Supplemental Material

Yamaguchi S, et al. Associations of dental health with the progression of hippocampal atrophy in community-dwelling individuals: The Ohasama Study

eMethods

Detailed information on the Ohasama study

The Ohasama Study is a prospective cohort study on hypertension and cardiovascular disease that has been conducted for over 30 years in Ohasama, Iwate Prefecture, located in northern Japan. Ohasama is a rural community located 100 km north of Sendai City, the main city in the Tohoku region of Japan. This cohort study is unique in that home blood pressure has been measured since the start of the examinations in1986. Home blood pressure is self-measured within 1 h of waking up each morning after resting for at least 2 min blood pressure measured at a clinic visit. Dental examinations began in 2005 and oral health information was recorded, including the number of teeth and periodontitis status. Ohasama consists of four districts, and from 1995 we examined the participants of one district in turn every year; therefore, data for each participant are collected every 4 years.

MRI preprocessing

The MR images were preprocessed using Statistical Parametric Mapping (SPM12, RRID: SCR_007037) and Computational Anatomy Toolbox for SPM (CAT12, RRID: SCR_019184) in MATLAB R2019b (MATHWORKS Corp., Natick, MA, USA). T1-weighted MR images defined the anterior commissure as the origin and were segmented into gray matter (GM) and white matter using the CAT12 module "Segment Longitudinal Data." Neuromorphometric atlases (http://www.neuromorphometrics.com/) were selected as the atlas for an automated ROI analysis. MRI findings that were outliers in CAT 12 module "Check sample homogeneity" were visually confirmed. Modulated GM images were normalized to the Montreal Neurological Institute-152 standard space with an isotropic voxel resolution of 1.5 mm. Image computation was performed on each individual’s modulated GM map to create symmetric percent change (SPC) images (200 × (follow-up GM map − baseline GM map)/(baseline GM map + follow-up GM map)). The SPC images were smoothed using a Gaussian kernel with a half width of 8 mm.

Methods for longitudinal VBM

Using the multiple regression model, the voxel value of the SPC images was set as the dependent variable, while the product term of NTP and mean PD were set as the independent variables. Age, sex, NTP, and mean PD were used as covariates. To examine the structural changes in the hippocampus, bilateral hippocampal ROI masks created with the WFU_Pickatlas (RRID: SCR_007378) were used. Cluster-level family wise error (FWE) was used for multiple comparison corrections. The initial voxel threshold was set to 0.001 uncorrected, and clusters were considered significant at a cluster-corrected pFWE <0.05.

eTable 1. Results of the simple regression analysis with the annual SPC of the left and right hippocampus as dependent variables

	Annual SPC of the left hippocampus		Annual SPC of the right hippocampus	
	B (95% CI)	*P*	B (95% CI)	*P*
Age	-0.051 (-0.073 to -0.028)	<.001	-0.055 (-0.079 to -0.032)	<.001
Female sex	-0.209 (-0.672 to 0.254)	.374	0.105 (-0.357 to 0.566)	.655
Hypertension	0.037 (-0.301 to 0.375)	.831	0.024 (-0.318 to 0.366)	.889
Diabetes	-0.241 (-0.859 to 0.378)	.443	-0.332 (-1.057 to 0.393)	.367
Hypercholesterolemia	-0.202 (-0.569 to 0.165)	.278	-0.186 (-0.567 to 0.194)	.335
Cerebrovascular/cardiovascular disease	0.658 (-0.405 to 1.721)	.224	0.878 (0.031 to 1.724)	.042
Smoking history	0.137 (-0.163 to 0.438)	.369	-0.021 (-0.311 to 0.269)	.888
Drinking history	0.049 (-0.150 to 0.247)	.629	-0.015 (-0.217 to 0.187)	.883
Duration of education	0.368 (0.017 to 0.719)	.040	0.391 (0.019 to 0.762)	.039
Body mass index	0.046 (0.009 to 0.100)	.104	0.041 (-0.026 to 0.107)	.229
log_hsCRP	0.033 (-0.099 to 0.165)	.621	0.103 (-0.037 to 0.243)	.147
SDS score	0.001 (-0.029 to 0.030)	.963	0.015 (-0.014 to 0.045)	.307
Baseline MMSE score	0.002 (-0.089 to 0.094)	.965	0.064 (-0.035 to 0.162)	.202
NTP	<0.001 (-0.033 to 0.033)	.998	0.001 (-0.033 to 0.034)	.973
Mean PD	0.319 (-0.052 to 0.690)	.091	0.241 (-0.105 to 0.586)	.171

*The dependent variable was the annual SPC of the right or left hippocampus.

