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Oral health status in relation to cognitive function among older Japanese

Masanori Iwasaki[1,6], Yumi Kimura[2], Akihiro Yoshihara[3], Hiroshi Ogawa[1], Takayuki Yamaga[1], Misuzu Sato[1], Taizo Wada[2], Ryota Sakamoto[2], Yasuko Ishimoto[2], Eriko Fukutomi[2], Wenling Chen[4], Hissei Imai[4], Michiko Fujisawa[2], Kiyohito Okumiya[2], George W. Taylor[5], Toshihiro Ansai[6], Hideo Miyazaki[1] & Kozo Matsubayashi[2,4]

[1]Division of Preventive Dentistry, Department of Oral Health Science, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[2]Center for Southeast Asian Studies, Kyoto University, Kyoto, Japan
[3]Division of Oral Science for Health Promotion, Department of Oral Health and Welfare, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[4]Department of Field Medicine, School of Public Health, Kyoto University, Kyoto, Japan
[5]Department of Preventive and Restorative Dental Sciences, University of California San Francisco, San Francisco, California, USA
[6]Division of Community Oral Health Development, Kyushu Dental University, Kitakyushu, Japan

Keywords

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Correspondence

Masanori Iwasaki Division of Community Oral Health Development, Kyushu Dental University, 2-6-1 Manazuru, Kokurakita-ku, Kitakyushu, 803-8580, Japan.
Tel: +81-93-582-1131 (ex. 2103)
Fax: +81-93-591-7736
E-mail: r14iwasaki@fa.kyu-dent.ac.jp

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Abstract

Epidemiologic data examining the relationship between oral health status and cognitive status are sparse, especially in Asian populations. This study aimed to assess whether periodontal disease and tooth loss were related to cognitive impairment among older Japanese. Study participants were 291 Japanese (101 men and 190 women, average age: 80.9 years), classified into three groups based on a clinical examination of oral health status: no periodontal disease, periodontal disease, and edentulous. Periodontal disease was defined using criteria recommended in the consensus report of the European Workshop in Periodontology with a modification. Cognitive impairment was defined using the results of the Mini-mental State Examination (MMSE) and Hasegawa Dementia Scale-Revised (HDS-R) scores. Multivariable logistic regression analyses assessed the relationship of the three-category oral health status variable (reference category = no periodontal disease) with low MMSE score (≤23) and low HDS-R score (≤20). Age, gender, years of education, body mass index, smoking status, drinking behavior, and history of cardiovascular disease were tested as potential confounders in the multivariable models. Periodontal disease and edentulous were significantly associated with greater odds of low cognitive performance after controlling for potential confounders. The multivariable adjusted odds ratios (ORs) (95% confidence intervals [CIs]) for low MMSE score associated with periodontal disease and edentulous were 2.21 (1.01–4.84) and 2.28 (1.06–4.90), respectively. The multivariable adjusted ORs (95% CIs) for low HDS-R score associated with periodontal disease and edentulous were 4.85 (1.29–18.15) and 3.86 (1.05–14.20), respectively. Poor oral health status was significantly associated with cognitive impairment among community-dwelling older Japanese. Additional well-controlled longitudinal studies are needed to elucidate whether there may be a possible cause-and-effect relationship between oral health status and cognitive function.

Introduction

Cognitive impairment and dementia are recognized as an important age-related public health problem. Japan has become a super-aged society, with the highest proportion of older people in the world. In 2010, there were 29.0 million people (22.7% of the total population) over the age of 65 (Cabinet Office, Government of Japan, n.d.). A recent study reported that the prevalence of dementia among those aged ≥65 years in Japan was >10%, which represents more than three million older individuals. This number is expected to increase to 3.25 million by 2020 (Asada, 2012). Dementia is characterized by irreversible decline in global intellectual, social, and physical functioning, which leads to a significant adverse impact on quality of life (Banerjee et al., 2006). In addition, the economic burden of dementia is immense. Hurd et al. (2013) reported that the yearly monetary cost per person that was attributable to dementia was up to $US56,000. In 2012, the Ministry of Health, Labor, and Welfare of Japan formulated a 5-year plan for the early detection of dementia and to improve care for people with dementia (“Orange Plan”) (Nakanishi & Nakashima, 2014).

