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The association between self-reported tooth loss and cognitive function in the REasons for Geographic And Racial Differences in Stroke study:

An assessment of potential pathways

Dr. Jonathan C. Matthews, DMD, MSPH,
Postdoctoral trainee, Institute of Oral Health Research, School of Dentistry, University of Alabama at Birmingham, when this article was written. He now is in private practice in Birmingham, Ala

Dr. Zhiying You, MD, PhD,
Assistant professor, Division of Preventive Medicine, Department of Medicine, University of Alabama at Birmingham

Dr. Virginia G. Wadley, PhD,
Associate professor, Department of Medicine, Division of Gerontology, Geriatrics, and Palliative Care, University of Alabama at Birmingham

Dr. Mary Cushman, MD, MSc, and
Professor of medicine, University of Vermont—Burlington, Vt

Dr. George Howard, DrPH
Chair and a professor, Department of Biostatistics, School of Public Health, University of Alabama at Birmingham

Abstract

Background—Several mechanisms may associate tooth loss and related oral inflammation with cognitive impairment. The authors studied the relationship between tooth loss and cognitive function.

Methods—The REasons for Geographic And Racial Differences in Stroke study is a national longitudinal study of more than 30,000 African American and white adults 45 years or older. Data for tooth loss, cognitive function and potential confounding variables were available for 9,853 participants at the time of analysis. The authors used incremental linear regression modeling to investigate the cross-sectional association between self-reported tooth loss and cognitive function.

Results—In unadjusted analysis (mean learning followed by recall; α level of significance of .05), the loss of six to 16 teeth and the loss of more than 16 teeth were associated with poorer cognitive function compared with the loss of no teeth. Attenuated associations persisted after the authors adjusted for demographic and systemic risk factors. The full model, which was adjusted for socioeconomic status (SES), revealed no association between tooth loss and cognitive function.

Conclusion—Tooth loss may be associated with cognitive function; however, this association is mediated by age and SES.

Address reprint requests to: Dr. Matthews at 1823 Cahaba Forest Cove, Birmingham, Ala. 35242, “ dravis@uab.edu”.

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Clinical Implications—Tooth loss due to periodontal disease may be a marker for low SES, and the interplay of these factors with advanced age may confer risk of having poorer cognitive function. Further studies are needed to clarify these associations.

Keywords

Cognitive function; tooth loss

Investigators in some studies have hypothesized or demonstrated an association between cognitive impairment and poor oral health, with higher levels of cognitive impairment in populations with worse oral health.[1–11] The investigators have suggested that cognitive impairment causes poor oral health, possibly owing to a lack of interest in or forgetting about oral hygiene. Results from a prospective study demonstrated an increased risk of experiencing cognitive decline with increased tooth loss, caries incidence and periodontal disease progression.[12] However, this relationship has been inconsistent across studies.[13–15] Poor oral health is associated with many diseases such as diabetes, cardiovascular disease, stroke and Alzheimer disease.[9] Tooth loss and associated factors due to periodontitis might be associated with cognitive impairment through at least three other potential, but not equally plausible, pathways.

The oral cavity is colonized by numerous species of bacteria. Evidence suggests that bacterial products[16] or whole bacteria can colonize the brain directly via the bloodstream[17] or the trigeminal nerve[18] and cause cognitive impairment.[18–22] The results of some studies refute these ideas.[23–27]

The primary culprits in the pathogenesis of periodontitis are gram-negative oral bacteria.[9] Their presence can stimulate the localized production of inflammatory cytokines[28–35] and systemic production of C-reactive protein (CRP),[33,34,36] all of which may injure and impair the brain directly.[37,38] Conversely, this disease process may be a local phenomenon in the brain.

Ischemic stroke and cerebrovascular health are risk factors for dementia[39] and cognitive impairment because they diminish short-term memory.[40] Severe periodontitis, edentulism and partial edentulism have been associated with increased risk of ischemic stroke.[41–45]

Memory and learning impairment are aspects of declining cognitive function.[9] We studied the association between tooth loss and cognitive function as measured by means of the word list learning (WLL) assessment in a cross-sectional analysis of data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. We hypothesized that people with more teeth would have better cognitive function and that this association would persist with incremental linear regression modeling, after adjusting for demographics. We also theorized that covariate adjustment for risk factors would mediate this association.

PARTICIPANTS, MATERIALS AND METHODS

The REGARDS study is a national longitudinal study of African American and white adults 45 years or older that has the primary objective of determining the causes for excess stroke mortality among blacks and residents of the “Stroke Belt.” The Stroke Belt is defined as the following eight states with high stroke mortality: Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina and Tennessee.[46] Study enrollment ended in 2007, and the follow-up is ongoing.

