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RESEARCH ARTICLE

Periodontitis and brain magnetic resonance imaging markers of Alzheimer's disease and cognitive aging

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Abstract

INTRODUCTION: We examined the association of clinical, microbiological, and host response features of periodontitis with MRI markers of atrophy/cerebrovascular disease in the Washington Heights Inwood Columbia Aging Project (WHICAP) Ancillary Study of Oral Health.

METHODS: We analyzed 468 participants with clinical periodontal data, microbial plaque and serum samples, and brain MRIs. We tested the association of periodontitis features with MRI features, after adjusting for multiple risk factors for Alzheimer's disease/Alzheimer's disease-related dementia (AD/ADRD).

RESULTS: In fully adjusted models, having more teeth was associated with lower odds for infarcts, lower white matter hyperintensity (WMH) volume, higher entorhinal cortex volume, and higher cortical thickness. Higher extent of periodontitis was associated with lower entorhinal cortex volume and lower cortical thickness. Differential associations emerged between colonization by specific bacteria/serum antibacterial IgG responses and MRI outcomes.

DISCUSSION: In an elderly cohort, clinical, microbiological, and serological features of periodontitis were associated with MRI findings related to ADRD risk. Further investigation of causal associations is warranted.

KEYWORDS
Alzheimer's disease, inflammation, magnetic resonance imaging, oral health, oral microbiome, periodontitis

1 | INTRODUCTION

Alzheimer's disease (AD) and related dementias (ADRD) are common in aging populations and have more than doubled in 25 years.[1] The etiology of AD is complex and half of the affected individuals have no apparent risk for dementia aside from aging.[2] Key indicators of disease including amyloid deposition and neurodegeneration are mechanistically linked in a process which begins years before the onset of clinical AD symptoms. In AD, clinical and biological changes become more apparent in the presence of a spectrum of cerebrovascular changes, including lacunar and cardioembolic stroke, microvascular white matter ischemia, and amyloid angiopathy.

Systemic inflammation and immune responses are recognized as key components of the pathogenesis of AD and ADRD by promoting accumulation of β-amyloid species, contributing to neurodegeneration,[3–5] with further pathobiological implications on the neurovascular unit.[6] Peripheral inflammation may play a role in the pathogenesis and progression of AD.[7] Oxidative stress affects brain protein aggregation, clearance and accumulation of amyloid and tau.[7] Furthermore, presence and progression of ADRD are linked to chronic vascular conditions associated with chronic inflammation, particularly diabetes mellitus and metabolic syndrome, hyperlipidemia, smoking, obesity and cardiovascular disease.[2]

Multiple studies demonstrated an association of poor oral health with risk of ADRD,[8,9] and of tooth loss and edentulism with both cognitive impairment[10–12] and incident dementia.[13–15] Features of periodontitis, including deep periodontal pockets and alveolar bone loss were associated with lower cognitive test performance[12,16–18] and an increased risk of incident dementia, including AD.[19,20] Smaller studies showed an association between periodontitis and higher brain amyloid load,[21] as well as plasma biomarkers of AD[22] and of periodontal microbial dysbiosis with lower levels of Aβ42 in the cerebrospinal fluid.[23]

Mechanistically, periodontitis is associated with systemic inflammation[24,25] and shares a number of risk factors with AD, including diabetes, obesity, and smoking.[26,27] The concept of infection-mediated AD changes has evolved, with a plausible mechanistic linkage through chronic low-grade inflammation triggered by exposure to infectious episodes over the life course. The chronicity of infectious exposure makes this linkage biologically plausible given the long preclinical phase of AD.[28,29] Mechanistically, preclinical studies in mice demonstrated that experimental periodontitis can cause brain inflammation and exacerbated brain Aβ deposition[30,31] as well as microglia activation towards a proinflammatory and phagocytic phenotype.[32,33] Multiple epidemiological neuroimaging studies of aging have identified associations with markers of chronic systemic inflammation.[34–36] Periodontal dysbiosis and the resulting increase in the systemic inflammatory burden could potentially mediate neurological alterations, and may underlie the association of poor periodontal health and AD. Furthermore, impaired chewing capacity following tooth loss may lead to an adverse diet associated with stroke and dementia[37] and with higher risk for cognitive decline.[8,11,38]

In our earlier work with the National Health and Nutrition Examination Survey III (NHANES-III) cohort, we identified an association between high levels of serum IgG to *Porphyromonas gingivalis* with impaired delayed verbal memory and calculation, after adjustments for socioeconomic and vascular variables.[39] Subsequently, in a case-cohort study design of participants drawn from the Washington Heights Inwood Columbia Aging Project (WHICAP), we analyzed serum antibody responses to a wider panel of common periodontal bacterial species and observed both protective and harmful associations with incident clinical AD.[40] Expanding these observations, a study that linked NHANES-III with mortality and insurance claims data[41] provided further evidence of an association between serological markers of periodontal infection and clinical AD incidence and mortality.

Our group is further engaged in the investigation of the association between periodontitis and ADRD in the ongoing WHICAP Ancillary Study of Oral Health. We documented that periodontitis is highly prevalent in WHICAP[42] and is associated with a complex microbiome[43] and a number of gene polymorphisms.[44] To date, there are few reports that analyzed features of periodontitis and brain imaging findings associated with impaired cognition and ADRD.[21,45–50] In this study, we examined the association of clinical, microbiological, and serological markers of periodontitis with magnetic resonance imaging (MRI) markers of atrophy and cerebrovascular disease in a tri-ethnic cohort of individuals over the age of 65 years.

2 | METHODS

The study has been performed according to the ethical standars of the 1964 Declaration of Helsinki and its later amendments. The study procedures have been approved by the Columbia University Irving Medical Center Institutional Review Board (protocol numbers AAAO9758, AAAO9804, and AAAK7122), and all participants signed written consent forms.

2.1 | Study participants

Through three successive waves of enrollment, WHICAP has serially assessed more than 6,000 local community members over the age of 65 years with respect to medical, social, and health behavior histories; general medical exams; and neuropsychological testing.[51,52] The

WHICAP Ancillary Study of Oral Health is a cohort study that recruited 1,130 individuals among the primary WHICAP study participants between December 2013 and June 2016, and analyzed clinical periodontal findings,[42] and subgingival microbial profiles.[43] This report includes WHICAP participants with available clinical, microbial, and serological data on periodontitis and brain MRI exams.[53] The time interval between the oral and the MRI examination was within 6 months for 180 participants (37% of the cohort), within 1 year for 189 (39%), within 2 years for 278 (57.2%), within 3 years for 390 (80%), and within 4 years for 470 participants (97% of the cohort). All 486 participants completed both the oral health and MRI assessments within 4.5 years of each other; 144 participants (29.6%) had their MRI >6 months prior to, and 153 (31.4%) >6 months after the oral examination.

