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Tooth loss and cognitive impairment

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Abstract

Objectives: Chronic subclinical inflammation may elevate the risk of cognitive impairment. Periodontitis is associated with subclinical inflammation and accounts in part for tooth loss. The hypothesis was tested that periodontitis and tooth loss as a proxy of chronic periodontitis is associated with cognitive impairment in the elderly.

Subjects and Methods: The population-based Study of Health in Pomerania comprises 1336 subjects (60–79 years). Cognitive impairment was assessed with the Mini-Mental Status Examination (MMSE). Tobit regression analyses were adjusted for potential confounders.

Results: A decreased number of teeth was associated with lower MMSE scores in females ($p < 0.001$) and males ($p = 0.007$) in age-adjusted models. In the fully adjusted models, tooth loss was associated with cognitive impairment in females ($p = 0.002$) but not in males ($p = 0.825$).

Conclusions: A significant association between tooth loss and cognitive impairment was found in females that was not accounted for by potential confounders. Former periodontitis may account for this association as periodontitis was frequently the cause for tooth extractions.

Key words: cognitive impairment; general population; periodontitis; tooth loss

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Dementia is projected to present as one of the largest emerging health problems during the next decades (Comas-Herrera et al. 2007). The contribution of systemic chronic inflammation in the aetiology and pathogenesis of neurodegenerative diseases such as Alzheimer disease or dementia has come into the focus of current research. It is known that inflammation is a critical component of the pathogenesis of Alzheimer disease (Finch & Morgan 2007). Although inflammation is not an initiator of this disorder, it nonetheless plays a pivotal role as a driving force that can modulate the neuropathology. Evidence from prospective studies is accumulating that elevations of pro-inflammatory serum markers [e.g. C-reactive protein, interleukin (IL)-1, TNF-α, IL-6 and α-1-antichymotypsin] may precede cognitive impairment (Yaffe et al. 2003, Dik et al. 2005, Tan et al. 2007). Schmidt et al. (2002) showed, in 1050 subjects of the Honolulu–Asia Aging Study followed over 25 years, that men in the upper three quartiles, compared with men in the lowest quartile (<0.34 mg/l) of high-sensitivity C-reactive protein, had a threefold increased risk of dementia; these relations were independent of cardiovascular risk factors and disease. In line with this pattern of risk exposure, obesity at midlife was significantly predictive of Alzheimer disease and vascular dementia on average 36 years later, independent of stroke, cardiovascular diseases and diabetes (Whitmer et al. 2007).

The local infectious/inflammatory nature of periodontal disease may lead directly or indirectly to a state of chronic low-grade systemic inflammation. Oral microbes or lipopolysaccharides (LPS) gain systemic access during bacteraemia following brushing or dental procedures (Forner et al. 2006). In subjects with periodontitis, LPS can be detected in a dose-dependent manner in serum according to disease severity (Geerts et al. 2002). Common periodontal pathogens have been observed in atherosclerotic carotid plaques (Haraszthy et al. 2000) and subjects with periodontal disease exhibit higher serum levels of inflammatory markers (Loos et al. 2000, Slade et al. 2003, Schwahn et al. 2004) than subjects without periodontal disease. Furthermore, treatment for periodontal disease decreases levels of systemic inflammation (D'Aiuto et al. 2005, Paraskevas et al. 2008).

One possible pathway between the local oral infection and inflammation and the inflammation in the brain may be that LPS affect the passage of other regulatory proteins across the blood–brain barrier. In mice, it was found that microglial activation can exacerbate the neuropathology and that LPS induces CNS inflammation. In human autopsies, antigen of oral treponemes was more often found in samples from subjects with Alzheimer disease (14 of 16) than in samples from control subjects (four of 18) (Riviere et al. 2002).

