coloured Progressive Matrices (RCPM) [7], and Logical Memory subtests of the Wechsler Memory Scale-Revised (LM-WMSR) [8]; 6) behavioral and psychological symptoms assessed using the Dementia Behavior Disturbance Scale (DBDS) [9]; 7) depression status assessed using Geriatric Depression Scale (GDS) [10]; 8) laboratory parameters, such as apolipoprotein E ε4; 9) ankle-brachial index and pulse wave velocity as indicators of arteriosclerosis [11] and the "impact" of pulse [12], respectively; 10) results of brain magnetic resonance imaging (MRI); and 11) lifestyle factors, such as living alone, physical exercise habits, daytime napping, and receiving Long-Term Care Insurance [13]. Clinical data were partially provided by the NCGG Biobank, which collects clinical data for research.

Risk factors

Hypertension was defined by a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg, and/or the use of anti-hypertensive drugs. Dyslipidemia was defined by a serum low-density lipoprotein cholesterol concentration of ≥140 mg/dL, a serum high-density lipoprotein cholesterol concentration of <40 mg/dL, a serum triacylglycerol concentration of ≥150 mg/dL, and/or the use of statins. Diabetes mellitus was defined by a hemoglobin A1c concentration of ≥6.5%, and/or the use of oral hypoglycemic drugs or insulin, and/or a fasting serum glucose concentration of ≥69.9 mol/L (126 mg/dL). Ischemic heart disease was defined by a history of physician-diagnosed angina pectoris and/or evidence of a prior myocardial infarction or coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass surgery). Serum creatinine was measured and the estimated glomerular filtration rate (eGFR) was determined using the equation proposed by the Japanese Society of Nephrology, as follows: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine [mg/dL])$^{-1.094}$ × (age [years])$^{-0.287}$ (× 0.739 if female). Chronic kidney disease (CKD) was defined by an eGFR of < 60 mL/min/1.73 m^2.

Brain imaging

Brain MRI scans were performed using a 3-Tesla MRI scanner (Magnetom Skyra, Siemens Healthineers AG, Munich, Germany). In cases where a 3-Tesla scanner was unavailable, we used a 1.5-Tesla MRI scanner (Philips Ingenia, Eindhoven, Netherlands). The MRI examination comprised standardized sequences used for analysis of the brain. T1-weighted, T2-weighted, fluid-attenuated inversion recovery imaging, T2*-weighted gradient echo imaging, and intracranial 3D time-of-flight MR angiography were conducted. The presence of cerebral small vessel disease (SVD) and its components, such as silent lacunar infarcts (SLIs), white matter hyperintensity (WMH), cerebral microbleeds (CMBs), and enlarged periventricular space, was assessed. In

accord with previous studies [14, 15], we rated the total MRI burden of SVD on an ordinal scale from 0 to 4 by summing the presence of each of these four features. The voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) software (Eisai Co., Ltd., Tokyo, Japan) was used to quantify cortical and hippocampal atrophy as an indicator of early Alzheimer's disease (AD). Participants underwent N-isopropyl-p-[^{123}I]-iodoamphetamine single photon emission computed tomography, in which low blood flow in the area of the posterior cingulate gyrus and/or precuneus was regarded as a surrogate marker of AD.

Dental examination

The dental examination was conducted by one trained periodontist (Y.I.) and dental hygienists, independent of the clinical data collection. First, dental history was obtained from the participants and their family members. Second, the number of teeth, clinical attachment loss, and probing pocket depth were measured. Clinical attachment loss is an indicator of periodontal disease (PeD), which means that the fibers of the gingiva and the fibers of the periodontal ligament are destroyed and detach from the cemental surface of the tooth's root, the junctional epithelium migrates to the surface of the tooth root, and the alveolar bone no longer supports the tooth [16]. Probing pocket depth reflects the destruction of fibers of the periodontal ligament and the resorption of the alveolar bone that occurs in parallel with the progressing attachment loss [16]. Participants were categorized into four groups (none, mild, moderate, and severe periodontitis) according to the Centers for Disease Control and Prevention in partnership with the American Academy of Periodontology definitions [17]. Six sites per tooth were examined with a CPUNC15 periodontal probe (Hu-Friedy Mfg. Co. LLC., Chicago, IL, USA), as previously reported [18].

REFERENCES

[1] Toba K (2005) The guideline for comprehensive geriatric assessment. *Nihon Ronen Igakkai Zasshi* **42**, 177-180.

[2] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[3] Fujiwara Y, Suzuki H, Yasunaga M, Sugiyama M, Ijuin M, Sakuma N, Inagaki H, Iwasa H, Ura C, Yatomi N, Ishii K, Tokumaru AM, Homma A, Nasreddine Z, Shinkai S (2010) Brief screening tool for mild cognitive impairment in older Japanese: validation of the Japanese version of the Montreal Cognitive Assessment. *Geriatr Gerontol Int* **10**, 225-232.

[4] Morris JC (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* **43**, 2412-2414.

[5] Rosen WG, Mohs RC, Davis KL (1984) A new rating scale for Alzheimer's disease. *Am J Psychiatry* **141**, 1356-1364.

[6] Dubois B, Slachevsky A, Litvan I, Pillon B (2000) The FAB: a Frontal Assessment Battery at bedside. *Neurology* **55**, 1621-1626.

