ORAL DISEASES
Leading in Oral, Maxillofacial, Head & Neck Medicine

Oral Diseases (2016) 22, 697–702 doi:10.1111/odi.12529

www.wiley.com

ORIGINAL ARTICLE

Association of cognitive function with tooth loss and mitochondrial variation in adult subjects: a community-based study in Beijing, China

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OBJECTIVES: Cognitive impairment is a common neurological problem in elderly people. In this study, we investigated whether tooth loss, periodontal parameters, and gene variations in the mitochondrial DNA displacement loop region are potential influencing factors on cognitive function.

DESIGN: We employed a linear regression model to estimate cross-sectional association between number of teeth lost, periodontal parameters and Mini-mental State Examination score, adjusting for demographic factors, socioeconomic factors, general health status, smoking, drinking, and life habits.

PARTICIPANTS: A total of 905 Han Chinese people, ≥50 years of age, with complete data, were enrolled. Blood samples of 567 of the subjects were analyzed for correlation between mitochondrial DNA variants and Mini-mental State Examination score.

RESULTS: The number of teeth lost ($\beta = -0.042$, 95% CI: −0.061, −0.024, $P < 0.001$), two single nucleotide polymorphism (SNP) points: A189G ($\beta = -1.540$, 95% CI: −2.818, −0.263, $P = 0.018$) and A16164G ($\beta = -1.053$, 95% CI: −2.054, −0.052, $P = 0.039$) in the mitochondrial DNA displacement loop region, and haplogroup Y ($\beta = -2.152$, 95% CI: −4.062, −0.242, $P = 0.027$) were found to be negatively associated with Mini-mental State Examination scores in the fully adjusted model. No correlation was found between periodontal parameters and Mini-mental State Examination scores.

CONCLUSION: Number of teeth lost, mitochondrial SNPs, and haplogroup Y were correlated with cognitive function in this study population.

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Received 17 February 2016; revised 12 June 2016; accepted 21 June 2016

Oral Diseases (2016) **22**, 697–702

Keywords: cognitive function; haplogroup; mitochondria DNA; tooth loss

Introduction

In recent years, the global proportion of elderly people has increased rapidly. Cognitive impairment is a common neurological problem among the elderly, with incidence varying from 14.89% to 22.2% in different parts of the world (Qiu *et al*, 2007). Decline in cognitive function not only affects quality of life, but also increases social and familial burden. Studies have reported that every year, 8–25% of patients with mild cognitive impairment progress to dementia, 10 times higher than normal incidence of dementia. However, with suitable intervention in the preclinical phase or initial stage of dementia, the progress of dementia can be effectively slowed (Ball *et al*, 2002; Olazaran *et al*, 2004).

Common risk factors for cognitive impairment include genetic factors, hypertension, diabetes mellitus, hyperlipidemia, vascular disease, and lifestyle factors such as smoking and alcohol use. Protective factors include education, exercise, and active social engagement (Campbell *et al*, 2013; Gordon and Martin, 2013). However, approximately half of the cognitive impairment risk remains unexplained (Barnes and Yaffe, 2011). As a result, a search for potentially causal indicators of cognitive impairment is necessary.

This study aimed to provide new ideas for prevention of cognitive impairment, by evaluating whether tooth loss, periodontal parameters, and gene variations in the mitochondrial DNA D-loop region (including SNPs and haplogroups) were correlated with cognitive function in a Han Chinese population of community-dwelling adults aged 50 years and above, after adjusting for traditional risk factors for cognitive impairment.

Materials and methods

Design and study population

The study was approved by the Institutional Review Board and Ethics Committee of Peking University Health Science Center. Data collection was performed between May and July 2005. Residents served by a community hospital (Gucheng Hospital, Beijing, China) were invited to participate and a total of 1058 adults volunteered participation and signed informed consent. A total of 91 people <50 years were excluded and 62 were excluded due to incomplete data. Finally, 905 people (471 male and 434 female) aged 50 years or older with completed data were enrolled.