2.2 | Clinical periodontal examination

Participants underwent a full-mouth clinical examination including assessments of pocket depth (PPD) and clinical attachment level (CAL) at six sites per tooth for all present teeth, assessed by a single calibrated dentist using a UNC-15 manual periodontal probe, as earlier described.[42]

2.3 | Assessment of periodontal microbiota

We collected four subgingival plaque samples per participant, each obtained from the mesio-lingual aspect of the most posterior tooth in every quadrant.[43] Each sample was split in two halves. The first halves were analyzed individually using checkerboard DNA-DNA hybridization[54] with respect to 11 bacterial species. The second halves were merged into a single pooled sample per participant and processed by means of the Human Oral Microbe Identification using Next Generation Sequencing,[55] allowing characterization of >600 microbial taxa.

2.4 | Assessment of serum immunoglobulin G antibody responses to periodontal microbiota

Serum immunoglobulin G (IgG) levels to the same 11 periodontal species were assessed using checkerboard immunoblotting as in our earlier studies.[56,57] For each participant, we also determined an "infection ratio" (ratio of antibody IgG over the homologous mean bacterial burden).[58,59]

2.5 | MRI of brain regions

MRI scan acquisition techniques have been previously described.[60] In brief, all MRI images were acquired in a 3T Philips scanner and included T1-weighted images (repetition time 6.6 ms, echo time 3.0 ms, field of view 256 × 256 × 165, 1.0 mm slice thickness), T2-weighted FLAIR images (repetition time 8,000 ms, echo time 337 ms, field of view 240 × 240 × 180, 0.43 mm slice thickness), and T2*-weighted susceptibility weighted imaging (SWI; repetition time 17 ms, echo time 24 ms, field of view 244 × 197mm^2, 2 mm slice thickness, in plane resolution 0.43 × 0.43 mm), or T2*-weighted gradient echo (GRE) scans (repetition time 15 ms, echo time 22 ms, field of view 220 × 181mm^2, 1 mm slice thickness).

The following variables were assessed and included in the analyses: *Cerebral microbleeds*, identified and quantified by visual inspection according to previously reported protocols[61] using SWI or GRE images, were coded as present, if one or more were detected, or absent. *Brain Infarcts* were identified as previously described[62] following a pathology-informed algorithm that segregates chronic brain infarcts from perivascular spaces.[63] Infarcts were coded as present, if one or more were detected, or absent. *White matter hyperintensity* (WMH) *volume* was quantitated on FLAIR images using an in-house developed software, as previously described.[60] Regional *hippocampal volume and entorhinal cortex volume* were derived using *FreeSurfer*; volumes were derived by averaging across hemispheres and were adjusted for intracranial volume. *"AD signature" composite* was derived by averaging cortical thickness measurements in nine regions associated with AD neurodegeneration,[64,65] including the rostral medial temporal lobe (entorhinal cortex and para-hippocampus), angular gyrus (inferior parietal lobe), inferior frontal lobe (pars opercularis, pars orbitalis, and

RESEARCH IN CONTEXT

1. **Systematic review**: Literature searches identified publications linking periodontitis with Alzheimer's disease (AD) and related dementias (ADRD). A limited number of studies have identified associations between periodontitis and brain magnetic resonance imaging (MRI) features, but findings vary across studies. Recurring limitations include quality and timing of the dental and imaging examinations. No study so far has examined concomitantly associations between clinical, microbiological, and serological evidence of periodontitis and brain MRI findings.
2. **Interpretation**: We demonstrate that higher tooth retention and lower severity of periodontitis were associated with favorable MRI findings. Certain bacterial and serological markers of periodontitis were associated with smaller brain volumes, while others with vascular brain changes.
3. **Future directions**: MRI findings corroborate earlier observations suggesting that periodontitis, a common, modifiable inflammatory condition may have a complex role in AD/ADRD. Longitudinal asssessments of both periodontitis and cognitive biomarkers may help clarify the temporality and strength of these relationships.

pars triangularis), inferior temporal lobe, temporal pole, precuneus, supramarginal gyrus, superior parietal lobe, and superior frontal lobe.

2.6 | Assessment of covariates

Covariates were selected a priori to address possible confounding by factors associated with clinical and/or imaging evidence of cognitive impairment as well as oral health status. Sociodemographic covariates included age, sex, race-ethnicity (Hispanic, non-Hispanic Black, or non-Hispanic White individuals) and education, categorized into three groups (low: ≤ 11 years, middle: 12-16 years, high: ≥ 17 years). Medical covariates included diabetes, based upon self-report or by medications indicated for the treatment of diabetes; hypertension, based upon self-report, medication use, or by blood pressure measurements (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg); cardiovascular disease (history of atrial fibrillation or other arrhythmias, coronary artery disease including myocardial infarction or angina pectoris, or congestive heart failure); smoking, determined by self - report, and classified as current, former, or never. Apolipoprotein E (APOE) genotype was determined[66,67] and participants were classified based on the presence (homozygous or heterozygous) or absence of the APOE ε4 allele.

2.7 | Data analyses

WMH volumes were log-transformed. Clinical periodontal status was expressed as tooth count, Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) class[68] (grouped as no/mild vs. moderate/severe periodontitis), and % of teeth with probing depth (PD)≥4 mm, and % of teeth with clinical attachment level (CAL)≥4 mm. We carried out simple and multiple regression analyses of the association between periodontitis-related clinical, microbiological, and serological features (independent variables) and each of the six MRI features described above as dependent variables. Model 1 adjusted for sex, age (continuous), and race and education (three level variables); model 2 included model 1 variables and further adjusted for diabetes, hypertension, cardiovascular disease, and smoking (all as dichotomous variables; smoking was dichotomized as current/former vs. never); model 3 included model 2 variables and further adjusted for APOE genotype.

3 | RESULTS

Of the 486 participants in the study, 485 also had assessments of cognition contemporaneous to the oral examination. The majority (407; 83.9%) were diagnosed as cognitively normal, 70 participants (14.4%) had mild cognitive impairment, and 8 (1.7%) had dementia. Table 1 summarizes sociodemographic and other covariate information, which were similar to that of the overall Ancillary Study of Oral Health cohort.[42]

TABLE 1 Sociodemographic characteristics and other co-variates in the subset of the WHICAP Ancillary Study of Oral Health participants with available data on clinical, microbial, and serological features of periodontitis and brain MRI imaging ($N = 486$).

Age (years)	Mean (SD)	74.1 (5.8)
	Range	63.5-98.2
	<69	134 (27.6%)
	70-74	177 (36.4%)
	75-79	83 (17.1%)
	80+	92 (18.9%)
Sex	Female	307 (63.2%)
Race/ethnicity	Hispanic	190 (39.1%)
	Non-Hispanic Black	164 (33.7%)
	Non-Hispanic White	132 (27.2%)
	Other	0 (0.0%)
Educational attainment	Low	155 (32.0%)
	Middle	220 (45.5%)
	High	109 (22.5%)
Hypertension	Present	375 (77.2%)
Cardiovascular disease	Present	154 (31.7%)
Smoking	Current/Former	224 (46.1%)
	Never	262 (53.9%)
APOE genotype	Present	152 (31.3%)

Table 2 summarizes findings from regression analyses that included each of the four clinical features of periodontitis (tooth count, CDC/AAP class, % of teeth with PD ≥ 4 mm, and % of teeth with CAL ≥ 4 mm as independent variables, and each of the six MRI features analyzed (presence of cerebral microbleeds and infarcts; and white matter hyperintensity, hippocampal volume, entorhinal cortex volume, and "AD signature" values) as dependent variables. The depicted values represent odds ratios in the case of cerebral microbleeds and infarcts, and regression coefficients for all other continuous variables.