Participants

From 2003 through 2007, we used commercially available lists of U.S. residents to select participants randomly, and we recruited them by mail and telephone. The resulting cohort consisted of 30,239 people of whom 42 percent were black and 58 percent were white. Fifty-six percent of the participants lived in the Stroke Belt and 44 percent lived in the remaining 40 contiguous states (non–Stroke Belt states) and the District of Columbia. People who lived in Alaska and Hawaii were not included because these states were "disconnected" from the contiguous states for which geographic patterns initially were described, and the number of blacks living in those states was so small that recruitment would have been a challenge. Staff members of the Survey Research Unit of the University of Alabama at Birmingham conducted a computer-assisted telephone interview to collect demographic data, administer medical history questionnaires and complete cognitive screenings. They obtained written informed consent from the participants during an in-home visit during which they collected blood and urine samples and obtained electrocardiographic, blood pressure and body mass index (BMI) measures. We contact participants by telephone every six months to monitor for stroke and coronary events, annually for cognitive screening status and biennially for a more extensive cognitive assessment. The institutional review boards of all participating institutions approved the REGARDS study.

We introduced the cognitive assessment outcome used in this study to the follow-up telephone calls made in February 2006. As of June 2008, data for 12,661 participants were available for analysis. We excluded participants if they did not have values for income, CRP, tooth loss, hyperlipidemia, BMI, depressive symptoms, diabetes, hypertension, smoking or education (these variables are defined below). A total of 2,808 (22.2 percent) participants were missing one or more of these values (primarily income), which left 9,853 participants for the final analyses.

Outcome measure (cognitive function—learning and recall)

The WLL assessment from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery[47] involves a standardized protocol of presentation, learning and recall to obtain scores for two primary domains: sum learning (attention and learning) and delay recall (memory). We administered the WLL assessment via telephone by playing a recording of the standardized CERAD instructions and the list of 10 words presented in the standardized CERAD order, which differs across the three learning trials (the three opportunities for participants to hear and repeat back the 10 words). To avoid problems that could be introduced by variations in regional accents, a professional orator recorded the instructions and word list presentations. As we assessed all of the participants in our study by telephone, we were not able to show participants the word lists. We instructed the participants at the beginning of each trial not to write anything down.

For each of the three learning trials, we asked the participants to repeat as many of the 10 words as possible. We calculated the sum learning score by totaling the number of correctly recalled responses across the three trials; the scores ranged from zero to 30. After an interval of approximately five minutes, during which we asked noncognitive interview questions, we obtained the delay recall score by asking the participant to recall as many of the 10 words as possible; the scores ranged from zero to 10. Finally, we calculated a mean learning score by averaging the scores for the three learning trials; the scores ranged from zero to 10. This mean learning score retained the properties of the sum learning score and had identical associations with both tooth loss and confounding factors. We calculated the mean learning score to facilitate comparisons to the delay recall score, which has the same range.

Primary exposure variable (tooth loss)

We asked the participants the following questions to assess tooth loss: "Have you lost any of your teeth owing to gum disease?" and "How many teeth have you lost owing to gum disease?" Although neither question has been validated, responses to the following questions have shown high specificity when compared with a radiographic verification of periodontal disease in a German study: "Have you ever had a tooth extracted due to bone loss?" and "Have you ever had a tooth extracted because it was loose?"[48] We think that both of our survey questions encompass these two domains of periodontal disease. We related our latter survey question to systemic inflammation in another REGARDS analysis.[49] We included third molars reported as lost owing to periodontal disease. We categorized the answers as none, one to five, six to 16 and more than 16 teeth lost.

Potential confounding factors

Demographics—We categorized self-reported residence as the Stroke Belt or non–Stroke Belt states. We categorized self-reported race as black or white and self-reported sex as male or female. We calculated age from date of birth and coded it into one of five categories: 45 to 54, 55 to 64, 65 to 74, 75 to 84 and 85 years or older.

Risk factors—We calculated BMI as kilograms per square meter and categorized it as normal (18.5–24.9), underweight (< 18.5), overweight (25–29.9) or obese (> 30). We took the logarithm of CRP (logCRP) to normalize the distribution of data points and analyzed it as a continuous variable, logCRP. We defined having diabetes as a participant's having a fasting glucose level of more than 126 milligrams per deciliter, a nonfasting glucose level of more than 200 mg/dL, or taking medicine or insulin for diabetes. We defined having hypertension as a participant's having systolic blood pressure of 140 millimeters of mercury or greater, diastolic blood pressure of 90 mm Hg or greater or self-reported hypertension confirmed by means of medication use. We defined having hyperlipidemia as a participant's having a total cholesterol level of 240 mg/dL or greater, a low-density lipoprotein cholesterol level of 160 mg/dL or greater, a high-density lipoprotein cholesterol level of 40 mg/dL or lower, or current use of lipid-lowering medication. We categorized smoking status as never, past smoker and current smoker.