Participant assessment

Participants' demographic information, as well as information on socioeconomic status, lifestyle, and history of systemic diseases, including hypertension, diabetes, hyperlipidemia, and stroke, were collected using a standardized questionnaire. Education level of the participants was classified as low (middle school or below, <9 years of education), middle (high school, >9 ≤ 12 years), and high (>12 years). Family income was classified as low (≤USD 120.85 per month), average (>USD 120.86 per month but ≤USD 362.54 per month), or high (≥USD 362.55 per month) (Yu *et al*, 2014). Participants were classified as smokers/drinkers (ever smoked/drank alcohol, including those who had quit) or never smokers/drinkers, married or divorced/single, and exercising regularly or not.

Sitting blood pressure was measured three times using a mercury sphygmomanometer after 5 min rest and the mean of three systolic and diastolic measurements pressure used. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or ever diagnosed with hypertension.

Cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, fasting blood glucose, and postprandial blood glucose were measured with an automatic analyzer (Model 7060; Hitachi, Tokyo, Japan). High-density lipoprotein was measured by a direct method; low-density lipoprotein was calculated using the Friedewald equation. Blood glucose was measured using the glucose-hexokinase method. Hyperlipidemia was defined as previous diagnosis of hyperlipidemia and/or triglycerides ≥1.70 mmol l^{-1}, and/or cholesterol ≥5.80 mmol l^{-1}, and/or high-density lipoprotein ≤1.10 mmol l^{-1}, and/or low-density lipoprotein ≥4.00 mmol l^{-1}. Hyperglycemia was defined as impaired fasting glucose and impaired glucose tolerance as follows. Impaired fasting glucose: fasting plasma glucose ≥6.1 mmol l^{-1} < 7.0 mmol l^{-1}; impaired glucose tolerance: postprandial blood glucose ≥7.8 mmol l^{-1} < 11.1 mmol l^{-1}; or diabetes: fasting plasma glucose ≥7.0 mmol l^{-1} and/or postprandial blood glucose ≥11.1 mmol l^{-1} and/or ever diagnosed with diabetes.

Periodontal examination

A specially trained dentist from the Peking University School of Stomatology, China performed the periodontal examinations. Plaque index (PLI), probing depth (PD), clinical attachment loss (AL), and bleeding index (BI) were measured at mesio-buccal and distal-lingual sites for all teeth, excluding the third molars, using a Williams probe (Hu-Friedy, Chicago, IL, USA). Odds of total identity and error range within 1 or 2 mm were used. Eighty-one sites of three randomly selected periodontal patients were examined twice to test the reproducibility of the examiner's findings. The values were 85.2%, 98.8% and 100% for probing depth and 74.1%, 80.2%, and 97.5% for AL. Number of lost teeth and mean PLI, PD, AL, and BI were used. The third molars were excluded when accounting for number of lost teeth.

Cognitive function

The Mini-Mental State Examination (MMSE) was used to assess cognitive function, administered by psychologists and trained nurses. The MMSE, which measures various domains of cognitive function including orientation, recall, literacy and so on, is the most widely used tool for the screening of cognitive impairment in the world. One point is scored per question, with a maximum total of 30.

Analysis of mitochondrial DNA variants in the D-loop region

To analyze the DNA sequence of the mitochondrial D-loop region, peripheral blood samples from 567 of the 905 study subjects were collected with their informed consent. Two pairs of primers were synthesized and purified (Shanghai Sangon Corporation, Shanghai, China) according to the method introduced by Andrews *et al* (1999). The mtDNA D-Loop region was amplified in two separate PCRs performed in 25 ml reaction volume. Sequences were compared with the revised Cambridge Reference Sequences (rCRS; Gen Bank accession number NC_012920) using Nucleotide BLAST in NCBI (http://blast.ncbi.nlm.nih.gov/) and MITOMAP (http://www.mitomap.org) (Anderson *et al*, 1981; Andrews *et al*, 1999). The haplogroup classification was based on the phylogeny proposed by Van Oven and Kayser (2009) (Figure 1).

Statistical analysis

Variables were categorized and expressed as frequencies and percentages. For multivariate analysis, multiple linear regression modeling was used, adjusting for traditional risk factors for cognitive impairment, including age, sex, marriage status, family income, educational level, hyperlipidemia, hypertension, diabetes, stroke, and drinking/smoking/regular exercise habits. Tolerance was >0.45 and the variance inflation factor was <2.5 in the linear model. Hence, multicollinearity was not a concern. SPSS 20.0 for Windows (IBM, Armonk, NY, USA) was used for statistical analysis; $P < 0.05$ was considered statistically significant.