[7] Raven J (1965) *Guide to using the coloured progressive matrices*. H.K. Lewis, London.

[8] Wechsler D (1981) Wechsler memory scale-revised. Psychological Corporation, San Antonio, TX.

[9] Baumgarten M, Becker R, Gauthier S (1990) Validity and reliability of the dementia behavior disturbance scale. *J Am Geriatr Soc* **38**, 221-226.

[10] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO (1982) Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* **17**, 37-49.

[11] Saji N, Kimura K, Yagita Y, Kawarai T, Shimizu H, Kita Y (2015) Comparison of arteriosclerotic indicators in patients with ischemic stroke: ankle-brachial index, brachial-ankle pulse wave velocity and cardio-ankle vascular index. *Hypertens Res* **38**, 323-328.

[12] Saji N, Toba K, Sakurai T (2016) Cerebral small vessel disease and arterial stiffness: tsunami effect in the brain? *Pulse (Basel)* **3**, 182-189.

[13] Saji N, Kimura K, Ohsaka G, Higashi Y, Teramoto Y, Usui M, Kita Y (2015) Functional independence measure scores predict level of long-term care required by patients after

stroke: a multicenter retrospective cohort study. *Disabil Rehabil* **37**, 331-337.

[14] Saji N, Murotani K, Hisada T, Tsuduki T, Sugimoto T, Kimura A, Niida S, Toba K, Sakurai T (2021) The association between cerebral small vessel disease and the gut microbiome: a cross-sectional analysis. *J Stroke Cerebrovasc Dis* **30**, 105568.

[15] Staals J, Makin SDJ, Doubal FN, Dennis MS, Wardlaw JM (2014) Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology* **83**, 1228-1234.

[16] Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis K, Taylor R (2012) Periodontitis and diabetes: a two-way relationship. *Diabetologia* **55**, 21-31.

[17] Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ (2012) Update of the case definitions for population-based surveillance of periodontitis. *J Periodontol* **83**, 1449-1454.

[18] Kataoka S, Kimura M, Yamaguchi T, Egashira K, Yamamoto Y, Koike Y, Ogawa Y, Fujiharu C, Namai T, Taguchi K, Takahashi M, Kameda A, Kasen T, Hano A, Kubota K, Sato M, Yamaga H, Nohara K, Shirasawa M, Sekine C, Fukuda M, Aoki A, Takeuchi Y, Mugiyama M, Mori K, Sawada K, Kashiwagi Y, Kitamura M, Hayashi T, Nakagawa T, Murakami S (2021) A cross-sectional study of relationships between periodontal disease and general health: The Hitachi Oral Healthcare Survey. *BMC Oral Health* **21**, 644.

Supplementary Table 1. Definitions of periodontal disease according to the CDC/AAP criteria[*]

Periodontal disease	Definition
None	No evidence of mild, moderate, or severe periodontitis
Mild	≥ 2 interproximal sites with AL ≥ 3 mm, and ≥ 2 interproximal sites with PD ≥ 4 mm or one site with PD ≥ 5 mm
Moderate	≥ 2 interproximal sites with AL ≥ 4 mm, or ≥ 2 interproximal sites with PD ≥ 5 mm
Severe	≥ 2 interproximal sites with AL ≥ 6 mm and ≥ 1 interproximal site with PD ≥ 5 mm

AL, clinical attachment loss; PD, probing depth.

[*] Definitions of periodontitis proposed by the workgroup from Centers for Disease Control and Prevention (CDC) in partnership with the American Academy of Periodontology (AAP).

Supplementary Table 2. Comparisons of background information of female and male participants

	Female (n = 91)	Male (n = 92)	p
Demographics			
Age, y	79, 74–83	79, 76–83	0.388
Education, y	12, 9–12	12, 9–16	0.123
Body mass index, kg/m^2	22.8, 20.4−25.0	23.0, 21.1−25.1	0.500
Risk factors			
Hypertension, *n* (%)	71 (78.0)	72 (78.3)	1.000
Diabetes mellitus, *n* (%)	24 (26.4)	36 (39.1)	0.083
Dyslipidemia, *n* (%)	69 (75.8)	61 (66.3)	0.193
Stroke, *n* (%)	11 (12.1)	17 (18.5)	0.305
CKD, *n* (%)	39 (42.9)	44 (47.8)	0.554
Smoking habit, *n* (%)	8 (8.8)	60 (65.2)	<0.0001
Alcohol consumption, *n* (%)	9 (9.9)	32 (34.8)	<0.0001
APOE ε4 carrier, *n* (%)	27 (29.7)	32 (34.8)	0.528
Comprehensive geriatric assessment			
Barthel Index	100, 100–100	100, 95–100	0.222
IADL impairment, *n* (%)	53 (58.2)	60 (65.2)	0.364
DBDS	9, 5–21	11, 5–19	0.217
GDS	2, 1–4.5	2, 1–4.8	0.807
Vitality index	10, 8–10	9, 8–10	0.155
History of fall in a year	27 (30.3)	31 (33.7)	0.637
Gait speed, m/s	1.04, 0.87−1.19	1.03, 0.87−1.17	0.744
Hearing impairment	41 (46.1)	63 (68.5)	0.003
MNA-SF	12, 10–13	12, 11–13	0.795
Cognitive function			
MMSE	23, 20–27	25, 20–29	0.387
MoCA-J	17, 13–23	18, 14–23	0.342
CDR-SOB	2.5, 1.0−4.0	2.0, 0.5−4.5	0.590
ADAS-cog	13.7, 8.5–19	12.7, 6.4–17.8	0.173
RCPM	25.5, 19–31	27, 22–30.5	0.284
FAB	10, 8–13	10, 7–13	0.702
LM-WMSR I	6, 3–13	6, 2–15	0.919