Abbreviations: SPC, symmetric percent change; NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SDS, Zung Self-Rating Depression Scale; log_hsCRP, log-transformed high-sensitivity C-reactive protein; B, partial regression coefficient; CI, confidence interval

**P-values* were determined using the simple regression analysis.

eTable 2. Results of the MMSE model

	MMSE model	
	B (95% CI)	*P*-value
Age	-0.014 (-0.027 to -0.002)	.027
Female sex	0.198 (-0.032 to 0.429)	.092
Hypertension	0.073 (-0.101 to 0.248)	.409
Diabetes	0.043 (-0.277 to 0.362)	.793
Hypercholesterolemia	0.030 (-0.126 to 0.187)	.702
Cerebrovascular/cardiovascular disease	-0.189 (-0.535 to 0.156)	.281
Smoking history	0.113 (-0.027 to 0.253)	.114
Drinking history	0.046 (-0.058 to 0.151)	.380
Duration of education	-0.069 (-0.243 to 0.106)	.437
Body mass index	0.004 (-0.022 to 0.031)	.753
log_hsCRP	-0.066 (-0.129 to -0.003)	.040
SDS score	-0.017 (-0.030 to -0.003)	.021
NTP	0.042 (0.007 to 0.077)	.018
Mean PD	0.259 (0.057 to 0.462)	.013
NTP × mean PD	-0.012 (-0.024 to -0.000)	.044

*The dependent variable was the annual change in MMSE.

Abbreviations: NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SDS, Zung Self-Rating Depression Scale; log_hsCRP, log-transformed high-sensitivity C-reactive protein; B, partial regression coefficient; CI, confidence interval

eTable 3. Linear mixed-effects model results predicting left hippocampal volume

	B	SE	df	t Value	*P*-value	95% CI
Time	-30.60	12.73	152.8	-2.404	0.017	-55.54 to -5.66
Age	-22.75	2.86	171.9	-7.949	<0.001	-28.36 to -17.14
Female sex	39.54	59.84	173.5	0.661	0.510	-77.74 to 156.83
Hypertension	-10.80	40.16	173.7	-0.269	0.788	-89.50 to 67.91
Diabetes	-60.52	60.37	174.1	-1.003	0.317	-178.83 to 57.80
Hypercholesterolemia	1.60	35.63	171.9	0.045	0.964	-68.24 to 71.43
Cerebrovascular/cardiovascular disease	-7.06	74.99	168.4	-0.094	0.925	-154.03 to 139.92
Smoking history	-31.93	34.47	172.0	-0.926	0.356	-99.49 to 35.63
Drinking history	-14.51	20.51	172.0	-0.707	0.480	-54.72 to 25.70
Duration of education	11.64	38.40	179.5	0.303	0.762	-63.63 to 86.90
Body mass index	1.72	6.36	172.4	0.270	0.787	-10.75 to 14.18
log_hsCRP	-9.53	14.71	173.1	-0.648	0.518	-38.36 to 19.31
SDS score	-7.06	2.98	174.7	-2.370	0.019	-12.90 to -1.22
Baseline MMSE score	-1.65	5.54	174.1	-0.297	0.767	-12.51 to 9.22
TIV	0.87	0.17	174.6	5.121	<0.001	0.54 to 1.20
NTP	-1.79	2.58	174.8	-0.696	0.487	-6.85 to 3.26
Mean PD	-37.40	29.76	164.6	-1.257	0.211	-95.72 to 20.93
Age × time	-0.97	0.30	152.8	-3.215	0.002	-1.57 to -0.38
Female sex × time	0.21	6.41	152.5	0.033	0.974	-12.36 to 12.78
Hypertension × time	-0.37	4.34	152.4	-0.085	0.932	-8.87 to 8.13
Diabetes × time	0.13	6.30	152.9	0.021	0.983	-12.22 to 12.49
Hypercholesterolemia × time	-2.71	3.71	152.3	-0.730	0.466	-9.99 to 4.57
Cerebrovascular/cardiovascular disease × time	-0.41	7.44	152.4	-0.055	0.956	-14.98 to 14.16
Smoking history × time	2.35	3.67	153.0	0.640	0.523	-4.85 to 9.55
Drinking history × time	-0.11	2.16	152.2	-0.052	0.959	-4.35 to 4.13
Duration of education × time	6.06	4.20	153.6	1.442	0.151	-2.18 to 14.30
Body mass index × time	1.55	0.68	152.3	2.286	0.024	0.22 to 2.87
log_hsCRP × time	-1.43	1.55	153.4	-0.923	0.357	-4.47 to 1.61
SDS score × time	0.13	0.33	153.0	0.397	0.692	-0.51 to 0.77
Baseline MMSE score × time	-1.60	1.37	160.8	-1.169	0.244	-4.29 to 1.08
TIV × time	-0.03	0.02	154.1	-1.819	0.071	-0.07 to 0.00
NTP × time	0.10	0.28	152.4	0.360	0.719	-0.45 to 0.65
Mean PD × time	2.81	2.69	152.2	1.045	0.298	-2.46 to 8.07
NTP × mean PD	2.24	3.26	166.9	0.686	0.494	-4.15 to 8.63
NTP × mean PD × time	-1.41	0.31	152.9	-4.599	<0.001	-2.01 to -0.81