Results

Subject background

A total of 905 Chinese Han subjects aged 50 years and above (471 male and 434 female) met the inclusion criteria. Characteristics of the study participants and their mean MMSE score in category are shown in Table 1. A total of 68 (6.74%) participants were edentulous and most people had lost ≤10 teeth (n = 651, 71.93%).

Tooth loss and cognitive function

The correlation between number of teeth lost, periodontal parameters and MMSE score is shown in Table 2, with only number of teeth lost significantly correlating with MMSE score, after adjusting for age, sex, marriage status, family income, educational level, hyperlipidemia, hypertension, diabetes, stroke, and drinking/smoking/regular exercise habits ($\beta = -0.042$, 95% CI: −0.061, −0.024, $P < 0.001$).

Mitochondrial D-loop variations and cognitive function

Of the 567 participants who had D-loop region DNA sequence analysis (Table 3), two SNPs were found to be negatively correlated with MMSE score after adjusting for

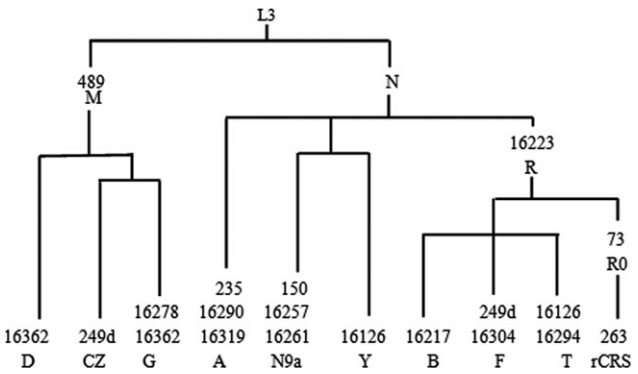

Figure 1 The phylogenetic tree of mitochondrial haplogroup classification, including revised Cambridge Reference Sequence (rCRS). The diagnostic mitochondrial D-Loop region DNA variation markers used for haplogroup classification, according to the mitochondrial DNA rCRS, are reported along the tree branches. The tree is rooted in macrohaplogroup L3. The suffix 'd 'indicates deletion.

Table 1 Characteristics of the study sample (total 905 subjects)

	Number (proportion, %)	*Mean MMSE (95% CI)*
Gender		
Female	434 (47.96)	27.78 (27.52, 28.05)
Male	471 (52.04)	28.15 (27.95, 28.35)
Age		
50–65	477 (52.70)	28.76 (28.62, 28.90)
66–75	379 (41.88)	27.32 (27.04, 27.60)
>75	49 (5.42)	25.39 (24.29, 26.49)
MMSE score		
≤23	62 (6.85)	21.19 (20.55, 21.84)
24–26	117 (12.93)	25.41 (25.28, 25.54)
27–30	726 (80.22)	28.97 (28.89, 29.04)
Education		
≤9 years	571 (63.10)	27.40 (27.17, 27.62)
<9 ≤ 12 years	192 (21.21)	28.79 (28.56, 29.02)
>12 years	142 (15.69)	29.19 (29.01, 29.37)
Income		
Low	84 (9.28)	27.50 (26.88, 28.12)
Moderate	718 (79.34)	27.90 (27.72, 28.08)
High	103 (11.38)	28.87 (28.55, 29.02)
Marital status		
Married	810 (89.50)	28.10 (27.93, 28.26)
Divorced or Single	95 (10.50)	26.95 (26.34, 27.56)
Pathoglycemia		
Yes	365 (40.33)	27.88 (27.62, 28.14)
No	540 (59.67)	28.04 (27.83, 28.25)
Hypertension		
Yes	726 (80.22)	27.94 (27.75, 28.12)
No	179 (19.78)	28.13 (27.81, 28.44)
Hyperlipidemia		
Yes	657 (72.60)	28.00 (27.81, 28.18)
No	248 (27.40)	27.92 (27.59, 28.24)
Stroke		
Yes	160 (17.68)	27.41 (26.94,27.88)
No	745 (82.32)	28.09 (27.93,28.26)
Regular exercise		
Yes	772 (85.30)	28.05 (27.89, 28.22)
No	133 (14.70)	27.57 (27.04, 28.11)
Drinking		
Yes	162 (17.90)	28.41 (28.13, 28.69)
No	742 (82.10)	27.88 (27.69, 28.06)
Smoking		
Yes	313 (34.59)	28.05 (27.81, 28.30)
No	592 (65.41)	27.93 (27.72, 28.14)
No. tooth lost		
0–10	651 (71.93)	28.37 (28.21, 28.54)
11–27	193 (21.33)	27.16 (26.75, 27.57)
28	61 (6.74)	26.26 (25.35, 27.17)