According to previous reports, there are several risk factors for cognitive decline and dementia: age, ethnicity, sex, physical activity, smoking, drug use, and alcohol consumption (Chen et al., 2009). Several cardiovascular risk factors (e.g., hypertension, dyslipidemia, and diabetes) (Fillit et al., 2008) and cardiovascular disease (CVD) itself (Stampfer, 2006) are also suggested to increase the risk of dementia. In addition, potentially significant associations between cognitive impairment and poor oral health status including periodontal disease and tooth loss have been reported in previous epidemiological studies. Kaye et al. (2010) demonstrated that, in older men, rates of periodontal disease progression and tooth loss were associated with increased risk of poor cognitive performance. However, evidence from well-designed studies is limited, especially among Asian populations. Further studies are needed to increase the generalizability and to reach a consensus on the association between cognitive status and oral health status. Therefore, this study was planned with the purpose of assessing whether periodontal disease and tooth loss were related to cognitive impairment among older Japanese.

Materials and Methods

Study design

This is a cross-sectional study.

Selection of study participants

In April 2010, all 960 individuals aged ≥75 years currently residing in the town of Tosa, Kochi Prefecture, Japan, except for 150 individuals living in hospitals or nursing homes, were sent a written request to participate in the geriatric health survey. Subsequently, 333 (34.7% [333/960]) responded positively to participating in the survey. In August 2010, study participants underwent dental examination, cognitive assessment, interviews, and anthropometric evaluation at a community center. Forty-two individuals did not submit complete data. Data were, therefore, available from 291 participants (101 men and 190 women, average age: 80.9 years).

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by The Ethical Committee of Faculty of Medicine, Kyoto University in Kyoto, Japan (E-514). Written informed consent was obtained from study participants. In case of incapacitated persons, close family members provided the consent.

Dental examination

Two qualified dentists, using sufficient artificial illumination, assessed the following parameters:

1. Attachment loss (AL): a pressure-sensitive probe (Vivacare TPS probe, Vivadent Co., Schaan, Liechtenstein) was used to measure to the nearest millimeter the distance from the cementoenamel junction (CEJ) to the base of the pocket, at six sites of all remaining teeth. In sites where the CEJ was unclear because it was concealed by the margin of the crown restoration, the position of the CEJ was estimated using adjacent landmarks and dental anatomy. When the CEJ could not be estimated, the site was excluded from the examination.
2. The number of teeth: the number of teeth (including the third molar) was counted (Moss et al., 2006). Dental implants were not included in the count.

Cognitive assessment

Cognitive status was assessed by a licensed clinical psychotherapist using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Hasegawa Dementia Scale-Revised (HDS-R) scores (Kato et al., 1991). MMSE and HDS-R are commonly used screening tests for cognitive impairment in older adults. The scores for both tests range from 0 to 30, and lower scores indicate poorer performance and greater cognitive impairment (Folstein et al., 1975; Kato et al., 1991).

Questionnaire and anthropometric evaluation

The participants completed a questionnaire containing items regarding age, years of school attendance, smoking status, drinking behavior, and history of CVD. All answers to the questionnaire were confirmed by trained nurses.

Anthropometric evaluation included measurements of height and weight to calculate body mass index (BMI).

Description of main exposure variable

The principal exposure variable was oral health status based on a clinical examination and categorized as no periodontal disease, periodontal disease, or edentulous. Periodontal disease was defined using criteria recommended in the consensus report of the European Workshop in Periodontology with a modification (Tonetti & Claffey, 2005).

