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P. S. Stein
University of Kentucky

R. J. Kryscio
University of Kentucky

M. Desrosiers
University of Kentucky

Sara J. Donegan
Marquette University, sara.donegan@marquette.edu

M. B. Gibbs
University of Kentucky

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P.S. Stein

Department of Anatomy and Neurobiology, College of Medicine,
University of Kentucky,
Lexington, KY

R.J. Kryscio

Sanders-Brown Center on Aging, College of Medicine,
Department of Statistics,
Department of Biostatistics,
University of Kentucky,
Lexington, KY

M. Desrosiers

Sanders-Brown Center on Aging, College of Medicine,
University of Kentucky,
Lexington, KY

S.J. Donegan

Department of General Dental Sciences, School of Dentistry,
Marquette University,
Milwaukee, WI

M.B.Gibbs

University of Kentucky College of Dentistry,
Chandler Medical Center,
Lexington, KY

Abstract: Our previous research suggests an association between a low number of teeth and increased risk of dementia. The aim of the present study was to determine if a low number of teeth is specifically related to memory decline as evidenced by low Delayed Word Recall scores. In addition, we examined the combined effect of a low number of teeth and the apolipoprotein E ϵ4 allele on Delayed Word Recall scores. We hypothesized that the scores of those who had the allele and a low number of teeth (0-9) would decline more rapidly over time than those participants with a greater number of teeth who lacked the allele. We found that individuals with both risk factors (the allele and fewer teeth) had lower Delayed Word Recall scores at the first examination and declined more quickly compared with participants with neither of these risk factors or with either risk factor alone.

Keywords: teeth, apolipoprotein E ϵ4, memory, delayed word recall, cognition

Introduction

The Delayed Word Recall examination is a diagnostic test often given to access an individual's memory and cognitive decline. This examination is part of a battery of cognitive tests that make up the Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Physicians often administer this battery of tests to determine specific cognitive problems and access the severity of dementia in their patients (Perani, 2006).

Of all of the cognitive examinations, the Delayed Word Recall test is the most discriminating test in identifying individuals with early Alzheimer's disease (Welsh *et al*., 1991) and has been found to be an extremely sensitive indicator of the early stages of this disease (Morris *et al*., 1989; Welsh *et al*., 1992). The Delayed Word Recall test involves presenting participants with 10 words on cards, waiting 5 min,

and then testing the individuals for recall of the 10 words. It was found (Knopman and Ryberg, 1989) that a recall score of 2 words or less accurately predicted Alzheimer's disease in 95% of the persons studied.

The apolipoprotein E (APOE) ϵ4 allele is the primary genetic risk factor for Alzheimer's disease (Corder *et al*., 1993). Individuals with the apolipoprotein E ϵ4 genotype have demonstrated memory deficits (Bondi *et al*., 1995; Bartres-Faz *et al*., 1999; Caselli *et al*., 1999; Dik *et al*., 2000). Similarly, the APOE ϵ4 allele has been associated with lower scores on the delayed recall examination (O'Hara *et al*., 1998).

Recent research has explored other, potentially modifiable, risk factors that may underlie cognitive impairments. In a previous longitudinal study, we found a low number of teeth (0-9) to be related to increased risk of both prevalence and incidence of dementia (Stein *et al*., 2007). In this study, we examined the effect of having both a low number of teeth and at least one APOE ϵ4 allele on delayed word recall in Nun Study participants. We hypothesized that the delayed word recall scores of those who had the allele and a low number of teeth (0-9) would decline more rapidly over time than those participants with a greater number of teeth but lacking the allele.

Methods

Participants

Approval for this study was obtained from the University of Kentucky Internal Review Board. Informed consent was obtained from all participants. Individuals participating in this study were participants in the Nun Study, a longitudinal study on aging and Alzheimer's disease. Details of this study have been described previously (Snowdon *et al*., 1996). Briefly, participants in the Nun Study are 678 Catholic sisters, members of the international congregation of the School Sisters of Notre Dame. Each participant agreed to annual cognitive and physical assessments and brain donation upon death. Cognitive assessments included a battery of tests, including the Delayed Word Recall Test (Morris *et al*., 1989).

We restricted our study to Nun Study participants from the Milwaukee province, since this was the only province with an on-site dental clinic. The province dentist, who currently practices in this clinic, has practiced there since 1964. One hundred and forty-eight Milwaukee participants had been patients of the province dentist both before and after their first cognitive examination in the Nun Study. Two of these 148 did not have data available on the presence or absence of APOE ϵ4, and two had a psychiatric history dating back many years. This reduced our final sample to 144 participants. The participants ranged in age from 75-98 yrs old (mean, 84) at their first cognitive examination in the Nun Study. The educational levels of the participants were similar: 85% had a bachelor's degree or greater, and 88% were teachers by profession. Twenty-two percent of the 144 participants in our subset had one or more copies of the APOE ϵ4 allele.