Periodontal disease is a common oral infection. Among the adult German population, 20–30% of all individuals exhibit moderate to severe periodontal disease. Periodontitis and tooth loss is more prevalent in East than in West Germany (Micheelis & Schiffner 2006), and East German dentists seem to favour tooth extraction as a treatment option for periodontal disease. Splieth et al. (2002) selected at random 500 extracted teeth from a dental waste company operating in East Germany and they showed that there was a marked increase in the frequency of extracted teeth that had lost only one-third loss of periodontal attachment. This observation may explain in part why the prevalence of missing teeth in East Germany is higher than that in West Germany (Micheelis & Schiffner 2006).

In all, we hypothesize an association between tooth loss as a proxy of periodontitis and cognitive decline. In order to address relevant gender-specific differences in education, access to health care, smoking, alcohol consumption and the putative effects of pregnancy and childbirth on tooth loss and cognitive status, gender-specific analyses were performed.

Subjects and Methods

Study sample

The *Study of Health in Pomerania* (SHIP) is a cross-sectional study of the adult population in West Pomerania, the north-eastern coastal region of Germany. The design of the study has already been presented in considerable detail (John et al. 2001, Hensel et al. 2003, Grabe et al. 2005). In brief, a sample from the population aged 20–79 years was drawn from population registries, stratified by age and gender. All participants gave informed written consent and the study was approved by the local Ethics Committee of the University of Greifswald, Germany.

For this article we selected subjects aged 60 or older (1336 subjects, 617 females and 719 males). Ninety-seven subjects (30 females and 67 males) were excluded from the analyses mainly because of a history of stroke (21 females and 55 males) and an additional 15 subjects (nine females and 12 males) because of traumatic injuries of the brain, Parkinsons' disease, multiple sclerosis or epilepsy. Furthermore, 180 subjects (90 females and 90 males) were excluded because of missing values mainly due to the variable ''income'' (48 females and 43 males) and Mini-Mental Status Examination (MMSE) scores (29 females and 25 males). The final study sample for complete case analyses for tooth loss comprised 1059 subjects (497 females and 562 males). Because in complete case analyses $>5\%$ of subjects were excluded, it is possible that this might have biased the results. We have, therefore, carried out an analysis based on multiple imputation with 587 females and 652 males.

Outcome and exposure measures

Cognitive status was assessed with the MMSE (Folstein et al. 1975). The MMSE includes simple questions and tasks in a number of areas: orientation, short-time memory tasks (repeating three words with delay), arithmetic tasks, language use and comprehension, and basic executive and motor skills. Scores above 24 (out of 30) are considered as normal. Scores of 20–24 indicate mild dementia; 10–19 indicates moderate dementia; and below 10, a severe dementia is suspected.

Calibrated licensed dentists performed the entire oral examination (John et al. 2001). The location and the number of teeth excluding the wisdom teeth were counted. Because the prevalence of edentulism cannot be ignored in an analysis restricted to dentate subjects, the results would be biased at least for two reasons: first, selection bias or more exactly survival bias on the basis of the presence or absence of teeth occurs. Second, among age groups without edentulism, higher attachment levels correspond to a higher degree of periodontal disease. But provided edentulism is caused by periodontal disease, subjects with highest attachment levels have to be considered periodontally healthier than edentoulus subjects. This

information bias, combined with the selection bias mentioned above, occurs among age groups with high proportions of edentulism. To avoid both selection and information bias, we analysed the number of teeth, but not periodontal disease, because the SHIP population ($\geqslant$60 years) is characterized by a remarkable proportion of edentulism.