Specifically, periodontal disease was defined as having interproximal AL ≥5 mm in ≥50% of teeth. Edentulous was defined as having lost all natural teeth.

Description of outcome variables

Two cognitive impairment outcome variables were defined based on the results of MMSE and HDS-R, respectively. A low MMSE score was defined using a cutoff point of 23/24. This cutoff point was reported to have a sensitivity of 83% and specificity of 93% in the diagnosis of dementia among Japanese (Mori et al., 1985). A low HDS-R score was defined using the cutoff point of 20/21. This cutoff point was reported to have a sensitivity of 90% and specificity of 82% in the diagnosis of dementia among Japanese (Kato et al., 1991).

Statistical analyses

Initially, analysis of variance for continuous variables and the chi-square test for categorical variables were used to test for differences in the means and percentages of selected characteristics among the three study groups. Bonferroni's multiple comparison correction was used for investigating differences between pairs.

Tests of the study's principal hypothesis – that poor oral health status is associated with cognitive impairment – included univariable and multivariable logistic regression modeling. The primary outcomes of the analyses were low MMSE score and low HDS-R score coded as binary variables. The principal exposure variable included the three-category oral health status variable with no periodontal disease as the reference category. Age, gender, years of education, BMI, smoking status, drinking behavior, and history of CVD were tested as potential confounders in the multivariable models based on previous studies (Stampfer, 2006; Chen et al., 2009).

The level of significance was set at $\alpha = 0.05$. All calculations and statistical analyses were performed using the statistical software package STATA (version 12) (Stata Corp., TX).

Results

Among 291 study participants, 108 (37.1% [108/291]) had no teeth. Of the remaining 183 dentate participants, 84 (45.9% [84/183]) were defined as having periodontal disease. Mean MMSE score was 25.9 (standard deviation [SD] = 3.4), and mean HDS-R score was 25.9 (SD = 3.8). Out of all study participants, 70 (24.1% [70/291]) had an MMSE score ≤23, and 32 (11.0% [32/291]) had an HDS-R score ≤20.

Table 1 shows study participants' characteristics by dentition status. Significant differences were observed in age, years of education, and BMI. Edentulous participants were older than participants with or without periodontal disease ($P < 0.05$). Participants with periodontal disease had fewer years of education than participants without periodontal disease ($P < 0.05$). Edentulous participants had lower BMI than participants without periodontal disease ($P < 0.05$).

Table 2 shows the results from logistic regression analyses of the relationship between oral health status and cognitive

Table 1. Selected characteristics of study participants by oral health status.

	All participants	Oral health status			
		No periodontal disease	Periodontal disease	Edentulous	
	n = 291	*n* = 99	*n* = 84	*n* = 108	*P*[†]
Demographic and socioeconomic status					
Age, mean (SD)	80.9 (4.5)	**79.4 (4.2)[a]**	**80.4 (4.0)[a]**	**82.6 (4.6)[b]**	**<0.01**
Gender, *n* (%)					
Men	101 (34.7)	32 (32.3)	36 (42.9)	33 (30.6)	0.17
Women	190 (65.3)	67 (67.7)	48 (57.1)	75 (69.4)	
Years of education, mean (SD)	8.9 (1.8)	**9.3 (2.0)[a]**	**8.5 (1.7)[b]**	**8.9 (1.6)**	**0.01**
Health status and health behavior					
BMI (kg/m^2) , mean (SD)	22.7 ± 3.3	**23.2 (3.0)[a]**	**22.8 (3.6)**	**22.0 (3.2)[b]**	**0.03**
Smoking status, *n* (%)					
Never smoked	210 (72.2)	75 (75.8)	60 (71.4)	75 (69.4)	0.59
Previous/current smoker	81 (27.8)	24 (24.2)	24 (28.6)	33 (30.6)	
Drinking behavior, *n* (%)					
Drink alcohol everyday	29 (10.0)	13 (13.1)	8 (9.5)	8 (7.4)	0.38
History of CVD, *n* (%)	60 (20.6)	21 (21.2)	16 (19.1)	23 (21.3)	0.92

Values in a row without a common superscript letter significantly differ as detected by multiple comparison tests (Bonferroni's method).
Bold text highlights statistically significant findings ($P < 0.05$); SD – standard deviation; BMI – body mass index; CVD – cardiovascular disease.
[†]*P* value for the comparison of selected characteristics among different study groups.