LM-WMSR II	0, 0–4	1, 0–8	0.034
Brain MRI findings			
SLI, *n* (%)	2 (2.2)	5 (5.4)	0.444
WMH, *n* (%)	44 (48.9)	42 (45.7)	0.767
CMB, *n* (%)	10 (11.1)	13 (14.1)	0.657
EPVS, *n* (%)	53 (58.2)	73 (79.4)	0.002
BG-PVS ≥ 2, *n* (%)	52 (57.1)	72 (78.3)	0.003
CS-PVS ≥ 3, *n* (%)	16 (17.6)	19 (20.7)	0.708
VSRAD	1.34, 0.86–2.25	1.24, 0.85–2.01	0.433
Arterial stiffness			
Ankle-brachial index	1.11, 1.07–1.15	1.14, 1.08–1.21	0.006
Pulse wave velocity, m/s	19.1, 16.5–21.8	19.0, 16.7–21.6	0.631
Laboratory findings			
BNP, pg/mL	35.9, 23.8–64.2	45.5, 16.4–79.4	0.840
HbA1c, %	5.8, 5.7–6.2	5.9, 5.6–6.4	0.426
eGFR, mL/min/1.73 m^2	63.2, 53.9–71.8	60.6, 51.1–70.7	0.158
CRP, mg/dL	0.04, 0.02–0.08	0.06, 0.02–0.15	0.093
Lifestyle			
Living alone, *n* (%)	14 (16.7)	3 (3.4)	0.004
Physical exercise habit	51 (62.2)	56 (62.9)	1.000
Receiving LTCI	26 (28.6)	32 (34.8)	0.428
Daytime napping			0.010
≥ 3 h, *n* (%)	6 (6.6)	8 (8.7)	
< 3 h, *n* (%)	51 (56.0)	63 (68.5)	
None, *n* (%)	34 (37.4)	21 (22.8)	

Data are presented as medians, interquartile ranges or number of patients (%). The Wilcoxon rank-sum test and χ^2 test were used.

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; *APOE*, apolipoprotein E; BG-PVS, enlarged perivascular spaces in the basal ganglia; BNP, brain natriuretic peptide; BP, blood pressure; CDR-SOB, Clinical Dementia Rating-Sum of Boxes; CKD, chronic kidney disease; CMB, cerebral microbleed; CS-PVS, enlarged perivascular spaces in the centrum semiovale; CRP, C-reactive protein; DBDS, Dementia Behavior Disturbance Scale; DLB, dementia with Lewy bodies; eGFR, estimated glomerular filtration rate; EPVS, enlarged periventricular space; FAB, Frontal Assessment Battery; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; IHD, ischemic heart disease; JDI, Japanese diet index; LM-

WMSR, Logical Memory subtests I and II of the Wechsler Memory Scale-Revised; LTCI, Long-term care insurance system; MMSE, Mini-Mental State Examination; MNA-SF, Mini-Nutritional Assessment-Short Form; MoCA-J, Montreal Cognitive Assessment-Japanese version; MRI, magnetic resonance imaging; RCPM, Raven's Coloured Progressive Matrices; SLI, silent lacunar infarct; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; WMH, white matter hyperintensity.

Supplementary Table 3. Comparisons of periodontal information between female and male participants

	female (n = 91)	male (n = 92)	p
Oral function			
Periodical visit to the dentist, *n* (%)	69 (75.8)	70 (76.1)	1.000
Number of remaining teeth, *n*	23, 15–27	21, 11–26	0.188
Attachment level, mm†	2.8, 2.3–3.4	3.0, 2.7–3.7	0.005
Probing depth, mm†	2.3, 2.0–2.7	2.5, 2.1–2.9	0.062
PeD			0.114
None, *n* (%)	5 (5.5)	2 (2.2)	
Mild, *n* (%)	35 (38.5)	30 (32.6)	
Moderate, *n* (%)	27 (29.6)	21 (22.8)	
Severe, *n* (%)	24 (26.4)	39 (42.4)	
Moderate or severe PeD, *n* (%)	51 (56.0)	60 (65.2)	0.228
Teeth brushing			
Times/day	2, 2–2.3	2, 1–2	0.006
≥ 3 times/day, *n* (%)	22 (24.2)	12 (13.0)	0.059
min/day	5, 2–7	3, 2–6	0.252
≥ 10 min/day, *n* (%)	15 (16.7)	14 (16.1)	1.000
Use of toothpaste, *n* (%)	67 (88.2)	70 (84.3)	0.502
Any use of denture, *n* (%)	40 (44.0)	55 (59.8)	0.039
Tongue brushing, *n* (%)	30 (36.1)	24 (26.7)	0.193

Data are presented as medians, interquartile ranges or number of patients (%).

The Wilcoxon rank-sum test and χ^2 test were used.

*Periodontal disease (PeD) was defined according to the classification proposed by the workgroup from Centers for Disease Control and Prevention in partnership with the American Academy of Periodontology (CDC/AAP criteria).