Measurements of confounders

Putative confounders for the association between dental status and cognitive impairment were selected based on the literature. From the interview, we used age, gender, school education ($<$10, 10, $>$10 years), smoking status (never, former and current smokers), use of antihypertensive medication, diabetes mellitus, total alcohol consumption (beer, wine and spirits) during the past weekend (continuous scale; g alcohol), physical activity (at least 1 h/week in summer or winter) and number of household members. From the questionnaire, we used household income and the number of children. Because income (in German Marks; 1 Euro = 1.956 German Marks) is a household-level variable, we used a commonly adopted procedure to obtain the ''equalized'' household income: the monthly household income was divided by the square root of the number of persons living in the household (Kawachi & Kennedy 1997). Social relations were assessed by the Social Network Index (SNI) (Berkman & Syme 1979) of the questionnaire, with modifications (John et al. 2001). This index was developed to measure the degree of social integration by assessing various types of social ties. The SNI measures four components: 1: marital status (married *versus* non-married, i.e., married but separated living, single, divorced, widowed), 2: number of close friends, relatives and children and frequency of contact with these people, 3: religious service attendance and church group membership and 4: participation in social groups. The church group membership was included in the component group associations, deviating from the original SNI. Participants were classified into four levels of social ties. Participants were classified into four levels of social ties, ranging from low ties (Level 1) to high (Level 4). The full-length version of the Medical Outcome Study Social Support Survey consisted of 19 items (Sherbourne & Stewart 1991); in this study, the perceived social support was assessed with a short version of five items regarding emotional, informational and tangible support. From the medical examination, the following confounders were considered: hypertension was defined as systolic blood pressure $\geqslant$140 mmHg or diastolic blood pressure $\geqslant$90 mmHg or use of antihypertensive medication. Measurement: after a 5-min resting period, systolic and diastolic blood pressure was measured three times on the right arm of seated participants, using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan), with each reading being followed by a further resting period of 3 min. One of two differently sized cuffs was applied according to the circumference of the participant's arm. The mean of the second and third measurement was calculated and used for the present analyses. Height and weight were measured for the calculation of the body mass index [BMI = weight (kg)/height^2 (m^2)]. The Anatomical-Therapeutic-Chemical code was used to assess the current intake of the following drugs: statines, fibrates, ibuprofen or non-steroidal antiphlogistics.

Statistical analyses

Data on quantitative characteristics are expressed as a mean and standard deviation. Data on qualitative characteristics are expressed as percent values. For continuous data, comparisons between groups were performed using the Mann–Whitney *U*-test, and using the χ^2 test for nominal data. To examine the type of trend between exposure and outcome, in preliminary analyses, we plotted moving averages of the MMSE scores across the number of lost teeth using different weights within an interval of the exposure range. The trend between the number of lost teeth and MMSE scores was clearly linear both in females and in males. Instead of linear models, we used Tobit regression analyses because MMSE is not completely normally distributed and the maximum, which represents about 10% of subjects, can be considered as right-censored (Table 1). Linear regression analyses, however, yielded results similar to the analyses presented and were used to calculate standardized coefficients. To model a possible J- or U-shaped curve between a confounder and the MMSE score age, income, BMI, alcohol consumption and number of children were categorized: age into 5-year age groups; income into quintiles over females and males ($\leqslant$1350, $>$1350–1700, $>$1700–2050, $>$2050–2300, $>$2300 DM); BMI into normal weight, overweight ($\geqslant$25–30 kg/m^2) and obesity ($\geqslant$30 kg/m^2); alcohol consumption into 0, $>$0–10, $>$10–20 and $>$30 g/day; and number of children into 0, 1, 2, 3, 4 and $\geqslant$5 children. To estimate the effect of a confounder on the relationship between the exposure and the outcome, we used the criterion of the change in the coefficient of interest: a substantial change was considered present if inclusion in the model led to $\geqslant$10% change in the coefficient of the dental variable. To evaluate an effect measure modification for the number of teeth by another factor, we tested the corresponding interaction. A value of $p<0.05$ was considered statistically significant. Main analyses were conducted using STATA/MP software, version 10.1 (StataCorp LP, College Station, TX, USA).