Depressive symptoms—We used the four-item version of the Center for Epidemiological Studies-Depression scale to evaluate depressive symptoms. Scores range from zero to 12; a score of four or greater indicates an elevated level of psychological distress.[50]

Socioeconomic status (SES)—We categorized income as less than $20,000, $20,000 to $34,999, $35,000 to $74,999 and $75,000 or higher per year. We categorized education as no high school diploma, high school diploma or general equivalency diploma, some college but no degree, and college degree or higher.

Statistical analysis

We assessed the associations between the exposure variable (tooth loss) and outcomes (mean WLL and delay recall scores) in incremental series of linear regression models by first examining the univariate or unadjusted association and then adjusting for risk factors in steps to see if the association might have been due to other factors. This approach has been called a "mediation analysis" and has been championed by Mackinnon and colleagues.[51] Mediation analysis approaches focus on the change in the magnitude of the coefficient associated with tooth loss on the addition of these demographic or risk factors to the model. If the demographic or risk factors are responsible for the observed univariate relationship,

then the magnitude of the coefficient for tooth loss will be attenuated completely to 1.0 with the addition of these mediating factors. Given the strong association between SES and tooth loss,[49] we thought that SES would represent the greatest potential for confounding, so we added it last. We used the Student-Newman-Keuls multiple range test in a univariate analysis of the following variables: logCRP, Center for Epidemiological Studies-Depression scale score, mean learning score and delay recall score. We performed post hoc analyses to assess potential age-by-tooth-loss and smoking-by-tooth-loss interactions. We performed all analyses with software (SAS for Windows, Version 9.1) by using two-tailed *P* values and an α level of significance of .05.

RESULTS

Among the 9,853 participants, 8,546 participants (86.7 percent) reported having lost no teeth, 424 (4.3 percent) reported having lost one to five teeth, 314 (3.2 percent) reported having lost six to 16 teeth, and 569 (5.8 percent) reported having lost more than 16 teeth owing to periodontal disease. Table 1 shows the distribution of teeth lost according to the participants' characteristics. We noted significant differences for all variables except for region.

Results for incremental linear regression modeling for the mean learning and delay recall outcome variables were similar and are presented in Table 2 and Table 3 (pages 386 and 387), respectively. Regression coefficients represent the association of each risk factor with a one-item (word) higher score from the recall list. The results of our unadjusted analysis showed that higher tooth loss was associated with poorer cognitive function. Participants who reported that they had lost six to 16 teeth (β = −0.26; 95 percent confidence interval [CI], −0.45 to −0.08; $P = .005$) and more than 16 teeth (β = −0.52; 95 percent CI, −0.65 to −0.38; $P < .001$) performed significantly worse than did participants who reported that they had lost no teeth (reference group), whereas those who reported that they had lost one to five teeth were not significantly different from the reference group in terms of mean learning score. Results for delay recall were similar to those for mean learning. These associations were attenuated after we adjusted for demographic factors, but significantly lower cognitive scores remained for those who reported that they had lost six or more teeth.

After we adjusted for BMI, we found further attenuation of the association between tooth loss and mean learning score for participants who reported that they had lost six or more teeth and between tooth loss and delay recall score for participants who reported that they had lost more than 16 teeth. However, adjustment for BMI revealed no attenuation of the association between tooth loss and mean learning score (before adjusting for BMI: β = −0.17; 95 percent CI, −0.34 to 0.00; $P = .048$; after adjusting for BMI: β = −0.17; 95 percent CI, −0.34 to 0.00; $P = .044$) for the participants who reported that they had lost six to 16 teeth. Only among participants who reported that they had lost more than 16 teeth did we note significant associations between tooth loss and mean learning scores (β = −0.25; 95 percent CI, −0.38 to −0.12; $P = .001$) and delay recall scores (β = −0.27; 95 percent CI, −0.44 to −0.10; $P = .002$) after adjusting for logCRP.

