Ph.D. Dissertation of Dentistry

Association between salivary flow rate and the risk of cognitive impairment among Korean elders: a cross-sectional study

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Abstract

Association between salivary flow rate and the risk of cognitive impairment among Korean elders: a cross-sectional study

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Background: Salivary function has been suggested to be associated with cognitive impairment. However, the effect of salivary flow rate (SFR) on cognitive impairment remains unclear. This study aimed to investigate whether SFR is associated with cognitive impairment among Korean elders.

Methods: This cross-sectional study included 649 elders aged 65 and older in the Korean community-dwelling population. Cognitive impairment was assessed using the Mini-Mental Status Examination. Unstimulated SFR was measured and dichotomized. Denture status, age, sex, education level, smoking, drinking, diabetes, hypertension, and obesity were considered confounders. Multivariable logistic regression analysis was applied to assess

the adjusted association. Stratified analysis by sex and denture status was performed to clarify the effect modification.

Results: Participants without cognitive impairment showed a higher SFR level than those with cognitive impairment (0.81mL/min for non-cognitive impairment versus 0.52 mL/min for cognitive impairment, $p < 0.001$). After controlling for confounders, participants with low SFR (< 0.3 mL/min) were more likely to have cognitive impairment by 1.5 times than participants with normal SFR (odds ratio [OR] = 1.5, confidence interval [CI] = 1.05−2.10). The association of low SFR with cognitive impairment was higher in women and dentate participants: about 10% higher in women (OR = 1.63, CI = 1.07−2.50) and about 22% higher in dentate participants (OR = 1.82, CI = 1.41−2.90).

Conclusions: Salivary flow rate is independently associated with cognitive impairment among Korean elders. The association was modified in females and dentate elders. Salivary flow rate could be early marker for cognitive impairment in early stage. Physicians and dentists should consider low SFR and cognitive impairment as a risk factor between them in clinics.

Keywords: cognitive impairment, elder, epidemiology, Korean, salivary flow rate

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Contents

Table list

Figure list

Supplement list

participants (n = 649).

Appendix list

1. BACKGROUND

Cognitive impairment (CI) in the older population has been a head-aching global health problem due to its unclear mechanism and complicated relationship with aging-related common disorders. The prevalence of dementia in people aged 60 and over is about 5-7% in most world regions,[1] The number of dementia was estimated at 50 million worldwide in 2018, and it was predicted being triple in 2050.[2] Korean population has gained the fastest aging globally and was expected to be a super-aged society in the next five years. The prevalence of mild CI among Korean elders was estimated to be as high as 24.1%, which would be a severe public health issue.[3] Thus, it is crucial to unmask the risk factors of this disorder screening and prevention.

Relationship between CI and oral health

CI has been associated with various oral health problems in late adulthood;[4] poorer oral health is more likely to diminish cognitive function. The relationship between periodontitis and CI has been investigated among Korean elders in the community.[5] The history of periodontitis was confirmed by the alveolar bone loss sign on the dental panoramic radiograph. The results showed that participants with periodontitis were more likely to have CI by two times than those without CI after controlling for various potential confounders. Another longitudinal study of community-dwelling men in America indicated that the progression of periodontitis could predict the

subsequent decline in cognitive function.[6]

The association between mastication and CI among the elderly was systematically reviewed.[7] The cross-sectional studies indicated that poor masticatory performance was associated with CI. Meanwhile, the prospective studies showed that decreased mastication was associated with a decline in cognitive function. Also, the mastication problem was considered as a risk factor for dementia or mild memory impairment.

Compared to those without cognitive impairment, older people with cognitive impairment were likely to have a higher number of lost teeth[8] and non-rehabilitated lost teeth.[9] A 9-year-longitudinal study of ≥ 60-year-old participants without dementia at baseline showed that tooth loss was significantly associated with a steeper cognitive decline.[8] Also, participants with tooth loss had significantly total lower brain volume and gray matter volume than the controls.[8] Data from a Korean community-based study showed that the elderly with a high number of non-rehabilitated teeth (≥ 5) was more likely to have CI by 3 times than those with a low number of rehabilitated teeth (<5).[9] The authors suggested that the rehabilitation of the lost teeth could be important for the maintenance of CI.