Values in *n* (%) or 95% confidence interval (CI).

traditional risk factors: A189G ($\beta = -1.540$, 95% CI: −2.818, −0.263, $P = 0.018$) and A16164G ($\beta = -1.053$, 95% CI: −2.054, 0.052, $P = 0.039$), respectively.

Mitochondrial haplogroup Y and cognitive function

A total of 12 haplogroups were found among the participants, including A, B, CZ, D, F, G, M, N, N9, R, T, and Y (Figure 1). After adjusting for traditional risk factors (Table 3), haplogroup Y, with a proportion of 0.88% of subjects, was found to be associated with cognitive function ($\beta = -2.152$, 95% CI: −4.062, −0.242, $P = 0.027$).

Tooth loss and cognitive function after adjusting for mitochondrial gene variants

After adjusting for traditional risk factors for cognitive impairment and mitochondrial DNA D-loop SNPs (Table 4), number of teeth lost ($\beta = -0.041$, 95% CI: −0.064, −0.018, $P = 0.001$) was significantly correlated with MMSE score in the multiple linear regression model.

Discussion

Our study found a significant correlation between tooth loss and cognitive function ($\beta = -0.042$, 95% CI: −0.061, −0.024, $P < 0.001$), after adjusting for age, sex, marriage status, family income, education level, hyperlipidemia, hypertension, diabetes, stroke, and drinking/smoking/regular exercise habits. Several cross-sectional studies conducted among different age groups (ranging from 28 to 77 years old) and different ethnicities (United States, Korea, Japan, South Korea, and Brazil) also found that tooth loss correlated with cognitive function, even after adjusting for common risk factors such as age, education level, hypertension and diabetes, and so on (Okamoto *et al*, 2010; Naorungroj *et al*, 2013a,b; Park *et al*, 2013; Peres *et al*, 2014). Longitudinal studies have further confirmed that risk of cognitive decline in elderly people increases as more teeth are lost (Kaye *et al*, 2010) as well as in edentulous people (Okamoto *et al*, 2010; Naorungroj *et al*, 2013a,b). However, a study conducted in 537 people aged 77 years and older in Sweden found no association between tooth loss and cognitive function, only that a perception of chewing difficulty was significantly related to cognitive function(Lexomboon *et al*, 2012).

Several reasons may account for the association between tooth loss and cognitive impairment. First, chewing deficiency caused by tooth loss could affect eating habits, leading to a softer diet either rich in cholesterol or lacking in essential vitamins (Sheiham and Steele, 2001). A high cholesterol diet is a known risk factor for the onset of stroke, which in turn is a risk factor for cognitive impairment. Meanwhile, intake of antioxidants in the form

Table 2 Multiple Linear Regression Analysis of MMSE and Periodontal Parameters for all subjects ($n = 905$)

Item	*Unadjusted* β *(95% CI)*	P *value*	*Fully adjusted* β *(95% CI)*	P *value*
No. tooth loss	−0.084 (−0.102, −0.066)	<0.001	−0.042 (−0.061, −0.024)	<0.001
Mean AL	−0.106 (−0.186, −0.027)	0.009	−0.002	0.960
Mean PD	0.216 (0.072, 0.359)	0.003	0.001	0.962
Mean PLI	0.042 (−0.199, 0.284)	0.731	−0.034	0.256
Mean BI	0.484 (0.266, 0.701)	<0.001	0.017	0.612

Multiple linear regression analysis fully adjusted model was adjusted for sex, age, educational level, family income, blood lipid level, hypertension, diabetes, stroke, drinking, and smoking.