Table 2. Logistic regression analyses of the relationship between oral health status and cognitive performance, showing effects as odds ratios and 95% confidence intervals.

	Outcome = MMSE score ≤23		
	Model 1 (oral health status only)	Model 2 (model 1 + age)	Model 3 (all predictor variables)
Oral health status			
No periodontal disease (reference)	1.00	1.00	1.00
Periodontal disease†	2.80 (1.33–5.92)*	2.68 (1.27–5.69)*	2.21 (1.01–4.84)*
Edentulous	2.79 (1.36–5.69)*	2.39 (1.14–5.02)*	2.28 (1.06–4.90)*
Demographic and socioeconomic status			
Age		1.05 (0.99–1.12)	1.00 (0.93–1.07)
Gender			
Women			1.00
Men			1.45 (0.76–2.80)
Years of education			0.77 (0.63–0.93)*
Health status and health behavior			
BMI (kg/m^2)			0.90 (0.82–0.98)*
Smoking status			
Never smoked			1.00
Previous/current smoker			0.69 (0.35–1.37)
Drinking behavior			
Drink alcohol everyday			0.40 (0.11–1.46)
History of CVD			1.56 (0.79–3.07)
	Outcome = HDS-R score ≤20		
	Model 4 (oral health status only)	Model 5 (model 4+ Age)	Model 6 (all predictor variables)
Oral health status			
No periodontal disease (reference)	1.00	1.00	1.00
Periodontal disease†	5.86 (1.61–21.33)*	5.14 (1.49–20.06)*	4.85 (1.29–18.15)*
Edentulous	5.57 (1.57–19.73)*	4.12 (1.13–15.04)*	3.86 (1.05–14.20)*
Demographic and socioeconomic status			
Age		1.10 (1.01–1.20)*	1.08 (0.99–1.18)
Gender			
Women			1.00
Men			1.19 (0.49–2.88)
Years of education			0.88 (0.68–1.13)
Health status and health behavior			
BMI (kg/m^2)			0.95 (0.85–1.08)
Smoking status			
Never smoked			1.00
Previous/current smoker			0.84 (0.34–2.13)
Drinking behavior			
Drink alcohol everyday			0.35 (0.04–2.90)
History of CVD			0.82 (0.31–2.17)

MMSE – Mini-mental State Examination; HDS-R – Hasegawa's Dementia Scale-Revised; BMI – body mass index; CVD – cardiovascular disease.
†Individuals who presented with interproximal attachment loss ≥5 mm in ≥50% of teeth.
*$P < 0.05$.

performance. Models 1–3 included low MMSE score as the outcome, and models 4–6 included low HDS-R score as the outcome. In the first column, models 1 and 4 show regression model results with only oral health status as a predictor (crude model). The second column, models 2 and 5, shows age-adjusted model results. The third column shows results for models 3 and 6 with modeling of all predictor variables (full model). In the development of the models, there were no interactions of oral health status with covariates in predicting cognitive impairment.

In models 1 and 4, periodontal disease and edentulous status were significantly associated with a greater odds of cognitive impairments. The crude odds ratios (ORs) (95% confidence interval [CI]) for low MMSE score associated with periodontal disease and edentulous were 2.80 (1.33–5.92) and 2.79 (1.36–5.69), respectively. The crude ORs (95% CI) for low HDS-R score associated with periodontal disease and edentulous were 5.86 (1.61–21.33) and 5.57 (1.57–19.73), respectively. For models 2 and 5, shown in the second column of Table 2, oral health status remained statistically significant.