†Fifteen participants had no data for attachment level and probing depth because they had no teeth as a result of severe periodontal disease.

‡Any use of removable partial denture or dental implant.

Supplementary Table 4. Comparisons of background information between participants with and without all-cause dementia

	Dementia (+) (n = 93)	Dementia (-) (n = 90)	p
Demographics			
Age, y	79, 75–84	79, 75–82	0.466
Sex, female, *n* (%)	50 (53.8)	41 (45.6)	0.302
Education, y	12, 9–12	12, 10–14	0.001
Body mass index, kg/m^2	22.5, 20.5−24.9	23.2, 21.3−25.6	0.189
Risk factors			
Hypertension, *n* (%)	77 (82.8)	66 (73.3)	0.153
Diabetes mellitus, *n* (%)	32 (34.4)	28 (31.1)	0.641
Dyslipidemia, *n* (%)	67 (72.0)	63 (70.0)	0.871
Stroke, *n* (%)	15 (16.1)	13 (14.4)	0.838
CKD, *n* (%)	43 (46.2)	40 (44.4)	0.882
Smoking habit, *n* (%)	31 (33.3)	37 (41.1)	0.289
Alcohol consumption, *n* (%)	13 (14.0)	28 (31.1)	0.008
APOE ε4 carrier, *n* (%)	37 (39.8)	22 (24.4)	0.028
Comprehensive geriatric assessment			
Barthel Index	100, 90–100	100, 100–100	<0.0001
IADL impairment, *n* (%)	80 (86.0)	32 (36.7)	<0.0001
DBDS	13, 8–25	6, 3–12	<0.0001
GDS	3, 2–6	2, 1–3	0.001
Vitality index	9, 8–10	10, 9–10	<0.0001
History of fall in a year	36 (39.1)	22 (24.7)	0.040
Gait speed, m/s	0.93, 0.70−1.09	1.06, 0.93−1.20	<0.0001
Hearing impairment	43 (46.2)	61 (67.8)	0.005
MNA-SF	11, 10–13	12, 11–14	0.002
Cognitive function			
MMSE	20, 18–22	28, 26–29	<0.0001
MoCA-J	13, 10–17	22, 19–25	<0.0001
CDR-SB	4, 3−6	1, 0.5−2	<0.0001
ADAS-cog	17.4, 13.4–24	6.7, 5–10.7	<0.0001
RCPM	22.5, 16–27	29, 25–32	<0.0001
FAB	9, 6–11	12, 10–14	<0.0001

LM-WMSR I	3, 0.8–5	14, 7–18	<0.0001
LM-WMSR II	0, 0–0	5, 1–12	<0.0001
Brain MRI findings			
SLI, *n* (%)	3 (3.2)	4 (4.5)	0.716
WMH, *n* (%)	54 (58.1)	32 (36.0)	0.003
CMB, *n* (%)	14 (15)	9 (10)	0.376
EPVS, *n* (%)	63 (70.0)	63 (67.7)	0.752
BG-PVS ≥ 2, *n* (%)	62 (66.7)	62 (68.9)	0.755
CS-PVS ≥ 3, *n* (%)	10 (10.8)	25 (27.8)	0.005
VSRAD	1.81, 1.14–2.48	0.97, 0.68–1.43	<0.0001
Arterial stiffness			
Ankle-brachial index	1.11, 1.08–1.17	1.12, 1.05–1.17	0.570
Pulse wave velocity, m/s	19.3, 17.2–21.3	18.5, 15.9–22.2	0.204
Laboratory findings			
BNP, pg/mL	39.2, 21.9–73.6	45.6, 20.5–70.4	0.804
HbA1c, %	5.9, 5.7–6.3	5.8, 5.6–6.3	0.519
CRP, mg/dL	0.04, 0.02–0.10	0.06, 0.03–0.12	0.103
Lifestyle			
Living alone, *n* (%)	12 (14.0)	5 (5.8)	0.079
Physical exercise habit	41 (48.2)	66 (76.7)	0.051
Receiving LTCI	45 (48.4)	13 (14.4)	<0.0001
Daytime napping			0.014
≥ 3 h, *n* (%)	12 (12.9)	2 (2.2)	
< 3 h, *n* (%)	58 (62.4)	56 (62.2)	
None, *n* (%)	23 (24.7)	32 (35.6)	

Data are presented as medians, interquartile ranges or number of patients (%). The Wilcoxon rank-sum test and χ^2 test were used.

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; *APOE*, apolipoprotein E; BG-PVS, enlarged perivascular spaces in the basal ganglia; BNP, brain Natriuretic Peptide; BP, blood pressure; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CMB, cerebral microbleed; CKD, chronic kidney disease; CS-PVS, enlarged perivascular spaces in the centrum semiovale; CRP, C-reactive protein; DBDS, Dementia Behavior Disturbance Scale; DLB, dementia with Lewy bodies; EPVS, enlarged periventricular space; FAB, Frontal Assessment Battery; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; IHD, ischemic heart disease; JDI, Japanese diet index; LTCI. Long-term care insurance system; LM-WMSR, Logical

Memory subtests I and II of the Wechsler Memory Scale-Revised; MMSE, Mini-Mental State Examination; MNA-SF, Mini-Nutritional Assessment-Short Form; MoCA-J, Montreal Cognitive Assessment-Japanese version; MRI, magnetic resonance imaging; RCPM, Raven's Coloured Progressive Matrices; SLI, silent lacunar infarct; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; WMH, white matter hyperintensity.