While the association between CI and several oral health indicators has been investigated, its relationship with salivary flow rate has not been well studied.

Neural regulation of saliva secretion

Salivary secretion is controlled by the autonomic nervous system and regulated by reflex pathways, including the salivation center in the brain.[10] The afferent pathway is initiated by the gustatory-salivary reflex involves sensory signals from taste-activated chemoreceptors in the taste buds in the lingual papillae,[11] masticatory-salivary reflex which is primarily induced by activation of mechanoreceptors in the periodontal ligament during mastication, and other factors such as olfactory, nociceptive, thermoreceptive and psychic stimuli.[12] These stimuli generate afferent signals which are transmitted to the salivation centers through fibers of the facial (cranial nerves VII), glossopharyngeal (cranial nerves IX), and trigeminal (cranial nerves V) (Fig.1).[10,13,14] In man, taste and mastication are by far the most important stimuli of salivary secretion. Parasympathetic efferent pathways for the sublingual and submandibular glands are from the facial nerve via the submandibular ganglion and for the parotid gland from the glossopharyngeal nerve via the otic ganglion. These pathways regulate fluid secretion by releasing acetylcholine (ACh) at the surface of the salivary gland acinar cells. Macromolecule secretion is regulated by noradrenaline (NorAd or norepinephrine, US) release from sympathetic nerves. Sympathetic post-ganglionic pathways are from the cervical ganglion of the sympathetic chain. The division between parasympathetic and sympathetic control of different

aspects of the secretory process is blurred slightly because parasympathetic nerves may also release peptides, such as substance P and Vasoactive Intestinal Polypeptide (VIP) and NorAd will also bind to Ca2+-mobilising α-adrenergic receptors.[12]

The inputs are integrated in the salivary centers, which generate nerve impulses in the parasympathetic and sympathetic neurons innervating the salivary glands.[14] Saliva centers comprise the parasympathetic superior and inferior salivary center in the brainstem (medulla oblongata) and the sympathetic salivation center in the upper thoracic segments of the spinal cord.[15,16]

The salivary reflex is also influenced by other centers in the brain. First, the salivary centers receive various inputs from the frontal cortex.[17] This central neural activity appears to contribute to the unstimulated SFR. Second, the primary parasympathetic salivary centers form connections with the lateral hypothalamus.[14] Third, suppression of impulse traffic from the salivary centers to salivary due to fear and anxiety involves a complex interaction with higher (limbic and cortical) centers in the brain.[13] Last but not least, cholinergic inputs to the salivary centers from other nuclei also affect the saliva secretion.[18]

The efferent part of the reflex consists of parasympathetic and sympathetic secretomotor neurons, which innervate the salivary glands.[12]

Overall, the parasympathetic innervation of the salivary gland cells is more abundant than sympathetic innervation. Sympathetic nerve stimulation evokes a protein-rich secretion whereas parasympathetic stimulation evokes a larger volume of saliva.[10,13]

Unstimulated salivary flow rate of Korean people

Normal salivary secretion is essential in maintaining efficient mastication and other oral functions.[10,19,20] Saliva lubricates and cleanses the teeth and oral mucosa, maintains neutral pH through its buffering capacity, prevents tooth demineralization, exerts antimicrobial actions, aids in taste and bolus formation, initiates enzymatic digestion of starch, and is imperative for mastication and swallowing and articulation of speech.[21,22] It also plays an important role in the formation of the acquired enamel pellicle and the mucosal pellicle, which apart from having a protective function also determines the initial adhesion and colonization of microorganisms and the composition of the resident oral microbiota.[10]

Patients with salivary hypofunction often complain of dry mouth and sleep deprivation.[23] Also, hyposalivation results in mucosal changes, increased activity of caries with lesions on cervical, incisal, and cuspal tooth surfaces, and oral fungal infections.[22] Disturbed taste sensation, impaired lubrication, and dysphagia may lead to behavioral changes and avoiding

certain foods. In turn, changes in dietary intake may result in nutritional deficiencies and atrophy of the masticatory muscles, and decreased masticatory ability.[7] Consequently, salivary gland hypofunction and its related symptoms and clinical consequences often have negative effects on social functioning and quality of life.[24,25]