After we adjusted for risk factors and depressive symptoms, we found that the association was further attenuated, with those who reported that they had lost more than 16 teeth remaining significantly different from the reference group for both cognitive measures (mean learning and delayed recall). In the final model, which included adjustments for income and education (SES variables), the association between tooth loss and cognitive function was extinguished (mean learning score: one to five teeth lost [β = 0.07; 95 percent CI, −0.06 to 0.21; $P = .30$]; six to 16 teeth lost [β = −0.03; 95 percent CI, −0.19 to 0.13; $P = .69$]; more than 16 teeth lost [β = −0.01; 95 percent CI, −0.13 to 0.12; $P = .91$]; delay recall

score: one to five teeth lost [β = 0.08; 95 percent CI, −0.11 to 0.27; *P* = .40]; six to 16 teeth lost [β = −0.06; 95 percent CI, −0.28 to 0.15; *P* = .57]; more than 16 teeth lost [β = −0.01; 95 percent CI, −0.17 to 0.16; *P* = .92]). We ran separate models, which included participants who were missing income data (n = 12,661). The results were similar to those from the original models (data not shown).

After we adjusted for demographics, we found approximately 46 percent and 48 percent reductions in regression coefficients for mean learning and delay recall scores, respectively, for the group of participants who reported that they had lost more than 16 teeth. We determined that the group of participants 65 years or older was largely responsible for this attenuation of the association. Therefore, we evaluated the interaction of age and tooth loss in relation to cognitive function. The interaction term was significant (mean learning score [β = 0.06; 95 percent CI, 0.01 to 0.10; *P* = .015]; delayed recall score [β = 0.07; 95 percent CI, 0.01 to 0.13; *P* = .022]) after we adjusted for demographics, BMI and logCRP, with people older than 54 years displaying a higher likelihood of poor cognitive function with tooth loss than did people aged 45 to 54 years. However, this finding became nonsignificant after we adjusted for risk factors, and it remained so after we adjusted for SES (data not shown). The results of our smoking-by-tooth-loss interaction analysis were similar; current smokers had a significantly higher likelihood of poor cognitive function with tooth loss after we adjusted for systemic risk factors than did those who never smoked. This association, however, became nonsignificant after we adjusted for depressive symptoms and for SES (data not shown).

DISCUSSION

The main finding of our study was that tooth loss due to periodontitis was not associated independently with lower scores for learning and recall in our full regression models. We accounted for the associations seen in earlier models by adjusting for other risk factors, mainly age and SES.

Interpreting the attenuating effect of SES can be complex, because SES might be associated with tooth loss and cognitive function via multiple pathways. In our study, we were unable to address whether tooth loss is a mechanism whereby SES relates to cognitive function. Tooth loss may be a surrogate marker for SES. Thus, the strong association between tooth loss and SES shown in Table 1 may make it impossible to assess their independent roles. For example, only 1.2 percent of participants with an annual family income of $75,000 or higher had lost 16 or more teeth compared with 11.7 percent of participants with an annual family income less than $20,000. The association of tooth loss and education was nearly as strong. This association of tooth loss and SES might make the interpretation of the association between the exposure and outcome variables problematic. Therefore, we do not suggest that tooth loss due to periodontal disease is an independent risk factor for cognitive impairment. Furthermore, nondental factors associated with SES may affect cognition. In this scenario SES would be a classic confounding factor in the relationship between tooth loss and cognitive function and thereby introduce an apparent association when there is none. Alternatively, tooth loss may be in the direct pathway of action between SES and cognitive function and may be one of the mechanisms through which lower SES is associated with lower cognitive function. Therefore, one should interpret the complete mediation of the effect of tooth loss with the addition of SES measures with caution.

We observed little confounding of the association of tooth loss and cognitive function owing to CRP concentration. This finding suggests that inflammation associated with tooth loss was not a mediator of lower cognitive function among those who had lost teeth in our study.

The limitations of our study were inherent in its cross-sectional design, which made determinations of directionality impossible, and in the self-reported tooth loss data, which could have resulted in low reliability. The cross-sectional design is relevant to the potential effect of CRP as a mediator. Although the progression of periodontitis is time dependent,[52] the severity of the disease may not be age dependent.[53–59] For example, a 25-year-old and a 65-year-old could have periodontitis of the same severity. Although the lack of significant age-by-tooth-loss and smoking-by-tooth-loss interactions in the full models in our study was consistent with findings from other studies,[11] this information was inconclusive because our results cannot be used to rule out smoking as a cause of tooth loss or clearly determine the relationship between age and tooth loss. It is, however, reasonable to hypothesize that the severity of periodontitis will be affected by the number of teeth remaining, as well as other factors such as hygiene and professional care. As teeth are lost and their sockets heal, these areas of the oral cavity theoretically no longer contribute to periodontitis and should lead to a reduction in oral inflammation. The design of our study cannot account for these likely changes in CRP concentrations and their potential effects on cognitive function across time.