Older age was also associated with greater OR of cognitive impairment in model 5. Models 3 and 6, shown in the third column of Table 2, indicated that oral health status remained significant after adjustment for other covariates. The multivariable adjusted ORs (95% CIs) for low MMSE score associated with periodontal disease and edentulous were 2.21 (1.01–4.84) and 2.28 (1.06–4.90), respectively. The multivariable adjusted ORs (95% CIs) for low HDS-R score associated with periodontal disease and edentulous were 4.85 (1.29–18.15) and 3.86 (1.05–14.20), respectively. Higher education and higher BMI were associated with lower ORs of cognitive impairment in model 3.

Discussion

In this study, an association was found between poor oral health status (periodontal disease and tooth loss) and cognitive impairment among community-dwelling older Japanese after adjusting for other important risk factors such as age and education level. This finding concurs with previous epidemiologic studies, although they included few Asian participants. Stewart and colleagues investigated the relationship between oral health status and cognitive function among adults participating in the Third National Health and Nutrition Examination Survey. They demonstrated that the proportion of sites with AL ≥3 mm was significantly associated with poor cognitive performance (Stewart et al., 2008). Kamer et al. (2012) reported that older adults with periodontal pockets ≥4 mm demonstrated impaired cognitive function. Grabe et al. (2009) reported that women with decreased number of teeth had lower scores in tests of cognitive function. Stein et al. (2007) used longitudinal data of dental and cognitive assessments of older individuals in the USA and demonstrated that a low number of teeth was associated with the higher incidence of dementia. The present study confirmed these previous findings and contributes additional evidence that suggests an association between oral health and cognitive function among older Japanese.

To the best of our knowledge, this is the first study performed in Japan demonstrating the association between poor periodontal status and cognitive impairment among older adults. On the other hand, one cross-sectional study conducted in Japan (Fujiwara-kyo Study) found no association between the periodontal status, assessed by means of Community Periodontal Index (CPI) and cognitive function test scores (Okamoto et al., 2010). Some researchers have expressed concern over discrepancies between partial-mouth examination and the full-mouth examination (Baelum et al., 1993; Eke et al., 2010). Because only 10 teeth were examined by the CPI method, it is likely that the prevalence of periodontal disease was underestimated. In addition, we recruited individuals aged ≥75 years, whereas the Fujiwara-kyo Study included individuals aged ≥65 years, resulting in a younger study population. The prevalence of dementia among people in their late 60s is about 1.5%, increasing to 7% in those in their late 70s and then rising dramatically in those in their 80s to between 12% and 16% (Shimokata, 2004). These facts could partially explain the difference in the findings between two studies, but further study would be necessary to clarify the reasons for the differences between the present study and the Fujiwara-kyo Study.

We chose not to apply the original definition proposed by the European Workshop in Periodontology to this very old study population because preliminary analysis revealed that the prevalence of periodontal disease among dentate participants based on the original definition was 57.4%. A nationwide survey in Japan reported that the prevalence of moderate or severe periodontal disease in people 75–84 years of age was 46.4% (The Ministry of Health, Labor, and Welfare, n.d.). This divergence may be explained by the fact that increasing age is a major risk factor for periodontal disease (Brown et al., 1994).

Increasing evidence suggests that periodontal disease poses a chronic systemic inflammatory burden, potentially contributing to vascular dysfunction and vascular disease, for example, atherosclerosis (Kinane & Lowe, 2000; Sprague & Khalil, 2009). Moreover, during the periodontal inflammatory response, excessive production of reactive oxygen species occurs, which causes oxidative stress (Chapple & Matthews, 2007). Vascular dysfunction and oxidative stress have important roles in the pathogenesis of dementia and cognitive impairment (Bennett et al., 2009; Liu & Chan, 2014). In addition, periodontal disease is suggested to be a risk factor for diabetes and CVD (Linden et al., 2013); therefore, periodontal disease may also have an effect on dementia indirectly through diabetes and CVD.