Number of Teeth

Dental records of the participants were provided by the Milwaukee province dentist and included charting, clinical notes, and radiographs. Using this information, another dentist determined the number of teeth present in each person at the time of her first Delayed Word Recall Test. Categories were determined based on numbers of existing teeth according to methodology previously described (Stein *et al*., 2007). A group with zero to 9 teeth was at one end of the spectrum, while a group with 10-32 teeth was created at the other end of the spectrum.

Delayed Word Recall

Each participant was evaluated by cognitive assessments performed annually by two field-trained gerontologists. The first cognitive assessments were conducted between 1991 and 1993. The Delayed Word Recall Examination was administered to each participant annually as part of her annual cognitive assessments. The Delayed Word Recall Examination was modeled after a procedure previously described in the Consortium to Establish a Registry for Alzheimer's Disease (Morris *et al*., 1989). Briefly, the procedure for the examination was as follows: Ten printed words were presented to

participants at a rate of one word every 2 sec. Five min later, participants were asked to recall as many of the words as possible. Participants were given a maximum of 90 sec to recall the words on the list.

Apolipoprotein E Genotyping

Genotyping was performed by two scientists blinded to the participants' cognitive test scores. A dichotomous variable indicated the presence or absence of at least one APOE ϵ-4 allele. In living participants, field-trained gerontologists obtained genetic material by scraping cells from the buccal mucosa of the oral cavity. In deceased individuals, genetic material was obtained from frozen or paraffin-embedded brain tissue collected during autopsy by a neuropathologist.

Statistical Methods

Longitudinal data of each participant's Delayed Recall Test scores were stratified by number of teeth and APOE ϵ4 status. Each participant had Delayed Word Recall Test scores recorded annually, with various numbers of assessments *per* participant. Specifically, the 144 participants had a total of 736 assessments, for an average of 5.1 assessments *per* participant (range, 1-12). In modeling of the decline in the Delayed Word Recall Test scores with age, the following two characteristics of the 736 observations had to be accounted for: (i) between- and within-participant variability, and (ii) floor and ceiling effects for the scores. The floor score was zero, while the ceiling score was 10, but these varied by participant. To account for (i) and (ii), we fitted the non-linear mixed-effects regression model (Martins *et al*., 2005) to these data. This model is the three-parameter logistic regression model:

$$Y_{it}=a/(1+\exp[b(age_{it}-c)]).$$

Here, Y_{it} represents the Delayed Word Recall Test score for the ith participant at age t, while age_{it} represents this age centered at 84, the average baseline age of the participants. The parameter a is the asymptote or highest score for a participant, which varies by participant, the parameter b is a scaling effect whose reciprocal

represents the time to fall from 75% to 50% of the asymptote, and the parameter c is the time when the curve is at 50% of the asymptote. We assumed that the parameters b and c depended only on the fixed effects, while the parameter a depended on both fixed and random effects. The fixed effects or covariates of interest were educational level (high school or less *vs*. more than high school), APOE ε4 status (presence or absence of at least one APOE ε4 allele), number of teeth (9 or fewer teeth *vs*. 10-32 teeth), and all possible interactions among these 3 indicator variables. The random effects (within as well as between) were assumed to follow independent normal distribution with mean zero and unknown variance. The purpose of the modeling was to determine how each parameter depended on these covariates after adjustment for the two sources of variability. Statistical significance for a covariate was determined at the 0.05 level, and only significant covariates were retained in the final model. All models were fitted with PROC NLMIXED in PC-SAS Version 9.