*The dependent variable was the volume of the left hippocampus.

Abbreviations: NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SDS, Zung Self-Rating Depression Scale; log_hsCRP, log-transformed high-sensitivity C-reactive protein; TIV, total intracranial volume; B, partial regression coefficient; SE, standard error; df, degrees of freedom; CI, Confidence Interval

eTable 4. Linear mixed-effects model results for subgroup (lower Mean PD)

	B	SE	df	t Value	*P*-value	95% CI
Time	-32.56	22.16	67.7	-1.469	0.146	-75.99 to 10.87
Age	-21.30	3.62	84.4	-5.882	<0.001	-28.39 to -14.20
Female sex	48.74	80.18	83.4	0.608	0.545	-108.4 to 205.88
Hypertension	-69.72	47.00	85.5	-1.483	0.142	-161.85 to 22.40
Diabetes	-121.38	77.99	84.0	-1.556	0.123	-274.25 to 31.49
Hypercholesterolemia	15.76	44.29	84.1	0.356	0.723	-71.05 to 102.57
Cerebrovascular/cardiovascular disease	8.27	103.49	81.7	0.080	0.937	-194.56 to 211.11
Smoking history	19.57	46.54	85.9	0.420	0.675	-71.66 to 110.79
Drinking history	-18.94	26.79	84.4	-0.707	0.481	-71.44 to 33.56
Duration of education	-58.21	47.08	92.5	-1.236	0.219	-150.49 to 34.06
Body mass index	13.26	7.70	85.2	1.722	0.089	-1.83 to 28.36
log_hsCRP	-40.14	17.99	86.8	-2.231	0.028	-75.40 to -4.88
SDS score	-8.02	3.64	85.4	-2.204	0.030	-15.16 to -0.89
Baseline MMSE score	2.13	9.16	83.8	0.232	0.817	-15.84 to 20.09
TIV	0.59	0.23	85.4	2.563	0.012	0.14 to 1.04
NTP	-1.22	3.41	86.8	-0.357	0.722	-7.90 to 5.47
Age × time	-0.84	0.50	68.2	-1.665	0.100	-1.82 to 0.15
Female sex × time	0.85	10.75	67.7	0.079	0.937	-20.22 to 21.92
Hypertension × time	-4.82	6.59	68.0	-0.730	0.468	-17.74 to 8.11
Diabetes × time	8.48	10.48	67.6	0.810	0.421	-12.05 to 29.02
Hypercholesterolemia × time	-5.30	6.00	67.7	-0.883	0.380	-17.07 to 6.47
Cerebrovascular/cardiovascular disease × time	4.18	13.60	67.8	0.307	0.760	-22.49 to 30.84
Smoking history × time	2.11	6.45	68.9	0.327	0.745	-10.53 to 14.74
Drinking history × time	4.70	3.67	67.6	1.282	0.204	-2.49 to 11.89
Duration of education × time	3.53	6.92	68.9	0.510	0.612	-10.04 to 17.10
Body mass index × time	0.35	1.06	68.3	0.331	0.742	-1.73 to 2.43
log_hsCRP × time	0.26	2.51	69.7	0.105	0.917	-4.66 to 5.19
SDS score × time	-0.11	0.52	68.6	-0.202	0.841	-1.13 to 0.92
Baseline MMSE score × time	-1.56	2.31	74.8	-0.676	0.501	-6.09 to 2.96
TIV × time	-0.07	0.03	70.0	-2.080	0.041	-0.13 to 0.00
NTP × time	0.61	0.48	68.0	1.262	0.211	-0.34 to 1.56