The findings indicate that, in the fully adjusted models, a higher tooth count was associated with lower odds for infarcts, lower volume of white matter hyperintensities, higher entorhinal cortex volume and higher "AD signature" values. In contrast, increasing extent of periodontitis, expressed through a higher percent of teeth with CAL ≥4 mm, was associated with lower entorhinal cortex volume and lower "AD signature" values. No significant associations emerged after adjustments between CDC/AAP classes or the percent of teeth with PD≥4 mm deep and any of the MRI features.

Tables 3 and 4 describe associations of periodontal microbial exposures, based on checkerboard DNA-DNA hybridization analysis, and 16S rRNA gene sequencing at the genus level, respectively, and the MRI features. Higher subgingival colonization by *T. forsythia* was associated with lower entorhinal cortex volume after adjustments, while higher colonization by *V. parvula* or *A. naeslundii* was associated with lower WMH volume (Table 3). Higher abundance by several genera was associated unfavorably with several MRI features in the fully adjusted

TABLE 2 Findings from regression analyses utilizing selected clinical features of periodontitis as exposures and MRI features (cerebral microbleeds; infarcts; white matter hyperintensity volume; hippocampal volume, entorhinal cortex volume and "AD signature") as outcomes.

	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
Tooth count						
Simple regression	1.020	0.961	−0.0237	0.0000	0.0084	0.0033
Model 1	1.020	0.956	−0.0210	0.0000	0.0061	0.0018
Model 2	1.030	0.959	−0.0186	0.0000	0.0060	0.0017
Model 3	1.030	0.959	−0.0185	0.0000	0.0060	0.0017
CDC/AAP						
Simple regression	0.926	1.107	0.1130	0.0000	0.0379	−0.0140
Model 1	0.917	1.125	0.0961	0.0000	0.0401	−0.0051
Model 2	0.926	1.205	0.0695	0.0000	0.0422	−0.0038
Model 3	0.917	1.206	0.0673	0.0000	0.0427	−0.0034
% teeth with PD≥4 mm						
Simple regression	1.190	1.263	0.3700	−0.0001	−0.0597	−0.0417
Model 1	1.380	1.233	0.3570	0.0000	−0.0851	−0.0331
Model 2	1.370	1.079	0.3040	0.0000	−0.0784	−0.0292
Model 3	1.360	1.078	0.3040	0.0000	−0.0784	−0.0292
% teeth with CAL≥4 mm						
Simple regression	0.820	1.908	0.3880	−0.0001	−0.1239	−0.0674
Model 1	0.885	1.913	0.2917	−0.0001	−0.1085	−0.0446
Model 2	0.876	1.764	0.2421	−0.0001	−0.1042	−0.0424
Model 3	0.876	1.761	0.2421	−0.0001	−0.1042	−0.0424

Note: For variable definitions, please see text. Values represent odds ratios for cerebral microbleeds and infarcts, and regression coefficients for all other continuous variables (regression coefficients of <0.0001 are reported as 0.0000).
Model 1 adjusted for age, sex, race, and education; Model 2 further adjusted for diabetes, hypertension, cardiovascular disease, and smoking; and Model 3 further adjusted for APOE4 genotype. Values are highlighted in color, if statistically significant. Green shades indicate "protective" associations with increasing levels of exposure, that is, a directional association towards a lower level of risk for ADRD, (e.g. lower odds for microbleeds/infarcts, less atrophy in the analyzed regions), while red shades indicate potentially "harmful" associations. Lighter color shades (green or red) indicate $p < 0.05$, darker color shades indicate $p < 0.01$.
Abbreviations: CAL, clinical attachment level; CDC/AAP, periodontal status according to the Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) classification; PD, probing depth.

models (Table 4) as follows: *Bacteroides* with entorhinal cortex volume; *Bulleidia* and *Pyramidobacter* with both lower entorhinal cortex volume and lower "AD signature" values; *Scardovia* with higher white matter hyperintensity burden; and *Schwartzia* with lower entorhinal cortex volume. In contrast, favorable associations with MRI features in fully adjusted models emerged for higher bacterial relative abundance by several genera including *Campylobacter* with "AD signature"; *Capnocytophaga* with WMH; *Cardiobacterium* with WMH and "AD signature"; *Corynebacterium* and *Granulicatella* with entorhinal cortex volume; and *Filifactor* with "AD signature."

Associations between serological markers of periodontitis and brain MRI features are presented in Table 5. Higher level of serum IgG to *P. gingivalis* was associated with higher entorhinal cortex volume, and higher *Prevotella intermedia* IgG was associated with higher hippocampal volume in the fully adjusted models. In contrast, antibody levels to *Fusobacterium nucleatum* were associated with higher odds for cerebral microbleeds and infarcts. Lastly, responsiveness to three periodontal species, expressed through the ratio of antibody response over the homologous bacterial colonization, was associated with distinct MRI features after full adjustments (Table 6). Thus, higher infection ratios to *P. intermedia* and *T. forsythia* were associated with higher hippocampal volume, while higher infection ratio to *F. nucleatum* was associated with higher odds for cerebral microbleeds.

4 | DISCUSSION

We observed that several clinical, microbiological, and host-response features of periodontitis are independently associated with MRI markers related to ADRD in an elderly, muti-ethnic cohort. In fully adjusted models that accounted for established risk factors for AD, a higher number of teeth present was associated with lower odds for infarcts, lower WMH volume, higher entorhinal cortex volume and less atrophy in regions associated with ADRD. In contrast, a higher extent of

TABLE 3 Findings from regression analyses utilizing mean bacterial load by each of the 11 bacterial species analyzed using checkerboard DNA-DNA hybridizations as exposures and the MRI features as outcomes