Unstimulated salivary flow rate (SFR) has been studied in different populations in Korea. In Korean elderly aged 65 and over who live in welfare centers, unstimulated SFR was 0.33 ± 0.17 mL/min. The SFR was significantly increased to 0.46 ± 0.23 mL/min after three months of application of oral muscle massage.[26] In elderly in the community, unstimulated was 0.27 ± 0.17 mL/min (0.36 ± 0.23 mL/min in male and 0.23 ± 0.12 mL/min in female). SFR was not associated with Zung self-rating depression score nor the oral health-related quality of life.[27] The unstimulated SFR was also reported in Korean adults aged 40 and over.[28] SFR was 0.47 ± 0.23 mL/min in male and 0.35 ± 0.21 mL/min in female. The SFR decreased by age from 0.4 ± 0.21 mL/min in the 40-50s to 0.38 ± 0.24 mL/min and 0.33 ± 0.18 mL/min in 61 and over. In a study of saliva in burning mouth syndrome, unstimulated SFR was lower in patients (aged 61.6 ± 10.1, SFR = 0.14 ± 0.12 mL/min) than in the controls (aged 65.1 ± 9.0, SFR = 0.2 ± 0.16 mL/min).[29]

The SFR seemed to be higher in younger Korean people. The unstimulated SFR was 0.46 ± 0.29 mL/min in Korean dental college students and it was not associated with Decayed, Missing, and Filled Surfaces (DMFS)

nor Decayed, Missing, and Filled Teeth (DMFT) indices.[30] In healthy people aged 20-39, unstimulated SFR was 1.037 ± 0.323 mL/min[31] while it was 0.5 ± 0.28 mL/min in healthy women (aged 22-32).[32] In Korean children, unstimulated SFR was 1.31 ± 1.03 mL/min in those without dental sealant and 1.27 ± 0.77 in those with over four sealant or resin dilled surfaces.[33]

Previous studies and its limitations on the relationship between SFR and CI

The autonomic dysfunctions observed in cognitive impairment may also contribute to hyposalivation.[34] However, only two papers have reported the relationship between cognitive impairment and SFR.[35,36]

A Danish longitudinal study[35] was done to compare the SFR between participants who suffered cognitive decline and those who did not. A total of 193 men were evaluated for their cognitive performance using an intellegence test at 18 years old and 56 years old, with an almost 40-year retest interval. Then, they were divided into two groups: with and without cognitive decline. Participants with neurodegenerative or major psychiatric disorders, dementia, major brain lesions, alcohol or drug abuse were excluded. At the age of 56, Danish men's median unstimulated SFR was 0.36 (0.04-2.02) mL/min. SFR was significantly different between men with and without cognitive decline (0.33 mL/min versus 0.41 mL/min). Also, the prevalence of hyposalivation (SFR < 0.1 mL/min) and low secretion (SFR < 0.2 mL/min) was significantly higher in the cognitive decline group compared with the control. Because the

participants were of the same age and had similar characteristics regarding comorbidities, health-related behaviors, and prescribed medication, it was likely that the decline in cognitive performance was attributed to decreased SFR.

However, this study had some limitations. Firstly, it focused on only middle-age-men. Secondly,the decline in cognitive performance over time, which was associated with SFR, differs from CI. Thirdly, different tools were used to evaluate the cognitive performance at the baseline and the end of the study. Fourthly, the association was not controlled for potential confounders.

In an early study in USA, the association between unstimulated SFR with CI was investigated,[36] SFR of twenty-eight community-dwelling participants with Dementia of Alzheimer type (DAT) was compared with healthy, age-matched controls. Submandibular SFR was significantly lower in DAT participants than in the controls (0.038 ± 0.007 mL/min versus 0.093 ± 0.011 mL/min). Also, the prevalence of participants with impaired SFR (SFR less than 10 percentile rank) was higher in the DAT group than in the control group. Unstimulated parotid SFR in men with DAT was found to be higher than in women (0.082 ± 0.014 mL/min versus 0.04 ±0.01 mL/min).

However, this study was not conducted in the community and had only a small sample size. Moreover, it included only dementia, which is only one type of CI. Also, multivariable analysis was not used to control for confounders.