Supplementary Table 5. Comparisons of periodontal information between participants with and without all-cause dementia

	Dementia (+) (n = 93)	Dementia (-) (n = 90)	p
Oral function			
Periodical visit to the dentist, *n* (%)	63 (67.7)	76 (84.4)	0.010
Periodontal disease*			0.001
None, *n* (%)	5 (5.4)	2 (2.2)	
Mild, *n* (%)	26 (28.0)	39 (43.3)	
Moderate, *n* (%)	20 (21.5)	28 (31.1)	
Severe, *n* (%)	42 (45.2)	21 (3.3)	
Number of remaining teeth, *n*	21, 7–26	23, 18–26	0.036
Attachment loss, mm†	2.4, 2.2–2.9	2.2, 2.0–2.6	0.002
Probing depth, mm†	3.0, 2.6–3.6	2.8, 2.5–3.4	0.088
Teeth brushing			
Times/day	2, 1–2	2, 2–3	<0.0001
≥ 3 times/day, *n* (%)	7 (7.5)	27 (30.0)	<0.0001
min/day	3, 1–5	5, 3–10	<0.0001
≥ 10 min/day, *n* (%)	3 (3.4)	26 (29.2)	<0.0001
Use of toothpaste, *n* (%)	61 (80.3)	76 (91.6)	0.064
Any use of denture, *n* (%)‡	50 (53.8)	45 (50.0)	0.658
Tongue brushing, *n* (%)	19 (22.6)	35 (39.3)	0.022

Data are presented as medians, interquartile ranges or number of patients (%). The Wilcoxon rank-sum test and χ^2 test were used.

*Periodontal disease was defined according to the classification proposed by the workgroup from Centers for Disease Control and Prevention in partnership with the American Academy of Periodontology (CDC/AAP criteria).

†Fifteen participants had no data for attachment level and probing depth because they had no teeth as a result of severe periodontal disease.

‡Any use of removable partial denture or dental implant.

Supplementary Table 6. Comparisons of background information of participants with periodontal disease (PeD; moderate and severe versus none and mild)

PeD	Moderate and severe (n = 111)	No and mild (n = 72)	p
Demographics			
Age, y	79, 75–83	78, 74–82	0.575
Sex, female, *n* (%)	51 (46.0)	40 (55.6)	0.228
Education, y	12, 9–12	12, 9–14	0.074
Body mass index, kg/m^2	23.1, 21.0−25.1	22.4, 20.0−24.4	0.189
Risk factors			
Hypertension, *n* (%)	90 (81.2)	53 (73.6)	0.273
Diabetes mellitus, *n* (%)	40 (36.0)	20 (27.8)	0.263
Dyslipidemia, *n* (%)	78 (70.3)	52 (72.2)	0.868
Ischemic heart disease, *n* (%)	15 (13.5)	6 (8.3)	0.347
Stroke, *n* (%)	17 (15.3)	11 (15.3)	1.000
CKD, *n* (%)	56 (50.5)	27 (37.5)	0.096
Smoking habits, *n* (%)	46 (41.4)	22 (30.6)	0.160
Alcohol consumption, *n* (%)	24 (21.6)	17 (23.6)	0.856
APOE ε4 carrier, *n* (%)	32 (28.8)	27 (37.5)	0.258
Comprehensive geriatric assessment			
Barthel Index	100, 95–100	100, 100–100	0.164
IADL impairment, *n* (%)	74 (66.7)	39 (54.2)	0.119
DBDS	11, 5–21.3	9, 5–13	0.148
GDS	2, 1–4.3	2, 1–5	0.949
Vitality index	9, 8–10	10, 9–10	0.037
History of fall in a year	36 (32.7)	22 (31.0)	0.871
Gait speed, m/s	1.02, 0.88−1.16	1.05, 0.83−1.21	0.625
Hearing impairment	65 (59.1)	39 (54.9)	0.645
MNA-SF	12, 10–13	12, 10–13	0.597
Cognitive function			
MMSE	23, 19–27	25, 21–29	0.045
MoCA-J	17, 13–22	19, 15–24	0.020
CDR-SOB	2.5, 1−4.5	2, 0.5−3.5	0.111
ADAS-cog	15, 7.3–21.3	10.8, 5.9–15.5	0.004
RCPM	25, 18.3–29.8	28, 24–31	0.009