Mean bacterial load	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
P. gingivalis						
Simple regression	1.001	0.999	0.0000	0.0000	−0.0002	−0.0001
Model 1	1.001	0.999	0.0001	0.0000	−0.0002	−0.0001
Model 2	0.999	0.999	0.0001	0.0000	−0.0002	−0.0001
Model 3	1.001	0.999	0.0001	0.0000	−0.0002	−0.0001
P. intermedia						
Simple regression	1.000	1.000	−0.0004	0.0000	−0.0001	0.0000
Model 1	0.993	1.000	−0.0004	0.0000	−0.0001	0.0000
Model 2	1.052	1.000	−0.0003	0.0000	−0.0001	0.0000
Model 3	1.000	1.000	−0.0003	0.0000	−0.0001	0.0000
T. forsythia						
Simple regression	1.000	1.000	0.0002	0.0000	−0.0002	0.0000
Model 1	1.000	1.000	0.0002	0.0000	−0.0002	0.0000
Model 2	1.000	1.000	0.0002	0.0000	−0.0002	0.0000
Model 3	1.000	1.000	0.0002	0.0000	−0.0002	0.0000
A. actinomycetemcomitans						
Simple regression	0.993	0.998	−0.0022	0.0000	0.0004	0.0002
Model 1	0.994	0.998	−0.0015	0.0000	0.0001	0.0002
Model 2	0.994	0.998	−0.0018	0.0000	0.0001	0.0002
Model 3	0.994	0.998	−0.0018	0.0000	0.0001	0.0002
F. nucleatum						
Simple regression	1.000	1.000	0.0001	0.0000	0.0000	0.0000
Model 1	1.000	1.000	0.0001	0.0000	0.0000	0.0000
Model 2	1.000	1.000	0.0001	0.0000	0.0000	0.0000
Model 3	1.000	1.000	0.0001	0.0000	0.0000	0.0000
T. denticola						
Simple regression	0.998	1.000	−0.0011	0.0000	−0.0003	0.0000
Model 1	0.998	1.001	−0.0005	0.0000	−0.0005	−0.0001
Model 2	0.998	1.001	−0.0006	0.0000	−0.0005	−0.0001
Model 3	0.998	1.001	−0.0006	0.0000	−0.0005	−0.0001
M. micros						
Simple regression	1.002	1.000	−0.0001	0.0000	0.0000	0.0000
Model 1	1.002	1.000	−0.0002	0.0000	0.0000	0.0000
Model 2	1.002	1.000	−0.0001	0.0000	0.0000	0.0000
Model 3	1.002	1.000	−0.0001	0.0000	0.0000	0.0000
C. rectus						
Simple regression	0.995	0.996	−0.0014	0.0000	−0.0002	−0.0001
Model 1	0.995	0.995	−0.0012	0.0000	−0.0002	0.0000
Model 2	0.995	0.996	−0.0010	0.0000	−0.0002	0.0000
Model 3	0.995	0.996	−0.0011	0.0000	−0.0002	0.0000

(Continues)

TABLE 3 (Continued)

Mean bacterial load	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
E. corrodens						
Simple regression	0.999	1.000	−0.0008	0.0000	0.0003	0.0001
Model 1	0.999	1.000	−0.0006	0.0000	0.0002	0.0001
Model 2	0.999	1.000	−0.0006	0.0000	0.0002	0.0001
Model 3	0.999	1.000	−0.0006	0.0000	0.0002	0.0001
V. parvula						
Simple regression	1.000	0.997	−0.0022	0.0000	−0.0001	0.0001
Model 1	1.000	0.997	−0.0022	0.0000	−0.0001	0.0001
Model 2	1.000	0.997	−0.0023	0.0000	−0.0001	0.0001
Model 3	1.000	0.997	−0.0024	0.0000	−0.0001	0.0001
A. naeslundii						
Simple regression	1.000	1.000	−0.0008	0.0000	0.0001	0.0000
Model 1	1.000	1.000	−0.0008	0.0000	0.0001	0.0000
Model 2	1.000	1.000	−0.0007	0.0000	0.0001	0.0000
Model 3	1.000	1.000	−0.0007	0.0000	0.0001	0.0000

Note: Values represent odds ratios for cerebral microbleeds and infarcts, and regression coefficients for all other continuous variables (regression coefficients of <0.0001 are reported as 0.0000).
Values are highlighted in color, if statistically significant. Model structure, colors, and shades as described in Table 2.

TABLE 4 Findings from regression analyses utilizing mean bacterial on the genus level assessed through 16sRNA sequencing and the MRI features as outcomes

Genus	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
Actinobacillus						
Simple regression	1.000	0.996	−0.00007	0.000000246	0.000522	0.000084
Model 1	0.997	0.996	0.00031	0.000000000	0.000529	0.000043
Model 2	0.997	0.997	0.00024	−0.000000090	0.000515	0.000034
Model 3	0.997	0.997	0.00032	−0.000000122	0.000501	0.000024
Actinomyces						
Simple regression	1.000	1.000	−0.00004	0.000000004	−0.000005	−0.000004
Model 1	1.000	1.000	−0.00003	0.000000000	−0.000007	−0.000005
Model 2	1.000	1.000	−0.00004	−0.000000003	−0.000007	−0.000005
Model 3	1.000	1.000	−0.00004	−0.000000003	−0.000007	−0.000005
Atopobium						
Simple regression	1.000	1.000	0.00009	−0.000000038	−0.000025	−0.000014
Model 1	1.000	1.000	0.00004	0.000000000	−0.000004	−0.000005
Model 2	1.000	1.000	0.00002	−0.000000027	−0.000003	−0.000004
Model 3	1.000	1.000	0.00002	−0.000000026	−0.000002	−0.000003
Bacteroides						
Simple regression	0.990	0.872	−0.00049	−0.000000716	−0.001025	−0.000138
Model 1	0.987	0.866	−0.00205	−0.000001000	−0.001298	−0.000128
Model 2	0.986	0.862	−0.00225	−0.000000919	−0.001279	−0.000107
Model 3	0.987	0.860	−0.00255	−0.000000834	−0.001249	−0.000080

(Continues)

TABLE 4 (Continued)

Genus	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
Bifidobacterium						
Simple regression	0.999	1.000	0.00025	0.000000060	−0.000050	−0.000011
Model 1	0.999	1.000	0.00026	0.000000000	−0.000032	−0.000006
Model 2	0.999	1.000	0.00025	0.000000056	−0.000032	−0.000006
Model 3	0.999	1.000	0.00026	0.000000053	−0.000034	−0.000007
Bulleidia						
Simple regression	1.000	1.000	0.00021	−0.000000024	−0.000081	−0.000023
Model 1	1.000	1.000	0.00019	0.000000000	−0.000079	−0.000023
Model 2	1.000	1.000	0.00018	−0.000000036	−0.000082	−0.000024
Model 3	1.000	1.000	0.00017	−0.000000031	−0.000080	−0.000023
Campylobacter						
Simple regression	1.000	1.000	−0.00003	0.000000006	0.000010	0.000009
Model 1	1.000	1.000	−0.00002	0.000000000	0.000008	0.000007
Model 2	1.000	1.000	−0.00001	0.000000006	0.000008	0.000007
Model 3	1.000	1.000	−0.00001	0.000000005	0.000007	0.000007
Capnocytophaga						
Simple regression	1.000	1.000	−0.00015	−0.000000015	0.000023	0.000008
Model 1	1.000	1.000	−0.00014	0.000000000	0.000021	0.000006
Model 2	1.000	1.000	−0.00012	−0.000000018	0.000021	0.000005
Model 3	1.000	1.000	−0.00012	−0.000000018	0.000020	0.000005
Cardiobacterium						
Simple regression	1.000	1.000	−0.00039	0.000000002	0.000044	0.000031
Model 1	1.000	1.000	−0.00037	0.000000000	0.000052	0.000037
Model 2	1.000	1.000	−0.00036	0.000000002	0.000049	0.000035
Model 3	1.000	1.000	−0.00035	0.000000001	0.000049	0.000035
Catonella						
Simple regression	1.000	0.999	−0.00021	−0.000000149	−0.000043	−0.000035
Model 1	1.000	0.999	−0.00029	0.000000000	−0.000078	−0.000044
Model 2	1.000	0.999	−0.00037	−0.000000124	−0.000072	−0.000039
Model 3	1.000	0.999	−0.00034	−0.000000121	−0.000071	−0.000038
Corynebacterium						
Simple regression	1.000	1.000	−0.00003	0.000000005	0.000009	0.000002
Model 1	1.000	1.000	−0.00003	0.000000000	0.000009	0.000002
Model 2	1.000	1.000	−0.00002	0.000000004	0.000009	0.000002
Model 3	1.000	1.000	−0.00002	0.000000004	0.000009	0.000002
Filifactor						
Simple regression	1.000	1.000	−0.00006	0.000000004	−0.000012	0.000017
Model 1	1.000	1.000	−0.00006	0.000000000	−0.000010	0.000016
Model 2	1.000	1.000	−0.00007	−0.000000002	−0.000008	0.000018
Model 3	1.000	1.000	−0.00007	−0.000000004	−0.000009	0.000017
Fusobacterium						
Simple regression	1.000	1.000	0.00000	−0.000000002	−0.000002	0.000000
Model 1	1.000	1.000	0.00000	0.000000000	−0.000001	0.000000