*The dependent variable was the volume of the left hippocampus.

Abbreviations: NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SDS, Zung Self-Rating Depression Scale; log_hsCRP, log-transformed high-sensitivity C-reactive protein; TIV, total intracranial volum; B, partial regression coefficient; SE, standard error; df, degrees of freedom; CI, confidence interval

eTable 5. Linear mixed-effects model results for subgroup (higher Mean PD)

	B	SE	df	t Value	*P*-value	95% CI
Time	-28.50	19.16	69.7	-1.488	0.141	-66.05 to 9.05
Age	-20.99	4.70	77.0	-4.464	<0.001	-30.20 to -11.77
Female sex	9.57	93.96	78.9	0.102	0.919	-174.59 to 193.73
Hypertension	33.27	70.07	77.2	0.475	0.636	-104.07 to 170.61
Diabetes	-84.94	99.94	77.8	-0.850	0.398	-280.82 to 110.93
Hypercholesterolemia	-21.09	59.40	77.0	-0.355	0.724	-137.51 to 95.33
Cerebrovascular/cardiovascular disease	-119.80	110.63	75.2	-1.083	0.282	-336.64 to 97.04
Smoking history	-58.46	56.21	77.4	-1.040	0.302	-168.63 to 51.72
Drinking history	-6.47	32.05	77.0	-0.202	0.841	-69.29 to 56.35
Duration of education	62.98	65.20	79.0	0.966	0.337	-64.82 to 190.77
Body mass index	-7.68	10.49	77.7	-0.732	0.466	-28.24 to 12.87
log_hsCRP	14.15	25.54	77.3	0.554	0.581	-35.90 to 64.21
SDS score	-7.41	5.28	78.0	-1.405	0.164	-17.76 to 2.93
Baseline MMSE score	1.18	8.33	77.4	0.142	0.888	-15.14 to 17.50
TIV	1.01	0.28	78.4	3.668	<0.001	0.47 to 1.56
NTP	0.78	3.99	77.1	0.196	0.845	-7.04 to 8.60
Age × time	-1.23	0.47	69.7	-2.624	0.011	-2.14 to -0.31
Female sex × time	-1.90	9.87	69.7	-0.192	0.848	-21.24 to 17.45
Hypertension × time	2.65	6.92	69.3	0.383	0.703	-10.92 to 16.22
Diabetes × time	-2.62	9.71	69.9	-0.270	0.788	-21.65 to 16.41
Hypercholesterolemia × time	-1.67	5.73	69.5	-0.292	0.771	-12.90 to 9.55
Cerebrovascular/cardiovascular disease × time	21.24	10.02	69.5	2.121	0.037	1.61 to 40.87
Smoking history × time	3.85	5.66	69.4	0.679	0.499	-7.25 to 14.95
Drinking history × time	-1.37	3.19	69.5	-0.429	0.669	-7.62 to 4.88
Duration of education × time	12.12	6.50	69.8	1.864	0.067	-0.63 to 24.87
Body mass index × time	2.05	1.05	69.4	1.941	0.056	-0.02 to 4.11
log_hsCRP × time	-3.16	2.50	69.6	-1.262	0.211	-8.07 to 1.75
SDS score × time	0.17	0.53	69.7	0.316	0.753	-0.87 to 1.20
Baseline MMSE score × time	-1.97	2.08	72.5	-0.946	0.347	-6.05 to 2.11
TIV × time	-0.01	0.03	69.5	-0.480	0.633	-0.07 to 0.04
NTP × time	-0.86	0.39	69.3	-2.201	0.031	-1.62 to -0.09