Ancillary analyses

Multiple imputation of missing data has been recommended to reduce potential bias because of missing values in a complete case analysis (Schafer & Graham 2002). We generated five imputations using S-PLUS 7.0 software (Insightful Corporation, Seattle, WA, USA). The five coefficients and the variances of the imputations were combined to present a single coefficient and adjusted CIs according to Rubin's rule (Schafer & Graham 2002). For the semicontinuous variable of tooth loss, we applied methods as described by Schafer (1997): provided tooth loss was categorically modelled in the affirmative, the number of teeth was continuously modelled. Each of the imputed variables is assumed to be missing at random what cannot be tested (Schafer & Graham 2002).

For linear and Tobit regression of complete case analyses, a non-parametric bootstrap approach with 10,000 replicates was performed to produce robust estimates. The validity of non-parametric bootstrapping estimates is not based on distributional assumptions.

Results

Both in females and males, the proportion of edentulism is $>$30% (Table 1). The characteristics of subjects who were included in and excluded from the complete case analyses are outlined in

Table 1. Characteristics of women and men included in complete case analyses and excluded because of missing data

Variable	Women			Men		
	excluded ($n = 118$)	included ($n = 497$)	p value	excluded ($n = 128$)	included ($n = 562$)	p value
Number of teeth (SE)	9.0 (0.8)	8.4 (0.4)	0.484	7.4 (0.8)	9.2 (0.4)	0.047
Proportion of edentulism (%)	30.2	32.2	0.740	37.3	30.1	0.137
Number of teeth among dentate subjects (SE)	12.9 (0.9)	12.4 (0.4)	0.576	11.8 (0.9)	13.1 (0.4)	0.196
Age (years; SE)	68.2 (0.6)	69.0 (0.3)	0.171	68.6 (0.5)	69.5 (0.2)	0.127
School education (%)			0.066			0.582
8 years	73.7	82.7		78.1	74.0	
10 years	17.8	10.7		10.2	13.2	
12 years	8.5	6.6		11.7	12.8	
Household income (DM; SE)	1719 (101)	1787 (29)	0.442	2001 (104)	2027 (31)	0.784
Smoking status (%)			0.491			0.049
Never smoker	71.9	70.0		15.1	18.9	
Ex-smoker	16.7	20.9		61.3	66.5	
Current smoker	11.4	9.1		23.5	14.6	
Hypertension ($\geqslant$140/90 mmHg or medication; %)	70.2	72.8	0.563	75.6	81.9	0.129
Diabetes mellitus (%)	17.8	17.7	1.000	14.1	16.7	0.509
Body mass index (kg/m^2; SE)	29.0 (0.4)	29.0 (0.2)	0.885	28.4 (0.3)	28.3 (0.2)	0.852
Alcohol consumption (last weekend; g; SE)	8.1 (1.4)	13.1 (0.9)	0.014	36.1 (3.4)	40.1 (2.0)	0.380
Number of children (SE)	2.2 (0.2)	2.2 (0.1)	0.959	2.2 (0.1)	2.4 (0.1)	0.328
Social network index	1.9 (0.09)	1.8 (0.04)	0.129	2.0 (0.09)	2.1 (0.04)	0.386
Physical activity (%)	37.7	29.2	0.091	31.9	28.5	0.439
Mini Mental Status Examination score, continuously (SE)	25.7 (0.4)	25.8 (0.1)	0.867	24.3 (0.5)	26.0 (0.1)	$<$0.001
Mini Mental Status Examination score (%)			0.485			0.004
$<$10 points	0.0	0.0		1.8	0.0	
10–19 points	3.4	4.8		5.3	3.7	
20–24 points	31.0	24.9		38.6	25.6	
25–29 points	51.7	61.2		49.1	59.6	
30 points	13.8	9.1		5.3	11.0	

Table 1. The females included tended to have higher alcohol consumption than those who were excluded. Among men, the subjects included had a higher number of teeth and higher MMSE scores than excluded subjects.