(Continues)

TABLE 4 (Continued)

Genus	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
Model 2	1.000	1.000	0.00000	−0.000000001	−0.000001	0.000000
Model 3	1.000	1.000	0.00000	−0.000000001	−0.000001	0.000000
Granulicatella						
Simple regression	1.006	1.009	0.00519	0.000000073	0.001169	0.000010
Model 1	1.005	1.009	0.00478	0.000000000	0.001299	0.000132
Model 2	1.005	1.009	0.00471	0.000000217	0.001327	0.000152
Model 3	1.006	1.009	0.00449	0.000000311	0.001380	0.000180
Lactobacillus						
Simple regression	0.989	1.014	−0.00002	−0.000000151	0.000258	−0.000106
Model 1	0.988	1.013	−0.00028	0.000000000	0.000285	−0.000063
Model 2	0.988	1.014	−0.00018	−0.000000066	0.000292	−0.000062
Model 3	0.988	1.014	−0.00011	−0.000000091	0.000280	−0.000069
Lautropia						
Simple regression	0.978	0.997	−0.00693	−0.000000392	0.000334	0.000000
Model 1	0.983	0.998	−0.00638	−0.000001000	0.000358	0.000062
Model 2	0.983	1.001	−0.00559	−0.000001070	0.000291	−0.000009
Model 3	0.983	1.001	−0.00541	−0.000001140	0.000256	−0.000030
Leptotrichia						
Simple regression	1.000	1.000	−0.00001	0.000000001	0.000002	0.000000
Model 1	1.000	1.000	−0.00001	0.000000000	0.000002	0.000000
Model 2	1.000	1.000	−0.00001	0.000000002	0.000002	0.000001
Model 3	1.000	1.000	−0.00001	0.000000002	0.000002	0.000000
Mogibacterium						
Simple regression	1.000	0.999	0.00006	−0.000000085	−0.000131	−0.000036
Model 1	1.000	0.999	−0.00001	0.000000000	−0.000103	−0.000026
Model 2	1.000	0.999	−0.00003	−0.000000099	−0.000105	−0.000027
Model 3	1.000	0.999	−0.00007	−0.000000084	−0.000098	−0.000023
Moryella						
Simple regression	1.000	1.000	−0.00004	0.000000029	0.000008	−0.000005
Model 1	1.000	1.000	−0.00005	0.000000000	0.000011	−0.000004
Model 2	1.000	1.000	−0.00005	0.000000025	0.000011	−0.000004
Model 3	1.000	1.000	−0.00005	0.000000025	0.000011	−0.000004
Mycoplasma						
Simple regression	0.999	0.990	−0.00067	0.000000003	0.000175	0.000080
Model 1	1.000	0.990	−0.00095	0.000000000	0.000141	0.000057
Model 2	1.000	0.990	−0.00087	−0.000000152	0.000145	0.000057
Model 3	1.000	0.990	−0.00085	−0.000000142	0.000150	0.000060
Neisseria						
Simple regression	0.970	0.946	−0.00856	−0.000000368	0.000088	0.000100
Model 1	0.969	0.949	−0.00881	−0.000001000	−0.000054	−0.000069
Model 2	0.970	0.952	−0.00813	−0.000000566	−0.000129	−0.000121
Model 3	0.970	0.952	−0.00806	−0.000000596	−0.000144	−0.000130

(Continues)

TABLE 4 (Continued)

Genus	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
Oribacterium						
Simple regression	1.000	1.000	0.00012	−0.000000045	−0.000002	−0.000001
Model 1	1.000	1.000	0.00008	0.000000000	0.000000	0.000001
Model 2	1.000	1.000	0.00006	−0.000000041	0.000000	0.000001
Model 3	1.000	1.000	0.00007	−0.000000042	0.000000	0.000000
Paludibacter						
Simple regression	1.000	1.000	−0.00001	0.000000027	0.000006	−0.000002
Model 1	1.000	1.000	−0.00003	0.000000000	0.000012	0.000000
Model 2	1.000	1.000	−0.00003	0.000000025	0.000012	0.000000
Model 3	1.000	1.000	−0.00004	0.000000026	0.000012	0.000000
Parvimonas						
Simple regression	1.000	1.000	−0.00002	−0.000000006	−0.000004	−0.000002
Model 1	1.000	1.000	−0.00004	0.000000000	−0.000004	−0.000002
Model 2	1.000	1.000	−0.00005	−0.000000009	−0.000005	−0.000002
Model 3	1.000	1.000	−0.00005	−0.000000008	−0.000005	−0.000002
Peptoniphilus						
Simple regression	0.992	0.991	0.00024	−0.000000733	0.000274	−0.000040
Model 1	0.992	0.991	0.00002	−0.000001000	0.000273	−0.000223
Model 2	0.992	0.990	−0.00017	−0.000000833	0.000242	−0.000237
Model 3	0.991	0.990	0.00004	−0.000000923	0.000201	−0.000263
Peptostreptococcus						
Simple regression	1.000	0.999	−0.00004	−0.000000027	−0.000006	−0.000003
Model 1	1.000	0.999	−0.00005	0.000000000	−0.000005	−0.000001
Model 2	1.000	0.999	−0.00006	−0.000000025	−0.000005	−0.000001
Model 3	1.000	0.999	−0.00006	−0.000000025	−0.000005	−0.000001
Porphyromonas						
Simple regression	1.000	1.000	−0.00003	0.000000003	0.000007	0.000005
Model 1	1.000	1.000	−0.00003	0.000000000	0.000003	0.000004
Model 2	1.000	1.000	−0.00004	0.000000000	0.000004	0.000004
Model 3	1.000	1.000	−0.00004	0.000000000	0.000004	0.000004
Prevotella						
Simple regression	1.000	1.000	0.00000	0.000000002	−0.000003	0.000001
Model 1	1.000	1.000	0.00000	0.000000000	−0.000002	0.000001
Model 2	1.000	1.000	0.00000	0.000000002	−0.000001	0.000001
Model 3	1.000	1.000	0.00000	0.000000002	−0.000001	0.000001
Pseudoramibacter Eubacterium						
Simple regression	0.994	1.000	0.00065	−0.000000534	−0.000580	−0.000218
Model 1	0.994	1.000	0.00004	0.000000000	−0.000436	−0.000142
Model 2	0.994	1.000	−0.00005	−0.000000371	−0.000444	−0.000148
Model 3	0.994	1.000	−0.00003	−0.000000380	−0.000449	−0.000150