The specificity and sensitivity of the survey items used to measure tooth loss may have added to measurement uncertainty. We cannot guarantee that all of the tooth loss we analyzed was due to periodontitis and not caries, trauma or elective extraction. Dietrich and colleagues[48] determined that some self-reported periodontitis items had low sensitivity and positive predictive value, although many of them had more than 90 percent specificity. This finding may be a bigger issue because some participants in our study may have had mild cognitive impairment when they were surveyed about tooth loss despite efforts to exclude them from the study. Blicher and colleagues,[60] however, suggested that self-reported measures of periodontitis show “good potential.”

Stein and colleagues[61] assessed periodontitis by measuring alveolar bone loss on dental radiographs. Although they found an association between a low number of remaining teeth and an increased risk of developing dementia, they failed to find a significant association between periodontitis, measured by means of radiographic evidence of alveolar bone loss, and dementia, measured by means of cognitive assessment. We recommend that more robust measures of periodontitis—such as levels of antibodies against periodontal pathogens, periodontal probing depths, attachment levels and standardized radiographs—be used to explore this potential relationship further.

A longitudinal study design with methods that Watts and colleagues[62] suggested may help elucidate the elements directly in the causal pathway. Investigators in future studies must consider age and SES carefully as potential confounding factors and incorporate the proper measurement of the proper variables into the design. Finding a measure of oral inflammation related to tooth loss that is independent of SES would be ideal given the complex role SES seems to play in the potential association. Although our assessment of possible effect modification and interaction was not hypothesis driven, we recommend incorporating these covariate assessments into the a priori analysis plan as Hyman[63] suggested.

CONCLUSIONS

In this analysis, the association of tooth loss and cognitive function as assessed by means of WLL was mediated largely by SES, by age of 65 years or older and to a lesser degree by other risk factors, including CRP as an inflammation marker. Therefore, we do not reject the null hypothesis that there is no association between tooth loss and cognitive function. We are considering future analyses.

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ABBREVIATION KEY

BMI	Body mass index
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CES-D	Center for Epidemiological Studies-Depression
CRP	C-reactive protein
DF	Demographic factors
logCRP	Logarithm of CRP
REGARDS	REasons for Geographic And Racial Differences in Stroke
RF	Risk factors
SES	Socioeconomic status
WLL	Word list learning

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TABLE 1

Participant characteristics, according to number of teeth lost.

CHARACTERISTIC	NUMBER OF TEETH LOST*				*P* VALUE†
	0	1–5	6–16	> 16	
Total (No. [%])	8,546 (86.7)	424 (4.3)	314 (3.2)	569 (5.8)	
Region					.212
Non–Stroke Belt	3,932 (86.6)	208 (4.6)	153 (3.4)	245 (5.4)	
Stroke Belt	4,614 (86.8)	216 (4.1)	161 (3.0)	324 (6.1)	
Race (No. [%])					< .001
White	5,603 (89.9)	228 (3.7)	134 (2.2)	266 (4.3)	
Black	2,943 (81.3)	196 (5.4)	180 (5.0)	303 (8.4)	
Sex (No. [%])					< .001
Male	4,046 (88.1)	192 (4.2)	135 (2.9)	219 (4.8)	
Female	4,500 (85.5)	232 (4.4)	179 (3.4)	350 (6.7)	
Age (Years) (No. [%])					< .001
45–54	867 (90.9)	41 (4.3)	28 (2.9)	18 (1.9)	
55–64	3,654 (87.4)	194 (4.6)	141 (3.4)	192 (4.6)	
65–74	2,830 (85.4)	124 (3.7)	108 (3.3)	250 (7.5)	
75–84	1,092 (85.0)	63 (4.9)	34 (2.6)	95 (7.4)	
85 or older	103 (84.4)	2 (1.6)	3 (2.5)	14 (11.5)	
BMI‡ (No. [%])					.024
Normal	2,041 (88.9)	87 (3.8)	62 (2.7)	107 (4.7)	
Underweight	75 (84.3)	5 (5.6)	2 (2.2)	7 (7.9)	
Overweight	3,238 (86.7)	167 (4.5)	126 (3.4)	203 (5.4)	
Obese	3,192 (85.5)	165 (4.4)	124 (3.3)	252 (6.8)	
Income ($) (No. [%])					< .001
< 20,000	1,402 (79.3)	77 (4.4)	82 (4.6)	207 (11.7)	
20,000–34,999	2,282 (84.9)	113 (4.2)	96 (3.6)	197 (7.3)	