A decreased number of teeth was associated with lower MMSE scores in females ($p < 0.001$) and males ($p = 0.007$) in models adjusted for age groups (Table 2). Based on the model adjusted for categories of age, school education and household income, the number of children but not medical confounders, changed the coefficient for the relation of interest $>10\%$. The inclusion of additional putative confounders (as described in the material and methods section) did not lead to such a change in the final model. In the fully adjusted models the number of teeth and MMSE scores were associated (Table 2) only in females ($p = 0.002$) and not in males ($p = 0.825$). Neither in females nor in males the effect for the number of teeth was modified by any other factor of the final model. The results from the fully adjusted Tobit regression analyses are given in Table 3. In order to generate standardized regression coefficients, a linear regression analysis was performed: the major predictors of MMSE scores, besides tooth loss (standardized coefficient: -0.14), were number of children (maximum of -0.22 for $\geqslant 5$ children), income (maximum of 0.16 for the top quintile) and school education (0.15 for >10 years, 0.10 for 10 years compared with <10 years) in females and income (maximum of 0.19 for the top quintile), school education (0.17 for >10 years, 0.08 for 10 years compared with <10 years) and number of children (maximum of -0.14 for $\geqslant 5$ children) in males.

Ancillary analyses

Compared with the complete case analyses, the models using the imputed values obtained similar results for the association between the number of teeth and MMSE scores (Tables 2 and 3). This association was also confirmed in non-parametric bootstrapping for the complete case analyses: in Tobit regression, the coefficient for the number of teeth was 0.052 (95% CI: 0.018–0.86; $p = 0.003$) in females and 0.004 (95% CI: -0.030–0.038; $p = 0.831$) in males. In linear regression, the corresponding coefficients were 0.050 (95% CI: 0.020–0.81; $p = 0.001$) and 0.005 (95% CI: -0.026–0.036; $p = 0.748$), in females and males, respectively.

Discussion

In our analyses, we found a significant association between tooth loss and cognitive impairment in females that was not accounted for by age, BMI, cardiovascular parameters and psychosocial parameters like school education, income, smoking and alcohol consumption. Our rigorous adjustment for putative psychosocial confounders, like education, income, social network and children, which could have affected both oral health status and cognitive function, argues for the validity of our results. Neither in females nor in males was the effect for the number of teeth on the cognitive status modified by any other factor of the final model (Hyman 2006). Unexpectedly, the number of children was associated with cognitive impairment in both genders, indicating psychosocial or psychobiological mechanisms for this association (Christensen et al. 1998).

Table 2. Relation between the number of teeth and cognitive impairment (Mini Mental Status Examination score)

Model	Women			Men		
	coefficient (SE)	95% CI	*p* value	coefficient (SE)	95% CI	*p* value
Complete case (women: $n = 497$; men: $n = 562$)						
Number of teeth adjusted for age	0.085 (0.017)	0.051–0.119	<0.001	0.045 (0.017)	0.012–0.078	0.007
Number of teeth adjusted for age, school education and household income	0.062 (0.017)	0.028–0.095	<0.001	0.015 (0.016)	−0.017–0.047	0.359
Number of teeth adjusted for age, school education, household income, smoking status, hypertension, diabetes mellitus, body mass index and alcohol consumption	0.061 (0.017)	0.027–0.095	<0.001	0.009 (0.017)	−0.023–0.042	0.570
Number of teeth adjusted for age, school education, household income, smoking status, hypertension, diabetes mellitus, body mass index, alcohol consumption and number of children	0.052 (0.017)	0.020–0.085	0.002	0.004 (0.017)	−0.029–0.037	0.825
Combined imputation (women: $n = 615$; men: $n = 690$)						
Number of teeth adjusted for age	0.076 (0.017)	0.042–0.110	<0.001	0.051 (0.017)	0.016–0.085	0.004
Number of teeth adjusted for age, school education and household income	0.054 (0.017)	0.020–0.088	0.002	0.020 (0.017)	−0.014–0.053	0.255
Number of teeth adjusted for age, school education, household income, smoking status, hypertension, diabetes mellitus, body mass index and alcohol consumption	0.053 (0.017)	0.019–0.087	0.003	0.016 (0.017)	−0.018–0.050	0.366
Number of teeth adjusted for age, school education, household income, smoking status, hypertension, diabetes mellitus, body mass index, alcohol consumption and number of children	0.045 (0.017)	0.011–0.079	0.010	0.011 (0.017)	−0.023–0.045	0.521

Tobit regression analysis, dependent variable Mini Mental Status Examination score. In complete case analyses, there were 45 right-censored observations at MMSE score $\geqslant 30$ in women and 62 right-censored observations in men.