Table 3 Multiple linear regression analysis of MMSE and mitochondrial DNA variations (n = 567)

Items	*No. (%)*	*Fully adjusted* β *(95% CI)* P *value*	*Plus perio* β *(95% CI)* P *value*	*MMSE (95% CI)*
A189 G	11 (1.94)	−1.540 (−2.818, −0.263) 0.018*	−1.506 (−2.711, −0.242) 0.020*	28.15 (27.96, 28.34) 26.82 (23.01, 30.63)
A16164G	18 (3.17)	−1.053 (−2.054, −0.052) 0.039*	−1.109 (−2.101, −0.118) 0.028*	28.16 (27.97, 28.35) 27.00 (24.5, 29.43)
Haplogroups				
A	30 (5.29)	0.028, 0.470	0.014, 0.718	28.28 (27.53, 9.01)
B	59 (10.4)	0.010, 0.795	−0.003, 0.929	28.12 (27.42, 28.82)
CZ	3 (0.529)	0.009, 0.821	0.010, 0.793	28.67 (27.23, 30.10)
D	171 (30.2)	−0.029, 0.447	−0.024, 0.536	28.04 (27.68, 28.40)
F	59 (10.4)	0.035, 0.360	0.022, 0.566	28.44 (27.98, 28.91)
G	15 (2.65)	0.014, 0.712	0.014, 0.708	28.87 (28.09, 29.65)
M	120 (21.2)	0.014, 0.711	0.009, 0.814	28.23 (27.83, 28.62)
N	31 (5.47)	−0.020, 0.602	0.011, 0.774	27.65 (26.87, 28.42)
N9	14 (2.47)	0.009, 0.808	−0.002, 0.951	28.29 (27.14, 29.43)
R	58 (10.2)	−0.023, 0.544	−0.004, 0.908	27.88 (27.01, 28.75)
T	2 (0.353)	0.045, 0.240	0.034, 0.364	30.00 (30.00, 30.00)
Y	5 (0.882)	−2.152 (−4.062, −0.242) 0.027*	−2.151 (−4.043, −0.060) 0.026*	26.00 (22.28, 29.72)

Multiple linear regression analysis fully adjusted model was adjusted for sex, age, educational level, family income, blood lipid level, hypertension, diabetes, stroke, drinking and smoking. Plus periodontal model was adjusted as above plus periodontal parameters.
*P < 0.05; **P < 0.01; ***P < 0.001.

Table 4 Multiple linear regression analysis of MMSE and Periodontal Parameters with mitochondrial DNA analysis (n = 567)

Item	*Unadjusted* β *(95% CI)*	P *value*	*Fully adjusted*	P *value*	*Fully adjusted +SNPs*	P *value*
No. tooth lost	−0.077 (−0.099, −0.054)	<0.001***	−0.042 (−0.066, −0.019)	<0.001***	−0.041 (−0.064, −0.018)	0.001**
Mean AL	−0.089 (−0.183, 0.006)	0.068	0.028	0.420	−0.002	0.954
Mean PD	0.174 (0.001, 0.346)	0.049*	0.020	0.612	0.001	0.973
Mean PLI	−0.043 (−0.339, 0.252)	0.774	−0.024	0.538	−0.054	0.170
Mean BI	0.424 (0.158, 0.690)	0.002**	0.042	0.307	0.023	0.587

Multiple linear regression analysis fully adjusted model was adjusted for sex, age, educational level, family income, blood lipid level, hypertension, diabetes, stroke, drinking and smoking. Plus DNA model was adjusted as above plus mitochondrial D-loop SNPs and haplogroups.
*P < 0.05 **P < 0.01 ***P < 0.001.

of vitamins C and E could potentially reduce cognitive impairment by decreasing the risk of cardiovascular disease such as stroke (Voko *et al*, 2003). Second, experimental studies conducted in humans have shown that chewing and clenching increase cerebral blood flow and may decrease the risk of cognitive impairment (Miyamoto *et al*, 2005; Hasegawa *et al*, 2007; Moriya *et al*, 2011). As a consequence, chewing deficiency induced by multiple tooth loss may increase risk of cognitive impairment. Furthermore, in animal studies, Kato *et al* found that, compared with dentate rats, young rats made surgically edentulous and fed nutritionally identical powder had significantly poorer spatial memory, with decreased stimulated acetylcholine release found in the parietal cortex (Kato *et al*, 1997). The mechanisms of this relationship were unclear, with speculation that mastication-induced sensory stimulation leading to degeneration of secondary neurons in the spatial pathway of the alveolar and trigeminal nerves may explain the cause (Gobel, 1984). A subsequent rat model with similar clinical findings further proved this mechanism through identification of hippocampal neuronal loss and decreased tropomyosin receptor kinase B-messenger RNA expression, suggesting decline of hippocampal synaptic transmission (Yamazaki *et al*, 2008).