(Continues)

TABLE 4 (Continued)

Genus	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
Pyramidobacter						
Simple regression	0.977	1.001	0.00039	0.000000003	−0.000117	−0.000046
Model 1	0.977	1.001	0.00036	0.000000000	−0.000124	−0.000041
Model 2	0.977	1.000	0.00034	0.000000005	−0.000125	−0.000042
Model 3	0.977	1.000	0.00035	0.000000000	−0.000127	−0.000043
Rothia						
Simple regression	1.000	1.000	0.00000	0.000000002	−0.000001	0.000000
Model 1	1.000	1.000	0.00000	0.000000000	−0.000001	0.000000
Model 2	1.000	1.000	0.00000	0.000000000	−0.000001	0.000000
Model 3	1.000	1.000	0.00000	0.000000000	−0.000001	0.000000
Scardovia						
Simple regression	1.000	1.000	0.00012	−0.000000017	−0.000038	0.000003
Model 1	1.000	1.000	0.00017	0.000000000	−0.000038	0.000000
Model 2	1.000	1.000	0.00019	−0.000000029	−0.000039	−0.000001
Model 3	1.000	1.000	0.00019	−0.000000028	−0.000038	0.000000
Schwartzia						
Simple regression	1.000	1.000	0.00037	−0.000000188	−0.000170	−0.000060
Model 1	1.000	1.000	0.00021	0.000000000	−0.000117	−0.000032
Model 2	1.000	1.000	0.00018	−0.000000126	−0.000121	−0.000032
Model 3	1.000	1.000	0.00017	−0.000000118	−0.000118	−0.000030
Sharpea						
Simple regression	1.000	1.000	0.00362	−0.000000247	0.000270	0.000029
Model 1	1.003	1.000	0.00031	0.000000000	−0.000072	−0.000197
Model 2	1.002	1.000	−0.00072	0.000000121	0.000020	−0.000137
Model 3	1.002	1.000	−0.00070	0.000000101	0.000011	−0.000143
SHD 231						
Simple regression	0.988	0.999	0.00005	−0.000000081	−0.000158	0.000009
Model 1	0.989	0.999	−0.00009	0.000000000	−0.000119	0.000035
Model 2	0.989	0.999	−0.00003	−0.000000088	−0.000120	0.000033
Model 3	0.989	0.999	−0.00009	−0.000000066	−0.000110	0.000040
Shuttleworthia						
Simple regression	0.998	1.001	0.00020	−0.000000121	−0.000051	0.000011
Model 1	0.998	1.001	0.00026	0.000000000	−0.000046	0.000006
Model 2	0.998	1.001	0.00025	−0.000000146	−0.000046	0.000006
Model 3	0.998	1.001	0.00023	−0.000000139	−0.000043	0.000009
Streptococcus						
Simple regression	0.998	0.999	−0.00010	−0.000000031	−0.000163	−0.000061
Model 1	0.998	0.998	−0.00025	0.000000000	−0.000084	−0.000016
Model 2	0.997	0.998	−0.00044	−0.000000125	−0.000092	−0.000021
Model 3	0.998	0.998	−0.00050	−0.000000103	−0.000081	−0.000015
Tannerella						
Simple regression	1.000	1.000	−0.00003	−0.000000004	0.000013	0.000008
Model 1	1.000	1.000	−0.00007	0.000000000	0.000016	0.000009

(Continues)

TABLE 4 (Continued)

Genus	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
Model 2	1.000	1.000	−0.00005	0.000000004	0.000017	0.000010
Model 3	1.000	1.000	−0.00006	0.000000007	0.000019	0.000010
TG5						
Simple regression	1.000	0.999	−0.00014	−0.000000003	0.000040	0.000019
Model 1	1.000	0.999	−0.00021	0.000000000	0.000035	0.000021
Model 2	1.000	0.999	−0.00023	−0.000000006	0.000036	0.000022
Model 3	1.000	0.999	−0.00025	0.000000002	0.000040	0.000025
Treponema						
Simple regression	0.978	1.001	−0.00084	0.000000037	0.000719	0.000183
Model 1	0.981	1.001	−0.00193	0.000000000	0.000798	0.000180
Model 2	0.981	1.001	−0.00221	−0.000000236	0.000766	0.000168
Model 3	0.982	1.001	−0.00235	−0.000000188	0.000791	0.000183
Veillonella						
Simple regression	0.999	1.006	0.00070	0.000000803	−0.000402	0.000022
Model 1	0.999	1.006	0.00137	0.000000000	−0.000457	−0.000022
Model 2	0.999	1.005	0.00110	0.000000353	−0.000443	−0.000011
Model 3	0.999	1.005	0.00119	0.000000317	−0.000461	−0.000022

Note: Values represent odds ratios for cerebral microbleeds and infarcts, and regression coefficients for all other continuous variables. Values are highlighted in color, if statistically significant. Model structure, colors, and shades as described in Table 2.

TABLE 5 Findings from regression analyses utilizing serum IgG response to 11 bacterial species analyzed using checkerboard immunoblotting as exposures and MRI features as outcomes

Serum IgG levels against	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
P. gingivalis						
Simple regression	1.000	1.000	0.000028	0.00000002	0.0000416	0.00000736
Model 1	1.000	1.000	0.000003	0.00000003	0.0000409	0.00000977
Model 2	1.000	1.000	−0.000002	0.00000003	0.0000419	0.00001040
Model 3	1.000	1.000	−0.000003	0.00000003	0.0000424	0.00001060
P. intermedia						
Simple regression	1.000	1.000	0.000002	0.00000009	0.0000244	0.00000668
Model 1	1.000	1.000	0.000038	0.00000007	0.0000088	0.00000185
Model 2	1.000	1.000	0.000054	0.00000008	0.0000059	−0.00000007
Model 3	1.000	1.000	0.000054	0.00000008	0.0000058	−0.00000011
T. forsythia						
Simple regression	1.000	1.000	−0.000015	0.00000001	−0.0000006	0.00000010
Model 1	1.000	1.000	−0.000012	0.00000000	−0.0000024	−0.00000041
Model 2	1.000	1.000	−0.000011	0.00000000	−0.0000027	−0.00000049
Model 3	1.000	1.000	−0.000012	0.00000000	−0.0000027	−0.00000043