Periodontal disease is one of the leading causes of tooth loss in the elderly (Locker et al., 1996). Tooth loss has been associated with impaired chewing ability and changes in food preference (Yoshihara et al., 2005). Individuals who are either edentulous or have fewer teeth have a greater risk of nutritional deficiencies (Sheiham & Steele, 2001). Poor nutritional status, especially in relation to B vitamins, also plays a significant role in the pathogenesis of dementia and cognitive impairment (Tucker et al., 2005). Furthermore, in animal models, tooth loss was associated with neuroanatomical and neurochemical changes, which ultimately have adverse effects on learning and memory (Onozuka et al., 2002; Ono et al., 2010).

Although this study provides a novel finding that an association between oral health status and cognitive function was observed in an Asian (Japanese) older population, there is a potential risk that our final sample analyzed may not be representative of the target study population – community-based older Japanese. Only 291 participants out of 960 individuals aged ≥75 years currently residing in the town of Tosa in 2010 were analyzed. Those who declined to participate in the survey or who did not submit complete data might be more likely to be less concerned with their overall health (Sackett, 1979) and to have higher prevalence of periodontal disease, tooth loss, and cognitive impairment. In this context, the present sample may be healthier than the general population; therefore, the results based on this single study should be interpreted with some caution, because this selection bias may lead to overestimation or underestimation of the true association. Several other limitations to the present study merit discussion. First, our study had a cross-sectional design, which prevented us from assessing a temporal relationship and establishing causality. An assertion of reverse causality (i.e,, cognitive status affects oral health status) can be made for our results. In fact, some studies reported that patients with dementia have higher risk for poor oral health due to impaired possibility to perform proper oral hygiene measures or to regularly attend a dentist for checkups and treatments (Chalmers et al., 2003; Henriksen et al., 2005). Second, because other information previously recognized as relevant to dementia, such as apolipoprotein E genotype, family history of dementia, comorbidity, physical activity, serum lipid profiles, and nutrition (Huang et al., 2004; Quadri et al., 2004; Podewils et al., 2005; Formiga et al., 2009; Reynolds et al., 2010), was not collected, a number of other potentially important confounders could not be included in the analyses. Residual confounding remains a risk.

Conclusion

In summary, the findings of the present study suggest that periodontal disease and tooth loss are significantly associated with cognitive impairment among community-dwelling older Japanese. Additional well-controlled longitudinal studies are needed to elucidate whether there may be a possible cause-and-effect relationship between oral health status and cognitive function.

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Conflict of Interest

None declared.

References

Asada, T., 2012. Prevalence of dementia in Japan: past, present and future (in Japanese). Rinsho Shinkeigaku 52, 962–964.

Baelum, V., Fejerskov, O., Manji, F., Wanzala, P., 1993. Influence of CPITN partial recordings on estimates of prevalence and severity of various. Community Dent. Oral. 21, 354–359.

Banerjee S., Smith, S.C., Lamping, D.L., Harwood, R.H., Foley, B., Smith, P., et al. 2006. Quality of life in dementia: more than just cognition. An analysis of associations with quality of life in dementia. J. Neurol. Neurosur. Ps. 77, 146–148.

Bennett, S., Grant, M.M., Aldred, S., 2009. Oxidative stress in vascular dementia and Alzheimer's disease: a common pathology. J. Alzheimers Dis. 17, 245–257.

Brown, L.F., Beck, J.D., Rozier, R.G., 1994. Incidence of attachment loss in community-dwelling older adults. J. Periodontol. 65, 316–323.

Cabinet Office, Government of Japan. Annual Report on the Aging Society; available at: http://www8caogojp/kourei/english/annualreport/2010/pdf/p2-3pdf. 2010. [last accessed 8 Aug 2014].