CHARACTERISTIC	NUMBER OF TEETH LOST*				*P* VALUE†
	0	1–5	6–16	> 16	
35,000–74,999	3,164 (88.1)	172 (4.8)	110 (3.1)	144 (4.0)	
75,000 or higher	1,698 (94.0)	62 (3.4)	26 (1.4)	21 (1.2)	
Education Level (No. [%])					< .001
No high school diploma	770 (80.8)	33 (3.5)	45 (4.7)	105 (11.0)	
High school diploma or general equivalency degree	2,117 (83.8)	97 (3.8)	92 (3.6)	220 (8.7)	
Some college but no degree	2,342 (86.8)	127 (4.7)	88 (3.3)	141 (5.2)	
College degree or higher	3,317 (90.2)	167 (4.5)	89 (2.4)	103 (2.8)	
Diabetes (No. [%])					< .001
No	7,013 (88.1)	331 (4.2)	234 (2.9)	386 (4.8)	
Yes	1,533 (81.2)	93 (4.9)	80 (4.2)	183 (9.7)	
Hypertension (No. [%])					< .001
No	3,811 (89.0)	176 (4.1)	117 (2.7)	179 (4.2)	
Yes	4,735 (85.0)	248 (4.5)	197 (3.5)	390 (7.0)	
Hyperlipidemia (No. [%])					.001
No	3,636 (87.8)	171 (4.1)	138 (3.3)	194 (4.7)	
Yes	4,910 (85.9)	253 (4.4)	176 (3.1)	375 (6.6)	
Smoking Status (No. [%])					< .001
Never	3,975 (90.5)	145 (3.3)	100 (2.3)	170 (3.9)	
Past smoker	3,535 (85.1)	201 (4.8)	146 (3.5)	271 (6.5)	
Current smoker	1,036 (79.1)	78 (6.0)	68 (5.2)	128 (9.8)	
logCRP§ (Mean ± SD¶)	0.74 ± 1.16[A]	0.87 ± 1.14[A]	1.05 ± 1.18[B]	1.18 ± 1.15[B]	< .001
CES-D# Scale Score (Mean ± SD)	0.95 ± 1.79[A]	1.32 ± 2.10[B]	1.34 ± 2.26[B]	1.33 ± 2.17[B]	< .001
Mean Learning Score ** **(Mean ± SD)**	5.81 ± 1.64[A]	5.82 ± 1.57[A]	5.55 ± 1.67[B]	5.29 ± 1.56[C]	< .001
Delay Recall Score†† **(Mean ± SD)**	6.39 ± 2.14[A]	6.41 ± 2.12[A]	6.08 ± 2.20[B]	5.82 ± 2.08[C]	< .001

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[*] Superscripted capital letters A, B or C indicate the grouping based on Student-Newman-Keuls multiple range test.

[†] All *P* values were based on χ^2 test or analysis of variance (for the last four variables with mean ± standard deviation).

[‡] BMI: Body mass index.

[§] logCRP: Logarithm of C-reactive protein.

[¶] SD: Standard deviation.

[#] CES-D: Center for Epidemiological Studies-Depression.

[**] Consortium to Establish a Registry for Alzheimer's Disease word list learning, average of responses across three trials (range, 0–10).

[††] Consortium to Establish a Registry for Alzheimer's Disease word list delay recall, number of responses to single recall trial (range, 0–10).

TABLE 2

Association between mean learning score* and other factors with incremental regression models† (n = 9,853).