FAB	10, 7–12	10.5, 9–14	0.026
LM-WMSR I	5, 2–12	7, 3–15	0.065
LM-WMSR II	0, 0–4	1, 0–10	0.135
Brain MRI findings			
SLI, *n* (%)	4 (3.6)	3 (4.2)	1.000
WMH, *n* (%)	51 (46.4)	35 (48.6)	0.879
CMB, *n* (%)	13 (11.8)	10 (13.9)	0.820
EPVS, *n* (%)	69 (62.2)	57 (79.2)	0.022
BG-PVS ≥ 2, *n* (%)	68 (61.3)	56 (77.8)	0.024
CS-PVS ≥ 3, *n* (%)	19 (17.1)	16 (22.2)	0.443
VSRAD	1.28, 0.89–2.16	1.28, 0.78–2.09	0.467
Arterial stiffness			
Ankle-brachial index	1.13, 1.08–1.18	1.10, 1.05–1.16	0.003
Pulse wave velocity, m/s	18.9, 16.6–22.2	19.3, 16.6–21.1	0.892
Laboratory findings			
BNP, pg/mL	45.6, 21.5–79.8	33.3, 17.7–62.1	0.127
HbA1c, %	5.9, 5.6–6.3	5.8, 5.7–6.3	0.624
CRP, mg/dL	0.05, 0.02–0.10	0.05, 0.02–0.12	0.946
Lifestyle			
Living alone, *n* (%)	13 (12.2)	4 (6.1)	0.293
Physical exercise habit	46 (43.4)	18 (27.7)	0.051
Receiving LTCI	41 (36.9)	17 (23.6)	0.074
Daytime napping			0.112
≥ 3 h, *n* (%)	11 (9.9)	3 (4.2)	
< 3 h, *n* (%)	72 (64.9)	42 (58.3)	
None, *n* (%)	28 (25.2)	27 (37.5)	

Data are presented as medians, interquartile ranges or number of patients (%). The Wilcoxon rank-sum test and χ^2 test were used.

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; *APOE*, apolipoprotein E; BG-PVS, enlarged perivascular spaces in the basal ganglia; BNP, brain natriuretic peptide; BP, blood pressure; CDR-SOB, Clinical Dementia Rating-Sum of Boxes; CKD, chronic kidney disease; CMB, cerebral microbleed; CS-PVS, enlarged perivascular spaces in the centrum semiovale; CRP, C-reactive protein; DBDS, Dementia Behavior Disturbance Scale; DLB, dementia with Lewy bodies; EPVS, enlarged periventricular space; FAB, Frontal Assessment Battery; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; IHD,

ischemic heart disease; JDI, Japanese diet index; LTCI, Long-term care insurance system; LM-WMSR, Logical Memory subtests I and II of the Wechsler Memory Scale-Revised; MMSE, Mini-Mental State Examination; MNA-SF, Mini-Nutritional Assessment-Short Form; MoCA-J, Montreal Cognitive Assessment-Japanese version; MRI, magnetic resonance imaging; RCPM, Raven's Coloured Progressive Matrices; SLI, silent lacunar infarct; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; WMH, white matter hyperintensity.

Supplementary Table 7. Comparisons of background information of participants with periodontal disease (PeD; moderate and severe versus none and mild)

PeD	Moderate and severe (n = 111)	No and mild (n = 72)	p
Oral function			
Periodical visit to the dentist, n (%)	77 (69.4)	62 (86.1)	0.013
Number of remaining teeth, n	21, 10–26	24, 16.3–27	0.009
Attachment loss, mm†	3.3, 2.7–4.0	2.6, 2.3–3	<0.0001
Probing depth, mm†	2.7, 2.3–3.1	2.1, 1.9–2.2	<0.0001
Teeth brushing			
Times/day	2, 1–2	2, 2–2	0.030
≥ 3 times/day, n (%)	18 (16.2)	16 (22.2)	0.335
min/day	3, 2–6	5, 2–7.8	0.051
≥ 10 min/day, n (%)	18 (17.1)	11 (15.3)	0.838
Use of toothpaste, n (%)	81 (84.4)	56 (88.9)	0.488
Any use of dentin bridge, n (%)	62 (55.9)	33 (45.8)	0.226
Tongue brushing, n (%)	30 (28.9)	24 (34.8)	0.503

Data are presented as medians, interquartile ranges or number of patients (%). The Wilcoxon rank-sum test and χ^2 test were used.

*Periodontal disease was defined according to the classification proposed by the workgroup from Centers for Disease Control and Prevention in partnership with the American Academy of Periodontology (CDC/AAP criteria).

†Fifteen participants had no data for attachment level and probing depth because they had no teeth as a result of severe periodontal disease.

Supplementary Table 8. Univariate logistic regression analyses for the presence of moderate or severe periodontal disease

	OR	95% CI	*p*
Cognitive function tests			
MMSE	0.93	0.88–1.00	0.016
CDR-sum of boxes	1.09	0.98–1.22	0.110
MoCA-J	0.94	0.89–0.99	0.019
ADAS-cog	1.06	1.02–1.11	0.003
RCPM	0.93	0.89–0.98	0.004
FAB	0.88	0.80–0.97	0.006
FAB items, 1 point decrease			
Similarities	1.29	0.94–1.75	0.109
Lexical fluency	1.49	1.08–2.06	0.013
Motor series	1.17	0.80–1.71	0.425
Conflicting instructions	1.22	0.92–1.63	0.167
Go-No-Go	1.23	0.88–1.72	0.226
Prehension behavior	0.57	0.21–1.54	0.225
MoCA-J items*, 1 point decrease			
Visuospatial function	1.47	1.10–1.96	0.007
Attention	1.25	1.00–1.55	0.039
Language	1.14	0.85–1.53	0.387
Executive function	1.24	0.98–156	0.070
Memory	1.18	0.96–1.45	0.120
Orientation	1.15	0.96–1.37	0.122
ADAS-cog items, 1 point increase			
Word Recall Task	1.22	1.05–1.43	0.010
Spoken Language	1.71	0.73–4.02	0.180
Comprehension	4.74	0.57–39.4	0.089
Word-Finding Difficulty†	ne	ne	ne
Following Commands	1.77	1.07–2.93	0.011
Naming Objects and Fingers	1.74	0.69–4.38	0.161
Constructional Praxis	1.24	0.85–1.80	0.260
Ideational Praxis	1.10	0.93–1.29	0.266
Orientation	1.12	0.95–1.32	0.155
Word Recognition Task	1.19	1.04–1.35	0.005

Remembering Test Directions	1.43	0.48–4.25	0.487

*MoCA-J items were categorized as follows: Visuospatial function (copy cube, draw clock); Attention (digit span, vigilance, serial 7s); Language (naming of three animals, sentence repetition); Executive function (trail making, verbal fluency, abstraction); Memory (Delayed recall of five words); Orientation (orientation).