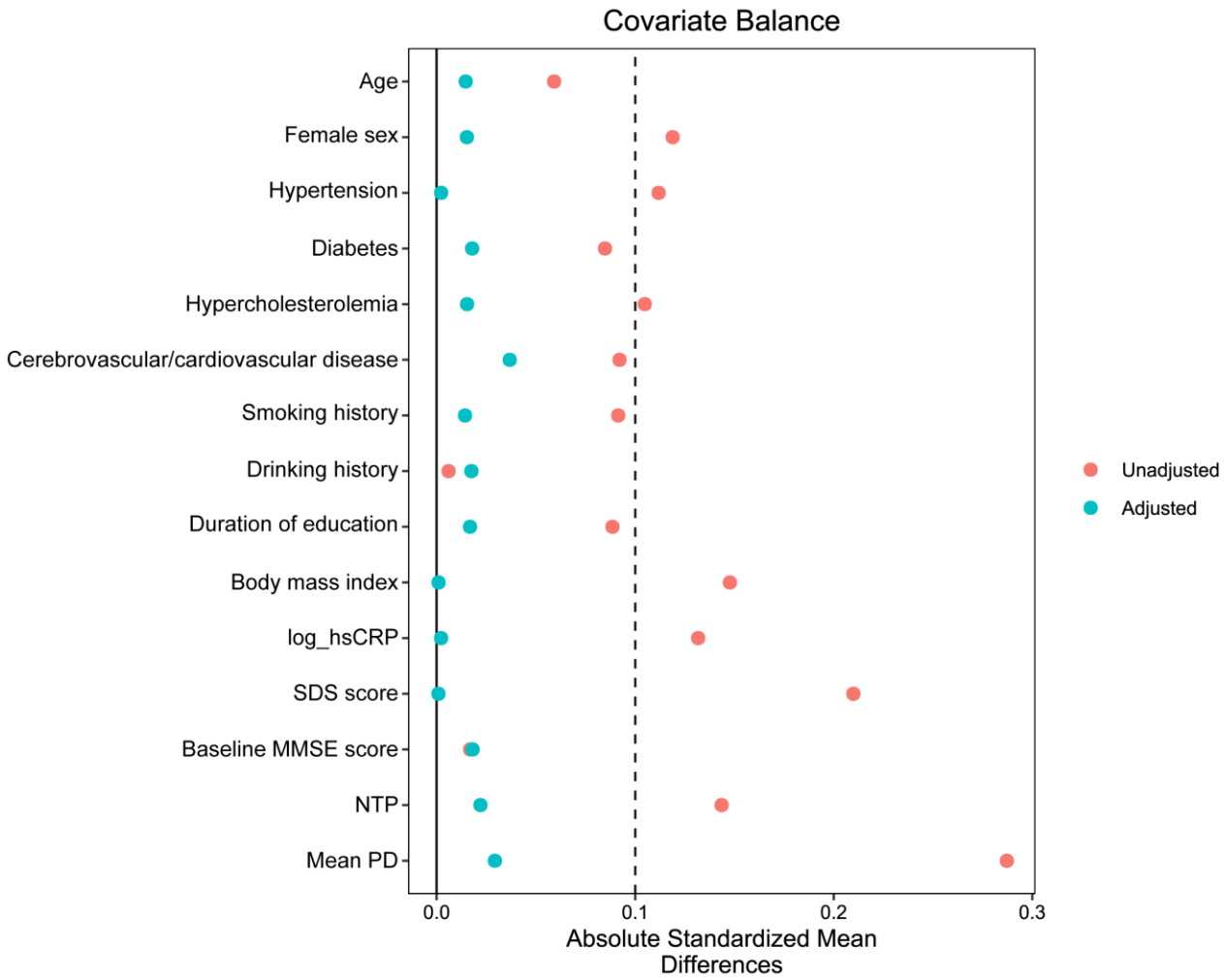
*The dependent variable was the volume of the left hippocampus.