As we assessed tooth loss cross-sectionally, we could not make valid statements about the cause of tooth loss. Thus, we have to discuss the limitations of our study and the different pathways between tooth loss and cognitive impairment: (i) tooth loss and periodontitis, (ii) tooth loss and SES and (iii) reversed causality.

People loose teeth for various reasons; in adolescents and young adults, nearly all teeth might be lost because of caries and in middle aged and older adults, tooth loss also reflects a long-term history of periodontal disease. Periodontitis is estimated to be responsible for 50% of all extraction in subjects >40 years of age (Reich & Hiller 1993, Phipps & Stevens 1995). In populations where a tangible portion of tooth loss results from ''periodontal'' treatment decisions (Splieth et al. 2002), tooth loss imposes a selection bias at the periodontal tooth level, in that only the periodontally less diseased teeth tend to remain for examination in epidemiologic studies. Thus, the periodontally most susceptible subjects do not have any longer teeth and subjects with remaining teeth, although periodontally diseased must be considered as ''survivors''. This paradoxical epidemiological finding seems to be, at first glance, counterintuitive for a clinician. Similiar findings have been repeatedly reported in different populations with different aspects of periodontal–systemic relationships (Desvarieux et al. 2003, Abnet et al. 2005, Michaud et al. 2008). In subjects in whom tooth loss is due to periodontal disease, the overt signs of periodontal disease are removed whereas the systemic damage may partly persist on slow-developing chronic diseases. The rate of periodontal disease progression is most pronounced in younger decades and seems to level off in older subjects (Schatzle et al. 2003). Thus, it may be hypothesized that the systemic impact of periodontal disease is more pronounced in younger than in older subjects as it has been shown for cardiovascular disease (Desvarieux et al. 2004, Grau et al. 2004, Dietrich et al. 2008). In conclusion, there is clear evidence that tooth loss reflects periodontal history and that periodontal disease is associated with systemic inflammatory diseases.

The second explanation of our finding relates to socio-economic status (SES). Research has shown that low SES, as defined by education (early life), and social class based on occupation or income (midlife) are significant risk factors for a number of negative health outcomes, including cognitive impairment (Schmand et al. 1997, Lee et al. 2003) and tooth loss (Gilbert et al. 2003, Thomson et al. 2004). When education and income are entered in our model, the age-adjusted coefficient of tooth loss is reduced by 28% in females. The coefficient, however, was only slightly attenuated when we included biological and behavourial variables such as hypertension, diabetes, BMI or smoking and alcohol consumption. But it was further reduced by 8% when the number of children was included. These changes of the coefficient point to the importance of SES and social support as important mechanisms that contribute both to tooth loss and cognitive impairment. It may be that our finding of tooth loss as a risk factor for cognitive impairment reflects residual confounding of SES.