Results

Of the 144 participants, 70 had 10 or more teeth and no APOE ε4 allele, 23 had 10 or more teeth and at least one APOE ε4 allele, 42 had 0-9 teeth and no APOE ε4 allele, and nine had 0-9 teeth and at least one APOE ε4 allele (Fig. 1).
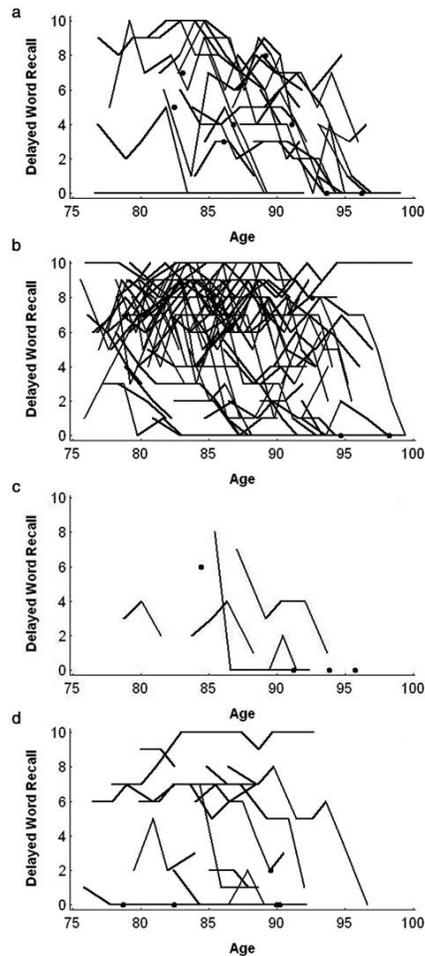
Figure 1. Plot of the longitudinal records of delayed recall scores (0-10) vs. age (75-100) for each participant in the study, stratified by number of teeth and APOE 4 status. Black dots were used when a participant had only one observation. (a) 0-9 teeth and no APOE 4 (n = 42). (b) 10 or more teeth and no APOE 4 (n = 70). (c) 0-9 teeth and APOE 4 (n = 9). It should be noted that four individuals in this group had only one Word Recall examination score and appear as 4 datapoints (black dots). (d) 10 or more teeth and APOE 4 (n = 23).

In the three-parameter logistic model, only the asymptote (highest score for a participant) and the midpoint depended on the covariates, with the asymptote adjusted downward for low education or for the presence of at least one APOE $\epsilon 4$ allele, while the midpoint was adjusted to the left for the presence of at least one 4 allele or for fewer than 10 teeth at baseline (Table). The presence of at least one APOE $\epsilon 4$ allele lowered the initial word recall status at 75 yrs of age from 5.5 to 3.0 and shifted the 50% decline in word recall scores to the left approximately 4.2 yrs earlier. Having fewer than 10 teeth shifted the decline in scores to the left approximately 5.7 yrs at the

midpoint. Hence, participants with both risk factors (at least one APOE ε4 allele and fewer teeth) had lower scores at the first examination and declined more quickly when compared with participants with neither of these risk factors or with either risk factor alone (Fig. 2). Finally, there was considerable variability in within-participant scores when compared with between-participant scores (Table).

Table. Beta Estimates and Standard Errors for the Significant Covariates in the Three-parameter Logistic Model

Parameter	Covariate	Beta (standard error)	P-value*
a = asymptote	Intercept	5.4584 (0.3277)	< 0.0001
	Low education	−3.5121 (0.9082)	0.0002
	APOE 4 present	−2.1107 (0.6712)	0.0020
b = scale	Intercept	0.3355 (0.05878)	< 0.0001
c = mid-point	Intercept	9.6072 (0.6024)	< 0.0001
	APOE 4 present	−4.1645 (1.0690)	0.0001
	# teeth < 10	−5.6955 (0.9194)	< 0.0001
Variability	Between	2.7354 (0.1583)	-
	Within	8.1904 (1.1698)	-

*P values based on *t* tests with 141 degrees of freedom.
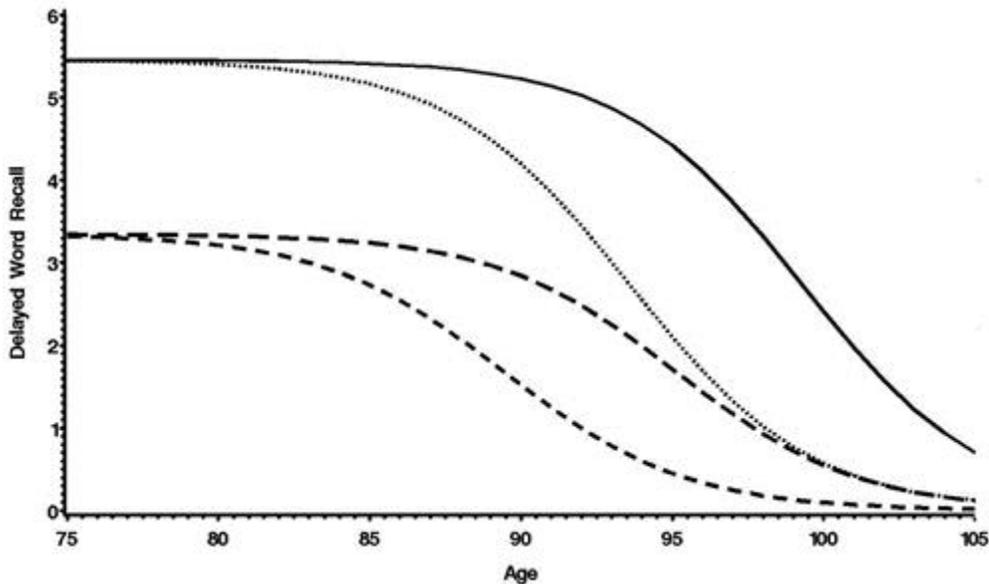
Figure 2. Fitted average decline in Delayed Word Recall test scores with age for participants with greater than a high school education by the four groups: 10 or more teeth and no APOE 4, n = 70 (solid line); fewer than 10 teeth but no APOE 4, n = 42 (dotted line); 10 or more teeth and at least one APOE 4 allele, n = 23 (longer dashed line); and fewer than 10 teeth and at least one APOE 4 allele, n = 9 (shorter dashed line).