Abbreviations: NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SDS, Zung Self-Rating Depression Scale; log_hsCRP, log-transformed high-sensitivity C-reactive protein; TIV, total intracranial volume; B, partial regression coefficient; SE, standard error; df, degrees of freedom; CI, confidence interval

eTable 6. Results of the longitudinal VBM in the hippocampus

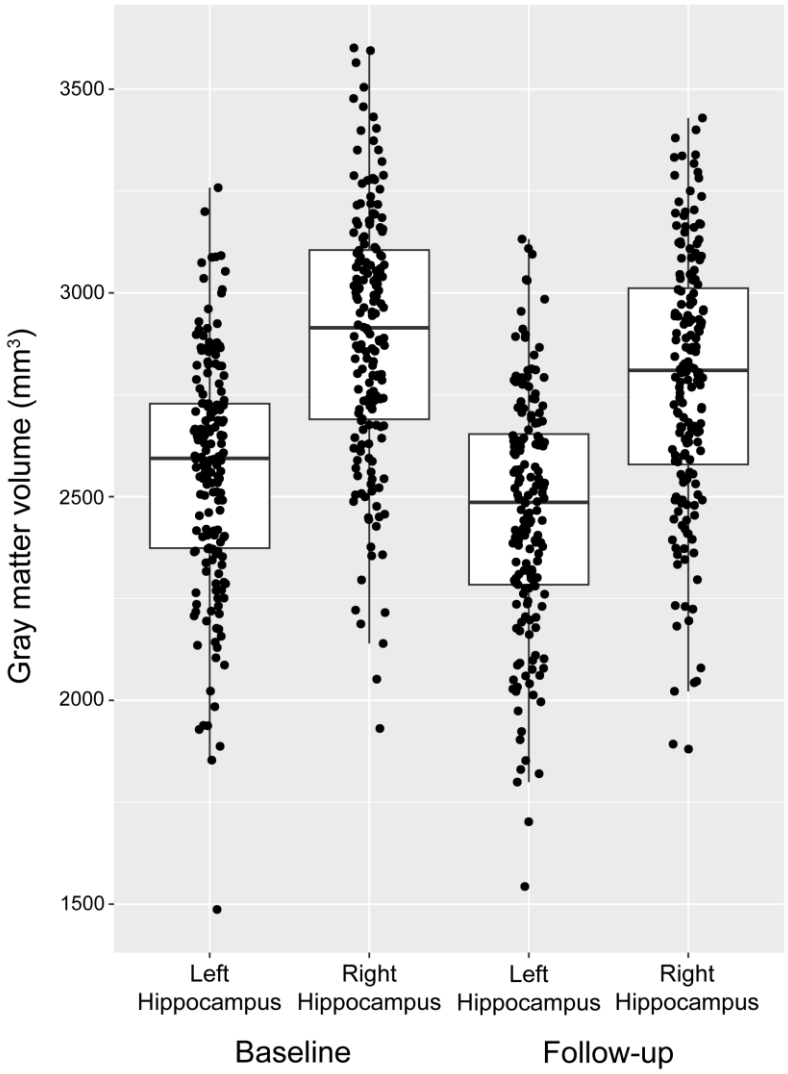
Cluster-level		Voxel-level		MNI coordinates			Brain region (AAL)
p FWE	Cluster size	p uncorrected	T	x	y	z	
0.035	92	<0.001	3.68	-30	-20	-17	Left hippocampus
0.123	18	<0.001	3.21	35	-11	-14	Right hippocampus

Abbreviations: MNI, Montreal Neurological Institute; FWE, family-wise error; VBM, voxel-based morphometry; AAL, Automated anatomical labelling atlas.