PREDICTOR VARIABLE	UNADJUSTED		ADJUSTED FOR DF‡		ADJUSTED FOR DF PLUS BMI§		ADJUSTED FOR DF PLUS BMI PLUS logCRP¶		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF#		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF PLUS CES-D**		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF PLUS CES-D PLUS SES††	
	Regression Coefficient (β [95% CI‡‡])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value
Teeth Lost (No.)														
0 (ref.)														
1–5	0.01 (−0.15 to 0.17)	.87	0.06 (−0.08 to 0.21)	.408	0.06 (−0.08 to 0.21)	.395	0.07 (−0.08 to 0.21)	.362	0.09 (−0.05 to 0.24)	.197	0.12 (−0.02 to 0.26)	.101	0.07 (−0.06 to 0.21)	.297
6–16	−0.26 (−0.45 to −0.08)	.005	−0.17 (−0.34 to 0.00)	.048	−0.17 (−0.34 to 0.00)	.044	−0.16 (−0.33 to 0.01)	.060	−0.12 (−0.28 to 0.05)	.163	−0.10 (−0.26 to 0.07)	.249	−0.03 (−0.19 to 0.13)	.689
> 16	−0.52 (−0.65 to −0.38)	< .001	−0.28 (−0.41 to −0.15)	< .001	−0.27 (−0.39 to −0.14)	< .001	−0.25 (−0.38 to −0.12)	.001	−0.18 (−0.31 to −0.05)	.005	−0.16 (−0.29 to −0.04)	.011	−0.01 (−0.13 to 0.12)	.913
Region														
Non–Stroke Belt (ref.)														
Stroke Belt	NA§§	NA	−0.19 (−0.25 to −0.13)	< .001	−0.18 (−0.24 to −0.12)	< .001	−0.18 (−0.24 to −0.12)	< .001	−0.16 (−0.22 to −0.10)	< .001	−0.16 (−0.21 to −0.10)	< .001	−0.10 (−0.15 to −0.04)	.010
Sex														
Male (ref.)														
Female	NA	NA	0.75 (0.69 to 0.81)	< .001	0.76 (0.70 to 0.82)	< .001	0.78 (0.72 to 0.84)	< .001	0.75 (0.69 to 0.81)	< .001	0.79 (0.73 to 0.85)	< .001	0.90 (0.84 to 0.96)	< .001
Age (Years)														
45–54 (ref.)														
55–64	NA	NA	−0.37 (−0.47 to −0.26)	< .001	−0.36 (−0.47 to −0.26)	< .001	−0.35 (−0.46 to −0.25)	< .001	−0.32 (−0.43 to −0.22)	< .001	−0.33 (−0.44 to −0.23)	< .001	−0.27 (−0.37 to −0.17)	< .001
65–74	NA	NA	−1.01 (−1.11 to −0.90)	< .001	−1.01 (−1.12 to −0.91)	< .001	−1.01 (−1.11 to −0.90)	< .001	−0.96 (−1.07 to −0.85)	< .001	−0.99 (−1.09 to −0.88)	< .001	−0.80 (−0.90 to −0.69)	< .001
75–84	NA	NA	−1.73 (−1.85 to −1.61)	< .001	−1.76 (−1.88 to −1.63)	< .001	−1.75 (−1.87 to −1.62)	< .001	−1.71 (−1.83 to −1.58)	< .001	−1.72 (−1.85 to −1.60)	< .001	−1.44 (−1.57 to −1.32)	< .001
85 or older	NA	NA	−2.35 (−2.63 to −2.07)	< .001	−2.39 (−2.67 to −2.11)	< .001	−2.38 (−2.66 to −2.10)	< .001	−2.39 (−2.67 to −2.11)	< .001	−2.38 (−2.66 to −2.10)	< .001	−2.12 (−2.38 to −1.85)	< .001
Income ($)														
< 20,000 (ref.)														
20,000–34,999	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.30 (0.21 to 0.39)	< .001
35,000–74,999	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.48 (0.39 to 0.57)	< .001

PREDICTOR VARIABLE	UNADJUSTED		ADJUSTED FOR DF‡		ADJUSTED FOR DF PLUS BMI§		ADJUSTED FOR DF PLUS BMI PLUS logCRP¶		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF#		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF PLUS CES-D**		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF PLUS CES-D PLUS SES††	
	Regression Coefficient (β [95% CI‡‡])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value
75,000 or higher	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.70 (0.59 to 0.81)	< .001
Education Level														
No high school diploma (ref.)														
High school diploma or general equivalency degree	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.44 (0.33 to 0.55)	< .001
Some college but no degree	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.67 (0.56 to 0.78)	< .001
College degree or higher	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.91 (0.80 to 1.02)	< .001

*Mean learning score: Consortium to Establish a Registry for Alzheimer's Disease word list learning, average of responses across three learning trials (range, 0–10).

†All *P* values are based on a likelihood ratio test.

‡DF: Demographic factors (region, race, sex, age).

§BMI: Body mass index.

¶logCRP: Logarithm of C-reactive protein.

#RF: Risk factors (diabetes, hypertension, hyperlipidemia, smoking).

**CES-D: Center for Epidemiological Studies-Depression. The scale ranges from zero to 12; a score of four or higher indicates an elevated level of psychological distress.

††SES: Socioeconomic status (income, education).

‡‡CI: Confidence interval.

§§NA: Not applicable.

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TABLE 3

Association between delay recall score[*] and other factors with incremental regression models[†] (n = 9,853).