Thirty-one of the 144 participants (21.5%) had dementia at baseline. Baseline dementia was associated with missing teeth, since 54.8% of those with dementia at baseline had 0-9 teeth, while only 30.1% of those without dementia at baseline had 0-9 teeth (P = 0.011).

Fourteen of the 144 participants (9.7%) had a low education (high school or less). Low education was also associated with missing teeth, since 85.7% of those with low education had 0-9 teeth, while only 30.0% of those with a better education had 0-9 teeth (P < 0.0001).

Discussion

Case-control studies have suggested that a low number of teeth may be a risk factor for Alzheimer's disease (Kondo *et al.*, 1994; Gatz *et al.*, 2006) or associated with incident dementia (Kim *et al.*, 2007). In a previous study, we demonstrated a low number of teeth (0-9) to be associated with an increase in both the prevalence (OR = 4.3) and incidence (OR = 2.2) of dementia (Stein *et al.*, 2007).

The model fitted in this study examined the decline in word recall scores as a participant ages. Of the 3 unknown parameters, our analysis showed that 2 of these parameters depended on the covariates of interest. The first of these parameters is the asymptote or initial word recall status at age 75. Our results showed that the initial word recall status was strongly affected by APOE ϵ4 and education, but was unaffected by the number of teeth.

The second parameter affected was the age at which the participant declined to 50% of her initial word recall status. This parameter was affected by both APOE ϵ4 and number of teeth. Specifically, a participant with fewer teeth (less than 10) declined to 50% of her initial word recall status approximately 5½ yrs earlier than a participant with 10 or more teeth, regardless of APOE ϵ4 status. A participant with an APOE ϵ-4 allele declined to 50% of her initial word recall status approximately 4 yrs earlier than a participant without the allele, regardless of the number of teeth. When word recall scores were observed over time, individuals with both risk factors (at least

one allele and fewer teeth) declined earlier when compared with participants with neither of these risk factors or with either risk factor alone.

Mechanisms underlying a potential association between oral disease and dementia have been previously described (Stein *et al*., 2006). Chronic inflammation associated with periodontal disease is perhaps the most probable of the mechanisms and has been suggested as the underlying mechanism for association with other systemic diseases, such as cardiovascular disease (DeStefano *et al*, 1993; Beck *et al*., 1996; Joshipura *et al*., 1996), stroke (Grau *et al*., 1997; Joshipura *et al*., 2003), and preterm birth (Dasanayake, 1998; Jeffcoat *et al*., 2001). Inflammation has been implicated in the pathophysiology of Alzheimer's disease (Rogers *et al*., 1996; Akiyama *et al*., 2000; Eikelenboom *et al*., 2006). Further, the use of non-steroidal anti-inflammatory drugs has been shown to decrease the risk of Alzheimer's disease (Stewart *et al*., 1997).

Although it seems biologically plausible that oral disease could influence cognition through inflammatory pathways, it is possible that a low number of teeth is simply marking other risk factors that affect cognition. We did find an association between a low number of teeth and both dementia at baseline and low education. Either of these risk factors could influence the ability to recall words over time.

Confounding was minimized in this study due to the homogeneity of the study population. It should be noted that the same factors that make this cohort homogeneous may affect extrapolation of the findings from this study to the general population. For example, participants did not smoke, did not marry, and did not have children. In addition, this was a single-sex study. It is unlikely, however, that including males would have modified our findings, since gender would not typically affect any of the established risk factors for Alzheimer's disease, *i.e*., the APOE ε4 allele, advanced age, family history, head injury, and Down Syndrome. The exception to this may be advanced age. Males do not have as long a life expectancy as females. Moreover, many participants in the Nun Study lived longer compared with both males and females for their generation (Danner *et al.*, 2001).

Although little research has been conducted to examine a potential relationship between oral disease and dementia, our findings add to the evidence suggesting that this area of study deserves further examination. If future studies can establish a link between periodontal disease and cognitive deficits, this would influence decisions about patient care. Armed with this evidence, physicians and dentists would likely make a strong case to their patients for diligent oral hygiene practices and regular dental preventive services. Insurance coverage could be influenced as well. Although researchers are just beginning to explore this potential oral-systemic linkage, it is important to continue work in this area.

Acknowledgments

Footnotes

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