(Continues)

TABLE 5 (Continued)

Serum IgG levels against	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
A. actinomycetemcomitans						
Simple regression	1.000	1.000	−0.000064	0.00000002	0.0000227	−0.00000086
Model 1	1.000	1.000	−0.000050	0.00000001	0.0000152	−0.00000446
Model 2	1.000	1.000	−0.000049	0.00000001	0.0000171	−0.00000394
Model 3	1.000	1.000	−0.000049	0.00000001	0.0000171	−0.00000393
F. nucleatum						
Simple regression	1.001	1.001	0.000077	−0.00000005	−0.0000059	−0.00001540
Model 1	1.001	1.000	0.000100	−0.00000005	−0.0000421	−0.00002030
Model 2	1.001	1.001	0.000134	−0.00000004	−0.0000467	−0.00002140
Model 3	1.001	1.001	0.000134	−0.00000004	−0.0000466	−0.00002140
T. denticola						
Simple regression	1.000	1.000	−0.000158	−0.00000001	0.0000269	0.00000610
Model 1	1.000	1.000	−0.000117	−0.00000001	0.0000128	0.00000035
Model 2	1.000	1.000	−0.000113	−0.00000001	0.0000105	−0.00000072
Model 3	1.000	1.000	−0.000112	−0.00000001	0.0000102	−0.00000090
M. micros						
Simple regression	1.000	1.000	−0.000062	−0.00000001	0.0000027	0.00000015
Model 1	1.000	1.000	−0.000052	0.00000000	−0.0000034	−0.00000107
Model 2	1.000	1.000	−0.000044	0.00000000	−0.0000059	−0.00000244
Model 3	1.000	1.000	−0.000044	0.00000000	−0.0000057	−0.00000235
C. rectus						
Simple regression	1.000	1.000	0.000018	0.00000000	−0.0000250	−0.00000897
Model 1	1.000	1.000	0.000036	0.00000000	−0.0000318	−0.00001150
Model 2	1.000	1.000	0.000042	0.00000000	−0.0000319	−0.00001160
Model 3	1.000	1.000	0.000042	0.00000000	−0.0000317	−0.00001150
E. corrodens						
Simple regression	1.000	1.000	−0.000215	0.00000004	−0.0000157	0.00001780
Model 1	1.000	1.000	−0.000215	0.00000005	−0.0000242	0.00001560
Model 2	1.000	1.000	−0.000235	0.00000005	−0.0000274	0.00001460
Model 3	1.000	1.000	−0.000236	0.00000005	−0.0000273	0.00001470
V. parvula						
Simple regression	1.000	1.000	−0.000039	−0.00000001	0.0000080	0.00000413
Model 1	1.000	1.000	−0.000026	−0.00000001	−0.0000014	0.00000076
Model 2	1.000	1.000	−0.000020	−0.00000001	−0.0000037	−0.00000065
Model 3	1.000	1.000	−0.000020	−0.00000001	−0.0000037	−0.00000071
A. naeslundii						
Simple regression	1.000	1.000	−0.000043	−0.00000002	0.0000138	0.00000710
Model 1	1.000	1.000	−0.000003	−0.00000002	0.0000014	0.00000119
Model 2	1.000	1.000	0.000001	−0.00000003	0.0000003	0.00000029
Model 3	1.000	1.000	0.000002	−0.00000003	0.0000000	0.00000009

Note: Values represent odds ratios for cerebral microbleeds and infarcts, and regression coefficients for all other continuous variables. Values are highlighted in color, if statistically significant. Model structure, colors, and shades as described in Table 2.
Abbreviations: AD, Alzheimer's disease; IgG, immunoglobulin G; MRI, magnetic resonance imaging.

TABLE 6 Findings from regression analyses utilizing infection ratio (the ratio of serum IgG response to each the 11 bacterial species assessed through checkerboard immunoblotting over the mean colonization by the homologous species assessed through checkerboard DNA-DNA hybridization) as exposures and MRI features as outcomes

Infection ratio	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
P. gingivalis						
Simple regression	1.000	0.995	0.0008	0.00000018	0.000272	0.000044
Model 1	0.999	0.995	0.0004	0.00000027	0.000313	0.000089
Model 2	0.999	0.994	0.0003	0.00000026	0.000333	0.000101
Model 3	0.999	0.994	0.0002	0.00000027	0.000336	0.000103
P. intermedia						
Simple regression	0.992	1.003	0.0018	0.00000221	0.000419	0.000193
Model 1	0.993	1.005	0.0026	0.00000204	−0.000004	0.000056
Model 2	0.993	1.005	0.0028	0.00000205	−0.000040	0.000030
Model 3	0.993	1.005	0.0028	0.00000204	−0.000046	0.000026
T. forsythia						
Simple regression	0.997	1.000	−0.0004	0.00000044	0.000120	0.000011
Model 1	0.997	1.000	−0.0004	0.00000038	0.000135	0.000018
Model 2	0.997	1.000	−0.0004	0.00000038	0.000130	0.000016
Model 3	0.997	1.000	−0.0004	0.00000038	0.000132	0.000017
A. actinomycetemcomitans						
Simple regression	1.000	1.000	−0.0002	0.00000008	0.000010	−0.000011
Model 1	1.000	1.000	−0.0001	0.00000003	−0.000040	−0.000033
Model 2	1.000	1.000	−0.0001	0.00000004	−0.000032	−0.000029
Model 3	1.000	1.000	−0.0001	0.00000004	−0.000032	−0.000029
F. nucleatum						
Simple regression	1.058	0.994	0.0145	−0.00000018	−0.004770	−0.000455
Model 1	1.086	0.998	0.0179	0.00000030	−0.009970	−0.001470
Model 2	1.088	1.001	0.0207	0.00000088	−0.010300	−0.001560
Model 3	1.089	1.002	0.0206	0.00000092	−0.010300	−0.001550
T. denticola						
Simple regression	1.002	0.999	−0.0034	−0.00000005	0.000664	0.000194
Model 1	1.000	1.000	−0.0037	0.00000028	0.000803	0.000231
Model 2	1.000	0.999	−0.0041	0.00000030	0.000792	0.000237
Model 3	1.000	0.999	−0.0041	0.00000028	0.000786	0.000233
M. micros						
Simple regression	0.895	0.995	−0.0008	−0.00000028	0.000420	0.000167
Model 1	0.962	0.996	0.0003	−0.00000042	−0.000017	−0.000017
Model 2	0.961	0.997	0.0007	−0.00000039	−0.000102	−0.000069
Model 3	0.960	0.997	0.0007	−0.00000038	−0.000096	−0.000066
C. rectus						
Simple regression	1.000	1.000	0.0000	0.00000004	0.000001	−0.000009
Model 1	1.000	1.000	0.0000	0.00000005	−0.000016	−0.000013
Model 2	1.000	1.000	0.0001	0.00000005	−0.000016	−0.000013
Model 3	1.000	1.000	0.0001	0.00000005	−0.000016	−0.000013