CI, confidence interval; ne; not estimated. OR, odds ratio.

†Not estimated because of skewed data (167 participants, score 0; 1 participant, score 1; 1 participant, score 2).

Supplementary Table 9. Multivariable logistic regression analyses of neurocognitive test for predicting the presence of moderate or severe periodontal disease

	OR	95% CI	*p*
MMSE, 1 point decrease	1.09	1.02–1.16	0.005
MoCA-J, 1 point decrease	1.07	1.01–1.13	0.025
ADAS-cog, 1 point increase	1.07	1.02–1.13	0.002
RCPM, 1 point decrease	1.07	1.02–1.13	0.006
FAB, 1 point decrease	1.16	1.04–1.30	0.005

The dependent variable was the presence of moderate or severe periodontal disease.
Model: adjusted for age, sex, risk factors such as hypertension, dyslipidemia, diabetes mellitus, a history of stroke, chronic kidney disease, smoking, alcohol consumption, and apolipoprotein E ε4.
ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CI, confidence interval; FAB, Frontal Assessment Battery; MMSE, Mini-Mental State Examination; MoCA-J, Montreal Cognitive Assessment-Japanese version; OR, odds ratio; RCPM, Raven's Coloured Progressive Matrices.

Supplementary Table 10. Multivariable logistic regression analyses for predicting the presence of moderate or severe periodontal disease

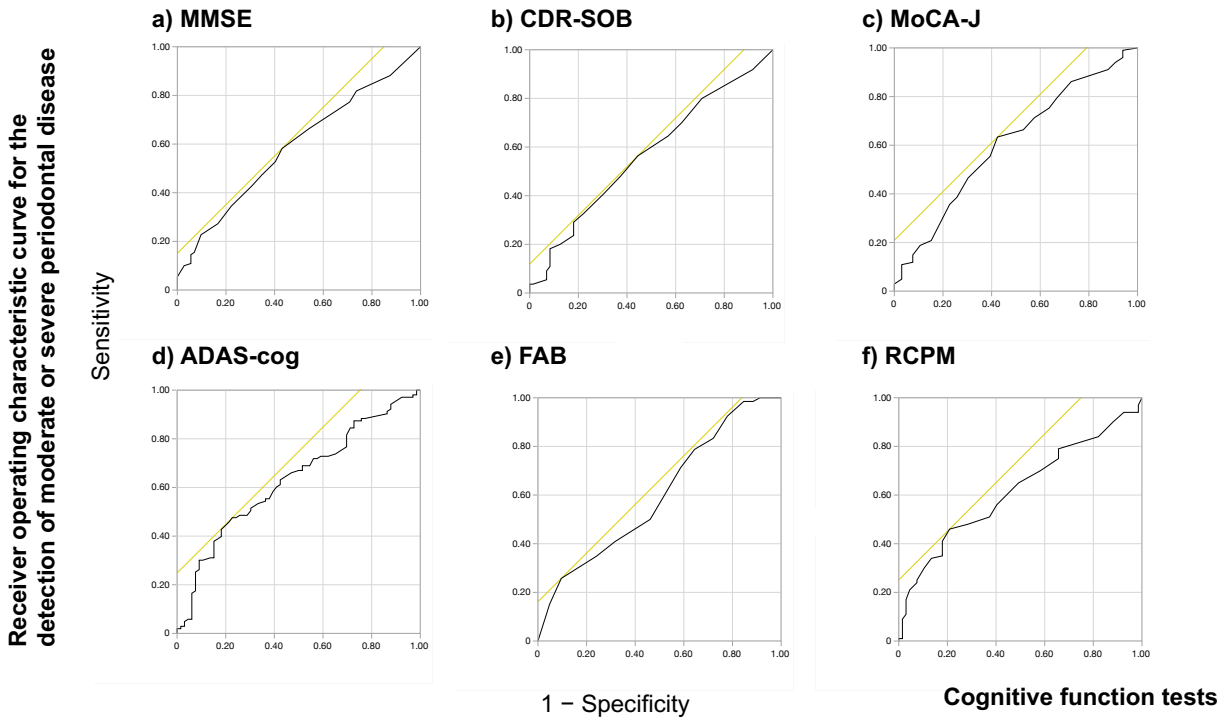
	OR	95% CI	*p*
MMSE			
Model 1	1.07	1.01–1.13	0.016
Model 2	1.08	1.01–1.14	0.012
Model 3	1.07	1.01–1.15	0.014
Model 4 (full model)			
MMSE	1.06	1.00–1.13	0.051
Smoking habit	2.79	1.33–5.85	0.005
EPVS	0.36	0.18–0.75	0.005
Years of education	0.86	0.75–0.98	0.025
Two MoCA items < 6*			
Model 1	2.25	1.18–4.29	0.012
Model 2	2.29	1.19–4.39	0.011
Model 3	2.07	1.04–4.13	0.038
Model 4 (full model)			
Two MoCA items < 6	2.11	1.04–4.29	0.037
Smoking habit	2.24	1.04–4.82	0.035
Years of education	0.85	0.74–0.99	0.031
EPVS	0.32	0.14–0.69	0.003
***Three ADAS-cog items ≥ 8**†*			
Model 1	3.04	1.58–5.83	<0.001
Model 2	3.24	1.66–6.38	<0.001
Model 3	3.26	1.61–6.59	<0.001
Model 4 (full model)			
Three ADAS-cog items < 8	2.80	1.41–5.32	0.003
Smoking habit	2.44	1.12–5.32	0.021
Years of education	0.86	0.74–1.00	0.045
EPVS	0.42	0.19–0.90	0.023