None of the periodontal parameters, including PD and AL, which indicate the degree of previous periodontitis, PLI, which indicates oral hygiene, and BI, indicating gingival inflammation, correlated with cognitive function in our study. Previous studies (mostly conducted in the US, with one in the UK) had different results. The association between gingival bleeding or PLI and cognitive function have been confirmed by several studies (Stewart *et al*, 2008, 2013). Data from the US National Health and Nutrition Examination Surveys showed that AL (Stewart *et al*, 2008) and periodontitis (defined as present when a person had at least 10% of sites with an AL ≥4 mm and at least 10% of sites with a PD ≥3 mm (Yu and Kuo, 2008) are associated with cognitive function. Furthermore, data from the National Atherosclerosis Risk in Communities (ARIC) study conducted in 1998 in the US showed that number of lost teeth and gingival bleeding were associated with lower cognitive scores, while mean probing periodontal pocket depth was not (Naorungroj *et al*, 2013a,b). More research is required to draw a precise conclusion on the relationship between periodontal parameters and cognitive function.

With the rapid development of molecular biology, genetic factors have been found to have an effect on onset and development in some cognitive impairment patients.

Gene apolipoprotein (APOE) ε4 allele is not only known to be correlated with both mild cognitive impairment and sporadic Alzheimer's disease, but also affects conversion from mild cognitive impairment to dementia (Slooter *et al*, 1998; Reitz and Mayeux, 2010; Stein *et al*, 2010). However, APOE gene ε4 allele explains only a small proportion of the genetic contribution to cognitive impairment in later life, leaving several genetic risk factors still to be identified.

The hypothesis of oxidative stress involvement and mitochondrial dysfunction in the pathogenesis of cognitive impairment and other diseases has been noticed by a growing number of researchers (Kann and Kovacs, 2007; Takasaki, 2008; Wang *et al*, 2014). Mitochondria are the energy-producing organelles in human cells. The mitochondrial DNA D-loop region ([np] 16024-576 = 1122 bp) is the only non-coding region that regulates the transcription and translation of coding regions. Several SNPs in D-loop region, such as T414G (Coskun *et al*, 2004), 303–304 insC (Tanaka *et al*, 2010), and C16390T (Chang *et al*, 2000) have been found to be significantly higher in people with cognitive impairment than in controls.

A189G and A16164G were correlated with cognitive function in our large-scale, community-based study. In previous studies, A189G (Coskun *et al*, 2004) and A16164G (Ikebe *et al*, 1995) have been found in individual patients with cognitive impairment; however, our study is the first large-scale community-based study, to establish a correlation between these two SNPs and cognitive function, after adjusting for traditional cognitive impairment risk factors.

A total of 12 haplogroups were found in our subjects, including A, B, CZ, D, F, G, M, N, N9, R, T, and Y (Table 1), in accordance with Yao (Yao *et al*, 2002), Our study, performed in the Chinese population for the first time referring to haplogroup and cognitive decline, found haplogroup Y to be negatively associated with cognitive function ($\beta = -2.152$, 95% CI: -4.062, -0.242, $P = -0.027$). Certain mtDNA haplogroups are known to contribute to genetic susceptibility to various disorders (Hofmann *et al*, 1997). Research conducted on Italian subjects found that haplogroups K and U appeared to be protective to the harmful effect of the APOEε4 allele for Alzheimer's disease patients (Carrieri *et al*, 2001). African-Americans with haplogroup L1 were at risk for developing dementia compared with those with common haplogroup L3 over 10–12 follow-up years (Tranah *et al*, 2014).