Chalmers, J.M., Carter, K.D., Spencer, A.J., 2003. Oral diseases and conditions in community-living older adults with and without dementia. Spec. Care Dentist. 23, 7–17.

Chapple, I.L., Matthews, J.B., 2007. The role of reactive oxygen and antioxidant species in periodontal tissue destruction. Periodontol. 2000 43, 160–232.

Chen, J.H., Lin, K.P., Chen, Y.C., 2009. Risk factors for dementia. J. Formos. Med. Assoc. 108, 754–764.

Eke P.I., Thornton-Evans, G.O., Wei, L., Borgnakke, W.S., Dye, B. A., 2010. Accuracy of NHANES periodontal examination protocols. J. Dent. Res. 89, 1208–1213.

Fillit, H., Nash, D.T., Rundek, T., Zuckerman, A., 2008. Cardiovascular risk factors and dementia. Am. J. Geriatr. Pharmacother. 6, 100–118.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.

Formiga, F., Fort, I., Robles, M.J., Riu, S., Sabartes, O., Barranco, E., et al. 2009. Comorbidity and clinical features in elderly patients with dementia: differences according to dementia severity. J. Nutr. Health Aging 13, 423–427.

Grabe, H.J., Schwahn, C., Volzke, H., Spitzer, C., Freyberger, H.J., John, U., et al. 2009. Tooth loss and cognitive impairment. J. Clin. Periodontol. 36, 550–557.

Henriksen, B.M., Engedal, K., Axell, T., 2005. Cognitive impairment is associated with poor oral health in individuals in long-term care. Oral Health Prev. Dent. 3, 203–207.

Huang, W., Qiu, C., von Strauss, E., Winblad, B., Fratiglioni, L., 2004. APOE genotype, family history of dementia, and Alzheimer disease risk: a 6-year follow-up study. Arch. Neurol. 61, 1930–1934.

Hurd, M.D., Martorell, P., Langa, K.M., 2013. Monetary costs of dementia in the United States. N. Engl. J. Med. 369, 489–490.

Kamer, A.R., Morse, D.E., Holm-Pedersen, P., Mortensen, E.L., Avlund, K., 2012. Periodontal inflammation in relation to cognitive function in an older adult Danish population. J. Alzheimers Dis. 28, 613–624.

Kato, S., Shimogaki, H., Onodera, A., Ueda, H., Hasegawa, K., 1991. Development of the revised version of Hasegawa's dementia scale. Jpn. J. Geriatr. Ps. 2, 1339–1347.

Kaye, E.K., Valencia, A., Baba, N., Spiro, A., 3rd, Dietrich, T., Garcia, R.I., 2010. Tooth loss and periodontal disease predict poor cognitive function in older men. J. Am. Geriatr. Soc. 58, 713–718.

Kinane, D.F., Lowe, G.D.O., 2000. How periodontal disease may contribute to cardiovascular disease. Periodontol. 2000 23, 121–126.

Linden, G.J., Lyons, A., Scannapieco, F.A., 2013. Periodontal systemic associations: review of the evidence. J. Clin. Periodontol. 40(Suppl 14), S8–S19.

Liu, L., Chan, C., 2014. The role of inflammasome in Alzheimer's disease. Ageing Res. Rev. 15C, 6–15.

Locker, D., Ford J., Leake J.L., 1996. Incidence of and risk factors for tooth loss in a population of older Canadians. J. Dent. Res. 75, 783–789.

Mori, E., Mitani, Y., Yamadori, A., 1985. Usefulness of a Japanese version of the Mini-mental State Test in neurological patients (in Japanese). Shinnkei Shinrigaku 1, 2–10.