(Continues)

TABLE 6 (Continued)

Infection ratio	Cerebral microbleeds	Infarcts	White matter hyperintensity volume	Hippocampal volume	Entorhinal cortex volume	AD signature
E. corrodens						
Simple regression	1.003	0.998	−0.0005	0.00000046	−0.000470	0.000099
Model 1	1.002	0.998	−0.0005	0.00000036	−0.000472	0.000106
Model 2	1.002	0.998	−0.0005	0.00000036	−0.000469	0.000111
Model 3	1.002	0.998	−0.0005	0.00000036	−0.000470	0.000110
V. parvula						
Simple regression	1.000	0.999	−0.0002	−0.00000005	0.000170	0.000091
Model 1	1.001	1.000	0.0002	−0.00000019	0.000067	0.000038
Model 2	1.001	1.000	0.0004	−0.00000019	0.000040	0.000020
Model 3	1.001	1.000	0.0004	−0.00000018	0.000045	0.000023
A. naeslundii						
Simple regression	0.997	0.999	0.0002	−0.00000014	0.000031	0.000095
Model 1	0.998	0.999	0.0011	−0.00000023	−0.000176	−0.000019
Model 2	0.998	0.999	0.0012	−0.00000023	−0.000193	−0.000031
Model 3	0.998	0.999	0.0013	−0.00000024	−0.000197	−0.000033

Note: Values represent odds ratios for cerebral microbleeds and infarcts, and regression coefficients for all other continuous variables.
Values are highlighted in color, if statistically significant. Model structure, colors, and shades as described in Table 2.
Abbreviations: AD, Alzheimer's disease; IgG, immunoglobulin G; MRI, magnetic resonance imaging.

periodontitis, expressed through a higher percentage of teeth with CAL ≥4 mm, was associated with lower entorhinal cortex volume and cortical thinning in regions implicated in AD. To our knowledge, our study is the first epidemiological study to identify differential associations between microbial and serological features of periodontitis and structural MRI findings related to ADRD, with subgingival bacterial abundance/load by several genera and species found to be either "favorably" or "unfavorably" associated with specific MRI features, as were several measures of host responsiveness to periodontal bacteria.

Several imaging features analyzed in the present study are associated with AD and cognitive impairment[62] and likely reflect a continuum of brain changes associated with cognitive aging as well as ADRD. In this study, the majority (83.9%) were cognitively normal at the time of the oral health assessment, while 16.1% had a diagnosis of MCI or dementia, minimizing the chance of reverse causality (i.e., forgetfulness causing a decline in oral health). Small group sizes precluded sensitivity analyses among those with or without cognitive impairment, or those who had their MRI performed before or after the periodontal examination.

Our findings on the association of tooth counts with brain MRI features related to ADRD are in agreement with the literature reporting lower total brain volume[46,69] or lower regional grey matter volume[70] among participants with severe tooth loss. Our finding linking a larger proportion of teeth with CAL ≥4 mm associated to unfavorable MRI markers aligns with at least two other studies, including one smaller study[45] that showed that radiographic evidence of alveolar bone loss was associated with a higher number of lacunar infarctions, and another larger study which also demonstrated greater burden of white matter hyperintensities.[49] The percentage of teeth with pockets ≥4 mm and CDC/AAP classes are both considered reflective of current, rather than the cumulative, exposure to periodontitis. In our study, neither of these indicators were associated with MRI findings. Notably, in the Atherosclerosis Risk in Communities (ARIC) Study, another diverse US-based cohort, no association was observed between clinically assessed periodontal status and brain volumes or microhemorrhages[47] in a subset of 1,306 study participants. However, WMH were not assessed in that study, and the particular system used to classify periodontitis as well as the lack of an updated dental examination concurrent with neuroimaging may underlie this null finding.

There is a sparsity of data in the literature focusing on the role of microbial features of periodontitis on cognitive outcomes, and a complete lack of studies associating oral microbial/antibody profiles and brain MRI features. Earlier studies have focused on linking features of the oral microbiome with AD-related pathologies in limited samples of post-mortem brain tissues.[71–73] In our study, we were able to examine associations for constituents of the subgingival microbiome as well aspects of host response using several different methodologies: we used checkerboard DNA-DNA hybridizations with respect to a limited number of species in individual subgingival plaque samples (up to four samples per participant), as well as 16S rRNA gene sequencing in a single, pooled sample per person. In these analyses, and to curtail the number of statistical tests to be performed, we opted to analyze the 16S rRNA data at the genus rather than the species level, in order to limit the number of statistical tests to be performed. With respect to host response, we used both the levels of serum IgG to the same 11

bacterial species as the ones included in the checkerboard microbial panel, and also infection ratios for each of these species that better reflect the host responsiveness by accounting for the level of homologous microbial colonization. As can be seen in Tables 3–6, several associations emerged in the fully adjusted models, including (i) those between higher colonization levels by *T. forsythia* and lower entorhinal cortex volume, and between higher colonization by *V. parvula* and *A. naeslundii* and lower WMH volume; (ii) "protective" associations between higher levels of serum IgG to *P. gingivalis* and *P. intermedia* with entorhinal cortex and hippocampal volumes, respectively; and (iii) a "protective" association between *T. forsythia* infection ratio and hippocampal volume. Multiple associations, either protective or unfavorable, were identified between specific genera and individual MRI features in fully adjusted models, pointing to a potential specificity with respect to the nature of the microbial exposure. However, it must be emphasized that these analyses (Tables 3–6) were largely exploratory, rather than hypotheses-driven. Nevertheless, this approach is necessary given that only 58% of periodontal pathogens are cultivable and therefore limits the collective understanding of the potential pathobiological impact of hundreds of these organisms when 16S may identify them individually or as part of models that were adjusted for multiple comparisons. Notably, only the association between higher colonization by *T. forsythia* with lower entorhinal cortex volume and those between higher colonization by *V. parvula* and *A. naeslundii* with lower WMH volume remained statistically significant at a false discovery rate of 0.05. Clearly, the role of infection by specific periodontal taxa in the context of ADRD is complex and requires further investigation, and MRI is just one methodology among many in exploring these relationships. Interestingly, recent studies showed that brief exposures to severe infection and intense inflammation are also associated with accelerated cognitive aging[74] and elevated AD biomarkers.[75]

Strengths of our study include the community-based nature of our sample, the multimodal assessment of periodontal status that included both clinical and microbiological/serological features of periodontitis, an expert assessment of MRI outcomes, and the ability to extensively adjust for established risk factors for ADRD including APOE genotype status. Obvious limitations include a relatively modest sample size and the cross-sectional nature of the analyses that preclude causal inferences. Nevertheless, our findings expand the current knowledge base on the important topic of the role of chronic exposure to infection/inflammation on biomarkers of cognitive aging and ADRD. Further investigation is warranted into the role of poor periodontal health as a contributor to the complex etiology of cognitive aging and AD.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants signed written informed consent statements.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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