The limitation of this study is that, this cross-sectional study could not demonstrate a cause-and-effect relationship between cognitive function. While, as for the novelty of this study, it is new in shows data on the mitochondrial DNA D-loop region, haplogroups, tooth loss, and MMSE correlation.

In conclusion, tooth loss and mitochondrial gene variants may have an effect on cognitive function in this study population, while further longitudinal study is required to identify the exact causal relationship between them.

Conflict of interest

This study was funded by the Capital Medical Development Funds, China (2009-1019), and the National clinical key subject construction project of China (2010). The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

Author's Contribution

Study concept and design (Qingxian Luan, Xingyu Wang and Wei Gao); data collection (Wei Gao, Xingyuu Wang and Xiaoxuan Wang); analysis and interpretation of data (Wei Gao, Xingyu Wang and Yu Cai); preparation of manuscript (Qingxian Luan and Wei Gao).

References

Anderson S, Bankier AT, Barrell BG *et al* (1981). Sequence and organization of the human mitochondrial genome. *Nature* **290**: 457–465.

Andrews RM, Kubacka I, Chinnery PF, Lightowlers RN, Turnbull DM, Howell N (1999). Reanalysis and revision of the Cambridge reference sequence for human mitochondrial DNA. *Nat Genet* **23**: 147.

Ball K, Berch DB, Helmers KF *et al* (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA* **288**: 2271–2281.

Barnes DE, Yaffe K (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* **10**: 819–828.

Campbell NL, Unverzagt F, LaMantia MA, Khan BA, Boustani MA (2013). Risk factors for the progression of mild cognitive impairment to dementia. *Clin Geriatr Med* **29**: 873–893.

Carrieri G, Bonafe M, De Luca M *et al* (2001). Mitochondrial DNA haplogroups and APOE4 allele are non-independent variables in sporadic Alzheimer's disease. *Hum Genet* **108**: 194–198.

Chang SW, Zhang D, Chung HD, Zassenhaus HP (2000). The frequency of point mutations in mitochondrial DNA is elevated in the Alzheimer's brain. *Biochem Biophys Res Commun* **273**: 203–208.

Coskun PE, Beal MF, Wallace DC (2004). Alzheimer's brains harbor somatic mtDNA control-region mutations that suppress mitochondrial transcription and replication. *Proc Natl Acad Sci U S A* **101**: 10726–10731.

Gobel S (1984). An electron microscopic analysis of the transsynaptic effects of peripheral nerve injury subsequent to tooth pulp extirpations on neurons in laminae I and II of the medullary dorsal horn. *J Neurosci* **4**: 2281–2290.

Gordon C, Martin DJ (2013). Mild cognitive impairment. *Expert Rev Neurother* **13**: 1247–1261.

Hasegawa Y, Ono T, Hori K, Nokubi T (2007). Influence of human jaw movement on cerebral blood flow. *J Dent Res* **86**: 64–68.

Hofmann S, Jaksch M, Bezold R *et al* (1997). Population genetics and disease susceptibility: characterization of central European haplogroups by mtDNA gene mutations, correlation with D loop variants and association with disease. *Hum Mol Genet* **6**: 1835–1846.

Ikebe S, Tanaka M, Ozawa T (1995). Point mutations of mitochondrial genome in Parkinson's disease. *Brain Res Mol Brain Res* **28**: 281–295.

Kann O, Kovacs R (2007). Mitochondria and neuronal activity. *Am J Physiol Cell Physiol* **292**: C641–C657.

Kato T, Usami T, Noda Y, Hasegawa M, Ueda M, Nabeshima T (1997). The effect of the loss of molar teeth on spatial memory and acetylcholine release from the parietal cortex in aged rats. *Behav Brain Res* **83**: 239–242.

Kaye EK, Valencia A, Baba N, Spiro AR, Dietrich T, Garcia RI (2010). Tooth loss and periodontal disease predict poor cognitive function in older men. *J Am Geriatr Soc* **58**: 713–718.

Lexomboon D, Trulsson M, Wardh I, Parker MG (2012). Chewing ability and tooth loss: association with cognitive impairment in an elderly population study. *J Am Geriatr Soc* **60**: 1951–1956.

Miyamoto I, Yoshida K, Tsuboi Y, Iizuka T (2005). Rehabilitation with dental prosthesis can increase cerebral regional blood volume. *Clin Oral Implants Res* **16**: 723–727.