Moss, K.L., Mauriello, S., Ruvo, A.T., Offenbacher, S., White, R.P., Jr., Beck, J.D., 2006. Reliability of third molar probing measures and the systemic impact of third molar periodontal pathology. J. Oral Maxillofac. Surg. 64, 652–658.

Nakanishi, M., Nakashima, T., 2014. Features of the Japanese national dementia strategy in comparison with international dementia policies: how should a national dementia policy interact with the public health- and social-care systems? Alzheimers Dement. 10, 468–476.

Okamoto, N., Morikawa, M., Okamoto, K., Habu, N., Iwamoto, J., Tomioka, K., et al. 2010. Relationship of tooth loss to mild memory impairment and cognitive impairment: findings from the Fujiwara-kyo study. Behav. Brain Funct. 6, 77.

Ono, Y., Yamamoto, T., Kubo, K.Y., Onozuka, M., 2010. Occlusion and brain function: mastication as a prevention of cognitive dysfunction. J. Oral Rehabil. 37, 624–640.

Onozuka, M., Watanabe, K., Fujita, M., Tomida, M., Ozono, S., 2002. Changes in the septohippocampal cholinergic system following removal of molar teeth in the aged SAMP8 mouse. Behav. Brain Res. 133, 197–204.

Podewils, L.J., Guallar, E., Kuller, L.H., Fried, L.P., Lopez, O.L., Carlson, M., et al. 2005. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. Am. J. Epidemiol. 161, 639–651.

Quadri, P., Fragiacomo, C., Pezzati, R., Zanda, E., Forloni, G., Tettamanti, M., et al. 2004. Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. Am. J. Clin. Nutr. 80, 114–122.

Reynolds, C.A., Gatz, M., Prince, J.A., Berg, S., Pedersen, N.L., 2010. Serum lipid levels and cognitive change in late life. J. Am. Geriatr. Soc. 58, 501–509.

Sackett, D.L., 1979. Bias in analytic research. J. Chronic Dis. 32, 51–63.

Sheiham, A., Steele, J., 2001. Does the condition of the mouth and teeth affect the ability to eat certain foods, nutrient and dietary intake and nutritional status amongst older people? Public Health Nutr. 4, 797–803.

Shimokata, H., 2004 Epidemiological statistics of dementia in Japan (in Japanese). Nihon Rinsho 62(Suppl 4), 121–126.

Sprague, A.H., Khalil, R.A., 2009. Inflammatory cytokines in vascular dysfunction and vascular disease. Biochem. Pharmacol. 78, 539–552.

Stampfer, M.J., 2006. Cardiovascular disease and Alzheimer's disease: common links. J. Intern. Med. 260, 211–223.

Stein, P.S., Desrosiers, M., Donegan, S.J., Yepes, J.F., Kryscio, R.J., 2007. Tooth loss, dementia and neuropathology in the Nun study. J. Am. Dent. Assoc. 138, 1314–1322; quiz 81–82.

Stewart, R., Sabbah, W., Tsakos, G., D'Aiuto, F., Watt, R.G., 2008. Oral health and cognitive function in the Third National Health and Nutrition Examination Survey (NHANES III). Psychosom. Med. 70, 936–941.

The Ministry of Health, Labour, and Welfare. 2011. Survey of Dental Diseases; available at: http://wwwmhlwgojp/toukei/list/62-23html. 2011. [last accessed 8 Aug 2014].

Tonetti, M.S., Claffey, N., 2005. Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research. Group C consensus report of the 5th European Workshop in Periodontology. J. Clin. Periodontol. 32(Suppl 6), 210–213.

Tucker, K.L., Qiao N., Scott T., Rosenberg I., Spiro A., 3rd., 2005. High homocysteine and low B vitamins predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study. Am. J. Clin. Nutr. 82, 627–635.

Yoshihara, A., Watanabe R., Nishimuta M., Hanada N., Miyazaki H., 2005. The relationship between dietary intake and the number of teeth in elderly Japanese subjects. Gerodontology 22, 211–218.