Reversed causality may also be a further explanation for our results. Cross-sectional and longitudinal studies have shown that patients with dementia are more likely to have or to develop poor oral health because they have impaired possibilities to perform proper oral hygiene measures or to regularly attend a dentist for checkups and prophylaxis (Ghezzi & Ship 2000, Chalmers et al. 2003, Henriksen et al. 2005, Musacchio et al. 2007). Most published

Table 3. Variables included in the final model for cognitive impairment (Mini Mental Status Examination score)

	Women						men					
	complete case $n = 497$			combined imputation $n = 615$			complete case $n = 562$			Combined imputation $n = 690$		
	β	SE	p value	β	SE	p value	β	SE	p value	β	SE	p value
Intercept	26.170	0.719	<0.001	26.426	0.663	<0.001	25.809	0.832	<0.001	25.488	0.829	<0.001
Number of teeth	0.052	0.017	0.002	0.045	0.017	0.010	0.004	0.017	0.825	0.011	0.017	0.521
Age groups (reference: 60 - 64 years)												
65–69 years	−0.403	0.386	0.296	−0.392	0.392	0.320	−0.235	0.381	0.538	−0.098	0.382	0.798
70–74 years	−0.118	0.382	0.757	0.177	0.357	0.621	−0.048	0.409	0.907	0.054	0.424	0.898
⩾75 years	−0.398	0.413	0.336	−0.244	0.413	0.556	−0.737	0.450	0.102	−0.511	0.426	0.230
School education (reference: 8 years)												
10 years	1.103	0.407	0.007	0.773	0.388	0.047	0.691	0.357	0.053	0.581	0.401	0.148
12 years	2.368	0.630	<0.001	1.976	0.623	0.002	1.986	0.376	<0.001	2.133	0.388	<0.001
Income (reference: 1st quintile)												
2nd quintile	0.758	0.438	0.084	0.711	0.449	0.117	−0.421	0.542	0.437	−0.014	0.544	0.979
3rd quintile	0.985	0.432	0.023	0.747	0.413	0.071	1.056	0.480	0.028	1.172	0.457	0.011
4th quintile	1.062	0.466	0.023	0.943	0.433	0.030	1.336	0.491	0.007	1.524	0.526	0.006
5th quintile	1.652	0.538	0.002	1.511	0.519	0.004	1.535	0.496	0.002	1.631	0.589	0.011
Smoke status (reference: never smoker)												
Ex − smoker	−0.247	0.357	0.490	−0.092	0.356	0.796	0.084	0.376	0.823	0.124	0.364	0.733
Current smoker	0.330	0.462	0.476	0.631	0.491	0.207	0.021	0.535	0.969	−0.422	0.532	0.428
Hypertension	0.217	0.351	0.537	0.108	0.326	0.741	−0.301	0.386	0.436	−0.144	0.377	0.703
Diabetes mellitus	−0.058	0.415	0.889	−0.156	0.376	0.678	−0.649	0.343	0.059	−0.552	0.341	0.107
Body mass index (reference: <25 kg/m^2)												
Overweight; ⩾25 kg/m^2	−0.644	0.391	0.101	−0.652	0.354	0.065	0.092	0.381	0.808	−0.082	0.379	0.829
Obesity; ⩾30 kg/m^2	−0.394	0.427	0.357	0.661	0.383	0.084	−0.131	0.426	0.760	−0.396	0.432	0.360
Alcohol consumption (reference: 0 g/day)												
>0–10 g	−0.376	0.367	0.305	−0.237	0.358	0.509	0.568	0.479	0.237	0.583	0.435	0.182
>10–20 g	0.559	0.449	0.214	0.424	0.450	0.348	0.403	0.394	0.307	0.112	0.428	0.794
>20–30 g	−0.497	0.701	0.479	−0.288	0.705	0.683	1.335	0.474	0.005	0.886	0.451	0.050
>30 g	0.532	0.595	0.372	0.425	0.605	0.482	0.546	0.364	0.134	0.589	0.366	0.110
Number of children (reference: 0)												
1	−1.068	0.578	0.065	−0.884	0.526	0.094	−0.978	0.519	0.060	−0.939	0.590	0.119
2	−1.218	0.566	0.032	−1.275	0.516	0.014	−0.121	0.481	0.802	−0.217	0.492	0.660
3	−1.637	0.659	0.013	−1.728	0.576	0.003	−0.829	0.577	0.151	−0.764	0.572	0.183
4	−0.950	0.717	0.186	−1.330	0.652	0.042	−1.226	0.648	0.059	−1.187	0.672	0.081
⩾5	−3.010	0.848	<0.001	−2.969	0.745	<0.001	−1.562	0.618	0.012	−1.573	0.589	0.008