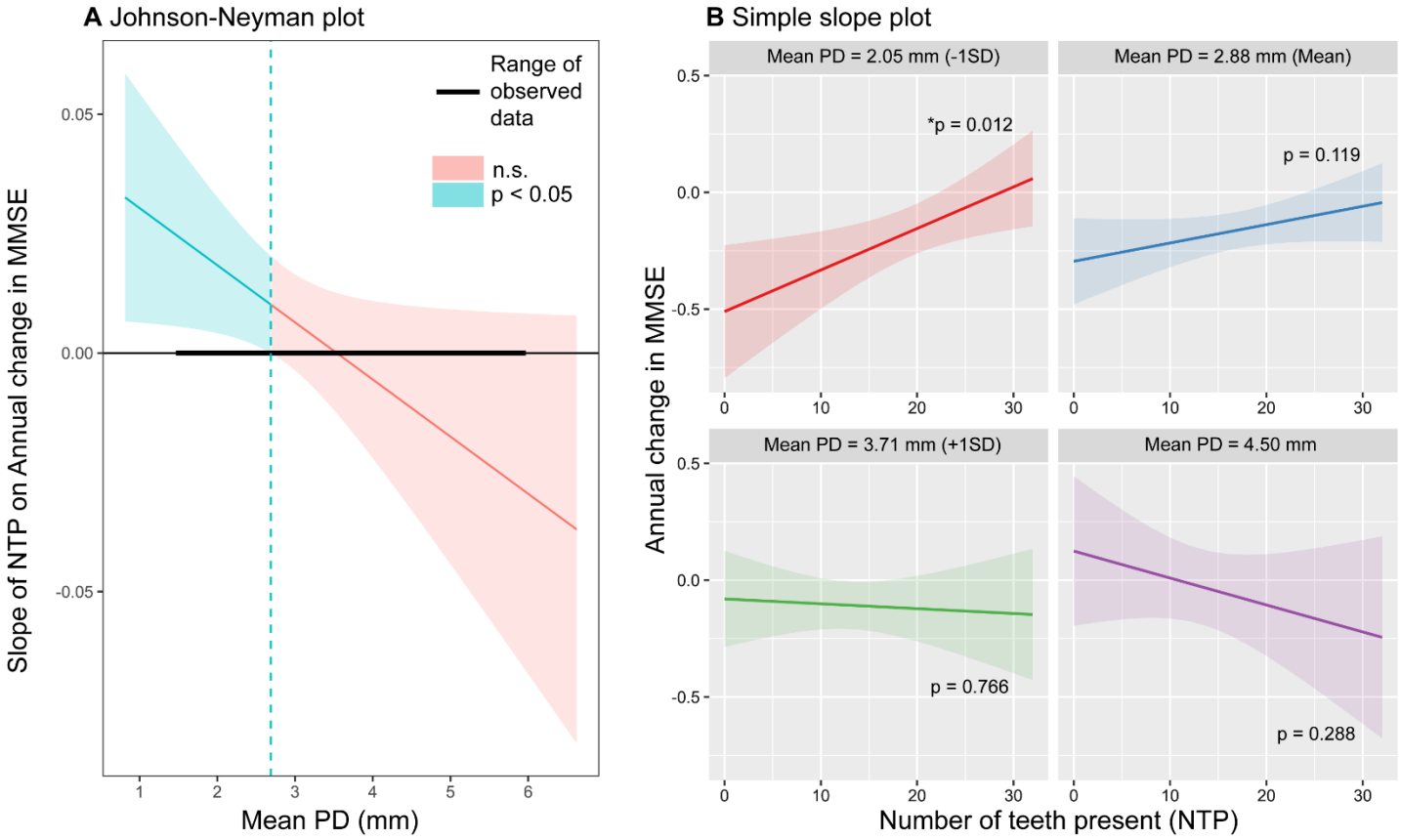


eFigure 1. Covariate balance of the follow-up and no follow-up groups before (unadjusted) and after (adjusted) inverse probability weighting

Abbreviations: NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SDS, Zung Self-Rating Depression Scale; log_hsCRP, log-transformed high-sensitivity C-reactive protein.



eFigure 2. Box-and-whisker plot of the ROI-based hippocampal volumes



eFigure 3. Interaction between the number of teeth present and the mean PD for annual change in MMSE scores

A, The Johnson to Neyman plot indicates the size and significance of the slope of number of teeth present on annual symmetric percentage change of the left hippocampus throughout all observed levels of the mean PD. The shaded regions indicate 95% confidence intervals. **B**, Simple slope plot of the interaction between number of teeth present and mean PD on annual change in MMSE for four levels (-1 SD, mean, +1 SD, and 4.5 mm) of the mean PD is shown. *Significant partial regression coefficient (*P*<.05). Abbreviations: NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SD, standard deviation.