PREDICTOR VARIABLE	UNADJUSTED		ADJUSTED FOR DF[‡]		ADJUSTED FOR DF PLUS BMI[§]		ADJUSTED FOR DF PLUS BMI PLUS logCRP[¶]		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF[#]		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF PLUS CES-D[**]		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF PLUS CES-D PLUS SES[††]	
	Regression Coefficient (β [95% CI[‡‡]])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value
Teeth Lost (No.)														
0 (ref.)														
1–5	0.02 (−0.19 to 0.23)	.86	0.07 (−0.12 to 0.26)	.458	0.07 (−0.12 to 0.27)	.451	0.08 (−0.11 to 0.27)	.424	0.10 (−0.09 to 0.29)	.296	0.13 (−0.06 to 0.32)	.183	0.08 (−0.11 to 0.27)	.401
6–16	−0.30 (−0.54 to −0.06)	.013	−0.20 (−0.43 to 0.02)	.072	−0.21 (−0.43 to 0.01)	.067	−0.20 (−0.42 to 0.03)	.085	−0.16 (−0.38 to 0.06)	.164	−0.13 (−0.35 to 0.09)	.235	−0.06 (−0.28 to 0.15)	.569
> 16	−0.56 (−0.75 to −0.38)	< .001	−0.29 (−0.46 to −0.13)	.001	−0.28 (−0.45 to −0.12)	.001	−0.27 (−0.44 to −0.10)	.002	−0.20 (−0.37 to −0.03)	.021	−0.18 (−0.35 to −0.01)	.036	−0.01 (−0.17 to 0.16)	.924
Region														
Non–Stroke Belt (ref.)														
Stroke Belt	NA[§§]	NA	−0.16 (−0.24 to −0.08)	< .001	−0.16 (−0.23 to −0.08)	.001	−0.15 (−0.23 to −0.07)	.001	−0.13 (−0.21 to −0.05)	.001	−0.12 (−0.20 to −0.05)	.002	−0.05 (−0.13 to 0.02)	.164
Sex														
Male (ref.)														
Female	NA	NA	0.92 (0.84 to 1.00)	< .001	0.93 (0.85 to 1.01)	< .001	0.95 (0.87 to 1.03)	< .001	0.92 (0.84 to 1.01)	< .001	0.97 (0.89 to 1.05)	< .001	1.10 (1.01 to 1.18)	< .001
Age (Years)														
45–54 (ref.)														
55–64	NA	NA	−0.48 (−0.62 to −0.34)	< .001	−0.47 (−0.61 to −0.34)	< .001	−0.47 (−0.60 to −0.33)	< .001	−0.43 (−0.57 to −0.29)	< .001	−0.44 (−0.58 to −0.30)	< .001	−0.36 (−0.50 to −0.23)	< .001
65–74	NA	NA	−1.23 (−1.38 to −1.09)	< .001	−1.24 (−1.39 to −1.10)	< .001	−1.23 (−1.38 to −1.09)	< .001	−1.16 (−1.31 to −1.02)	< .001	−1.20 (−1.34 to −1.05)	<. 001	−0.98 (−1.12 to −0.83)	< .001
75–84	NA	NA	−2.16 (−2.33 to −2.00)	< .001	−2.19 (−2.35 to −2.02)	< .001	−2.18 (−2.34 to −2.01)	< .001	−2.11 (−2.28 to −1.94)	< .001	−2.12 (−2.29 to −1.96)	< .001	−1.80 (−1.97 to −1.63)	< .001
85 or older	NA	NA	−2.74 (−3.11 to −2.37)	< .001	−2.78 (−3.15 to −2.40)	< .001	−2.77 (−3.14 to −2.40)	< .001	−2.74 (−3.11 to −2.37)	< .001	−2.74 (−3.11 to −2.37)	< .001	−2.42 (−2.79 to −2.06)	< .001
Income ($)														
< 20,000 (ref.)														
20,000–34,999	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.38 (0.26 to 0.50)	< .001
35,000–74,999	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.60 (0.48 to 0.72)	< .001

PREDICTOR VARIABLE	UNADJUSTED		ADJUSTED FOR DF‡		ADJUSTED FOR DF PLUS BMI§		ADJUSTED FOR DF PLUS BMI PLUS logCRP¶		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF#		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF PLUS CES-D**		ADJUSTED FOR DF PLUS BMI PLUS logCRP PLUS RF PLUS CES-D PLUS SES††	
	Regression Coefficient (β [95% CI‡‡])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value	Regression Coefficient (β [95% CI])	*P* Value
75,000 or higher	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.83 (0.68 to 0.98)	< .001
Education Level														
No high school diploma (ref.)														
High school diploma or general equivalency degree	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.55 (0.40 to 0.70)	< .001
Some college but no degree	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.75 (0.50 to 0.90)	< .001
College degree or higher	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.97 (0.82 to 1.13)	< .001

*Delay recall score: Consortium to Establish a Registry for Alzheimer's Disease word list learning, number of responses to sole recall trial (range, 0–10).

†All *P* values are based on a likelihood ratio test.

‡DF: Demographic factors (region, race, sex, age).

§BMI: Body mass index.

¶logCRP: Logarithm of C-reactive protein.

#RF: Risk Factors (diabetes, hypertension, hyperlipidemia, smoking).

**CES-D: Center for Epidemiological Studies-Depression. The scale ranges from zero to 12; a score four or higher indicates an elevated level of psychological distress.

††SES: Socioeconomic status (income, education).

‡‡CI: Confidence interval.

§§NA: Not applicable.