Tobit regression analysis, dependent variable: Mini Mental Status Examination score; SE: standard error; income is related to the income per square root of the number of household members.

reports have investigated community residents or institutionalized populations with severe dementia who were impeded in their oral care (Ghezzi & Ship 2000). As SHIP is a general population survey, the degree of cognitive impairment was low in most of the older subjects recruited; the MMSE scores had a mean of 26 out of 30 (with 0 being the worst and 30 being healthy). We assume that participants in our study had sufficient mental resources to perform proper oral home care or to attend a dentist. Furthermore, we did not include institutionalized subjects in our population.

A further issue merits discussion: why did we find a significant association between tooth loss and cognitive impairment only in females but not in males? This finding is in contrast to reports of the association of CVD and periodontitis where associations were reported only in younger males (Dietrich et al. 2008). Men included in our complete case analyses were healthier (e.g. more teeth, higher MMSE scores, less frequently smokers) than those excluded because of missing data. On the contrary, the women excluded from the complete case analyses had better education, less alcohol consumption and showed more physical activity. Therefore, women included in the complete case analyses were relatively sicker by selection than those excluded. However, we additionally performed imputation analyses that statistically simulated the cases with missing data in some of the parameters. These analyses confirmed the results of the complete case analyses. Thus, a selection bias because of missing data could not explain the differences in gender that were observed in our study. It is noteworthy that males (age-adjusted model) also showed an association between the number of teeth and MMSE scores. However, parameters like education and income emerged as potent confounders for this association in males but not in females.

Considering the recent prospective findings of an association of elevated systemic pro-inflammatory markers and

the development of dementia and the systemic effects of chronic periodontitis, our findings lend support to the hypothesis that longstanding chronic inflammatory conditions because of periodontitis may be related to cognitive impairment. Our cross-sectional results support a longitudinal finding of the Nun Study with 144 nuns, who have been followed over a decade. The authors reported that subjects with fewest teeth had the highest risk of incidence of dementia (Stein et al. 2007). Our findings have been corroborated by recent analyses of NHANES (1999–2002) by Wu et al. (2008). In a review, Kamer et al. (2008) summarized and discussed evidence for an association between periodontitis and Alzheimer's dementia.

There are several lines of reasoning indicating why the putative association between periodontitis and cognitive impairment may be relevant from a public health perspective: (1) Periodontitis is highly prevalent and leaves 20–30% of the adult population at a high risk for chronic inflammatory processes. (2) Because more teeth are saved from caries and because life expectancy is extended, more teeth will be at risk for periodontitis (Micheelis & Schiffner 2006). (3) In an ageing population, the prevalence of cognitive impairment increases tremendously. (4) In an ageing population, systemic inflammatory conditions may interact with immune functions in the brain and trigger the progression of Alzheimer's neuropathology. (5) Periodontitis is a curable disease. (6) The treatment of periodontits and retention of teeth could delay or alleviate cognitive impairment.

The hypothesis that periodontitis, as a chronic pro-inflammatory condition, increases the long-term risk for cognitive impairment should be investigated in prospective studies.

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Clinical Relevance

Scientific rationale for the study: Currently, an extensive search is ongoing for modifiable risk factors for cognitive impairment. Chronic subclinical inflammation may elevate the risk of cognitive impairment. We tested the hypothesis that tooth loss as a sequel of chronic periodontitis is associated with cognitive impairment in the elderly.

Principal findings: In the fully adjusted models, tooth loss was associated with cognitive impairment in females but not in males.

Principal implications: Only longitudinal studies with a sufficient observation time will allow to understand the potential pathways of how periodontitis and/or tooth loss acts on cognitive impairment.