Moriya S, Tei K, Murata A *et al* (2011). Associations between self-assessed masticatory ability and higher brain function among the elderly. *J Oral Rehabil* **38**: 746–753.

Naorungroj S, Schoenbach VJ, Beck J *et al* (2013a). Cross-sectional associations of oral health measures with cognitive function in late middle-aged adults: a community-based study. *J Am Dent Assoc* **144**: 1362–1371.

Naorungroj S, Slade GD, Beck JD *et al* (2013b). Cognitive decline and oral health in middle-aged adults in the ARIC study. *J Dent Res* **92**: 795–801.

Okamoto N, Morikawa M, Okamoto 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.

Olazaran J, Muniz R, Reisberg B *et al* (2004). Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease. *Neurology* **63**: 2348–2353.

van Oven M, Kayser M (2009). Updated comprehensive phylogenetic tree of global human mitochondrial DNA variation. *Hum Mutat* **30**: E386–E394.

Park H, Suk SH, Cheong JS *et al* (2013). Tooth loss may predict poor cognitive function in community-dwelling adults without dementia or stroke: the PRESENT project. *J Korean Med Sci* **28**: 1518–1521.

Peres MA, Bastos JL, Watt RG, Xavier AJ, Barbato PR, D'Orsi E (2014). Tooth loss is associated with severe cognitive impairment among older people: findings from a population-based study in Brazil. *Aging Ment Health* **19**: 876–884.

Qiu C, De Ronchi D, Fratiglioni L (2007). The epidemiology of the dementias: an update. *Curr Opin Psychiatry* **20**: 380–385.

Reitz C, Mayeux R (2010). Use of genetic variation as biomarkers for mild cognitive impairment and progression of mild cognitive impairment to dementia. *J Alzheimers Dis* **19**: 229–251.

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.

Slooter AJ, Cruts M, Kalmijn S *et al* (1998). Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam Study. *Arch Neurol* **55**: 964–968.

Stein PS, Kryscio RJ, Desrosiers M, Donegan SJ, Gibbs MB (2010). Tooth loss, apolipoprotein E, and decline in delayed word recall. *J Dent Res* **89**: 473–477.

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

Stewart R, Weyant RJ, Garcia ME *et al* (2013). Adverse oral health and cognitive decline: the health, aging and body composition study. *J Am Geriatr Soc* **61**: 177–184.

Takasaki S (2008). Mitochondrial SNPs associated with Japanese centenarians, Alzheimer's patients, and Parkinson's patients. *Comput Biol Chem* **32**: 332–337.

Tanaka N, Goto Y, Akanuma J *et al* (2010). Mitochondrial DNA variants in a Japanese population of patients with Alzheimer's disease. *Mitochondrion* **10**: 32–37.

Tranah GJ, Yokoyama JS, Katzman SM *et al* (2014). Mitochondrial DNA sequence associations with dementia and amyloid-beta in elderly African Americans. *Neurobiol Aging* **35**: 442.e1–442.e8.

Voko Z, Hollander M, Hofman A, Koudstaal PJ, Breteler MM (2003). Dietary antioxidants and the risk of ischemic stroke: the Rotterdam Study. *Neurology* **61**: 1273–1275.

Wang X, Luan Q, Chen Q, Zhao L, Guo Y (2014). Mitochondrial polymorphisms and dysfunction related to aggressive periodontitis: a pilot study. *Oral Dis* **20**: 490–498.

Yamazaki K, Wakabayashi N, Kobayashi T, Suzuki T (2008). Effect of tooth loss on spatial memory and trkB-mRNA levels in rats. *Hippocampus* **18**: 542–547.

Yao YG, Kong QP, Bandelt HJ, Kivisild T, Zhang YP (2002). Phylogeographic differentiation of mitochondrial DNA in Han Chinese. *Am J Hum Genet* **70**: 635–651.

Yu YH, Kuo HK (2008). Association between cognitive function and periodontal disease in older adults. *J Am Geriatr Soc* **56**: 1693–1697.

Yu H, Qi LT, Liu LS *et al* (2014). Association of carotid intima-media thickness and atherosclerotic plaque with periodontal status. *J Dent Res* **93**: 744–751.