The dependent variable was the presence of moderate or severe periodontal disease.

Model 1: univariate analysis. Model 2: adjusted for age and sex. Model 3: adjusted for model 2 factors and risk factors (hypertension, dyslipidemia, diabetes mellitus, a history of stroke, chronic kidney disease, smoking, alcohol consumption, and apolipoprotein E ε4). Model 4: backward stepwise multivariable logistic regression analysis adjusted for model 3 factors, years of education, components of cerebral small vessel disease (silent lacunar infarcts, white matter hyperintensity, cerebral microbleeds, and enlarged perivascular spaces), and VSRAD score.

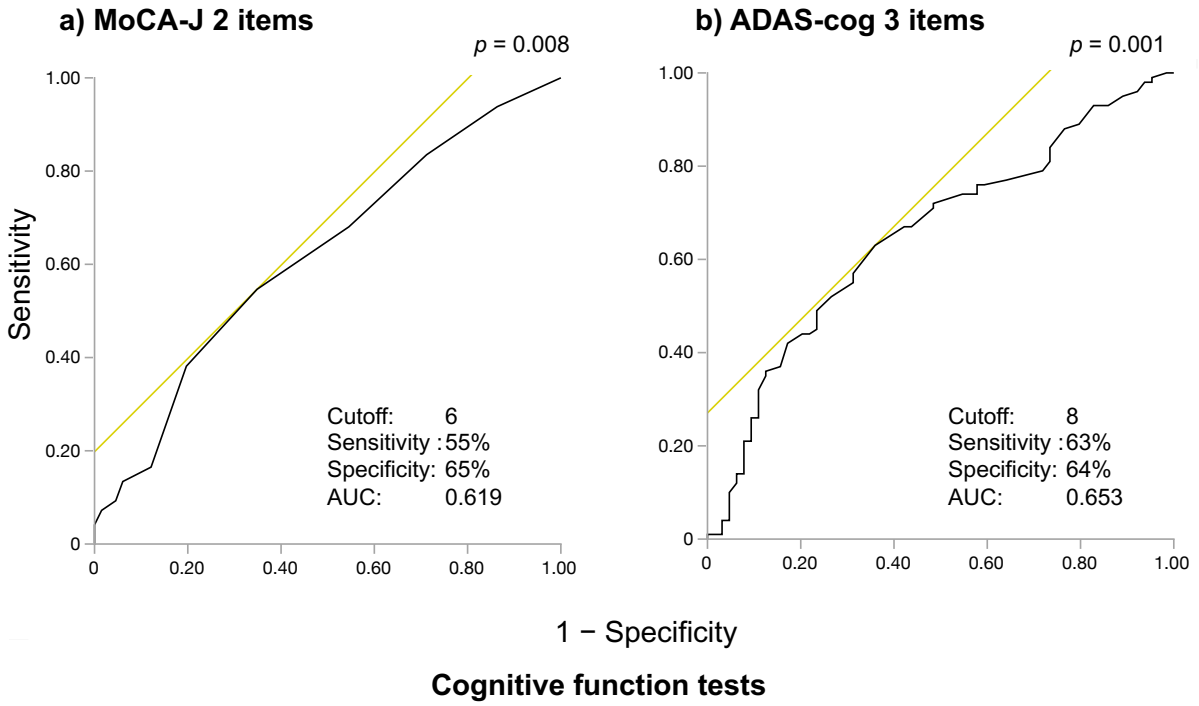
*† Cutoff scores for the detection of moderate or severe periodontal disease.

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CI, confidence interval; EPVS, Enlarged Periventricular Space; MMSE, Mini-Mental State Examination; MoCA-J, Montreal Cognitive Assessment-Japanese version; OR, odds ratio.



Supplementary Figure 1. Receiver operating characteristic curve for the detection of moderate or severe periodontal disease

Neurocognitive test values for the detection of moderate or severe periodontal disease are shown (a–f).



Supplementary Figure 2. Receiver operating characteristic curves of cognitive function test for the detection of moderate or severe periodontal disease.

Two MoCA-J items **(a)** and three ADAS-cog items **(b)** values for the detection of moderate or severe periodontal disease are shown.

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; AUC, area under the curve; MoCA-J, Montreal Cognitive Assessment-Japanese version.

Two MoCA-J items consists of visuospatial function and attention. Three ADAS-cog items consist of the word recall task, following commands task, and word recognition task.