Question and Hypothesis on the relationship between SFR and CI

The salivary secretion is controlled by the autonomic nervous system and regulated by reflex pathways. So, whether the degeneration of the central nervous system in cognitive impairment could alter the afferent or efferent reflex, decreasing the salivary flow rate? Despite many studies of SFR in Korea, the relationship between cognitive impairment and SFR has not been reported.

Hence, we hypothesized that SFR was associated with cognitive impairment after controlling for various confounders including denture status, socio-demographic factors[37] such as age, sex and education level, behaviors[37,38] such as smoking and drinking, and general health problems[39-41] such as diabetes, hypertension and obesity.

Objective of study

This cross-sectional study aimed to evaluate the adjusted association of SFR with cognitive impairment among Korean elders and its effect modification by sex and denture status.

2. METHODS

Ethical considerations and study design

This study was approved by the Institutional Review Board for Human Subjects at the Seoul National University School of Dentistry and Seoul National University College of Medicine (approval number: S-020190017 and C-1803-117-932). All participants provided written, informed consent of their record. This study was the baseline (2018-2019) of the community health education cohort, which combined medical and dental health. After several weeks of the advertising period which was performed in advance of the survey, participants were recruited. The survey was conducted at a community health center in Songbuk-Gu, Seoul. Systemic health status and oral health status were assessed by trained medical and dental health professionals in the project who received calibration training beforehand.

Study population

Songbuk-gu in Seoul metropolitan city was select as a pilot program area by KCDC (Korea Centers for disease Control and Prevention) because Songbuk-gu was a representative cluster of elder in Korea.[42] The proportion of population aged 65 and over was 16.5% which is almost same as the average of 16.0% in Seoul.[43] Area (dong) stratified random sampling procedure was created to recruit equal number of participants in each area (dong).

The inclusion criteria were as follows: 1) community-dwelling people aged 65 and above who lived in Songbuk-gu, 2) elders without critical diseases encompassing cancer, paralysis, stroke, and cardiovascular diseases (angina pectoris, myocardial ischemia, or heart failure), 3) no problem and willing to follow the recommendation of the cohort procedures, 4) voluntarily joined with self-written informed consent, and 5) without any missing information for this study.

Total of 73,158 elders aged 65 and above, 743 elders in Songbuk-gu were voluntarily recruited in this study. They completed the health assessment and questionnaires. After excluding 94 participants with incomplete information, 649 elders were included in the final analysis (Fig. 2).

Assessment of Cognitive Impairment

Cognitive impairment is when a person has trouble remembering, learning new things, concentrating, or making decisions that affect their everyday life.[44] The Mini-Mental State Exam (MMSE) is a widely used screening tool for cognitive function.[45] The Korean version (MMSE-KC) was developed as a part of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet.[46] The MMSE-KC contains 19 items adding up to 30 points (10 points for orientation, 6 points for verbal memory, 5 points for concentration and calculation, 5 points for language, 3 points for praxis, 1 point for visuospatial construction), with higher scores indicating better cognitive performance. Because of the high

prevalence of illiteracy in elderly Koreans, two items focusing on judgment ability replaced the reading and writing items of the original version of MMSE in the MMSE-KC. The MMSE-KC showed adequate diagnostic accuracy for moderate dementia, with an area under the receiver operating characteristic curve of approximately 0.9. The total score was used to determine cognitive impairment (≤ 23 points) and non-cognitive impairment (> 23 points) according to the previous studies.[47,48]

Unstimulated salivary flow rate measurement

Participants were advised not to eat or drink (except for water) about 8 hours before the procedure in the morning in March (Spring) and September (Autumn). When coming to the test office, they were instructed to rinse their mouth with distilled water and take a rest for several minutes. The participants were instructed to swallow once before measurements began, then to keep on drooling for five minutes into a tube with previous weight measurement. They were also advised to minimize the movement of their mouth and not swallow any saliva during the procedure. The collected saliva was weighed and converted to volume (1:1 from grams to milliliters). The SFR (mL/min) was calculated by dividing the volume by time. Although previous studies[35,49,50] adopted hyposalivation (SFR < 0.1 mL/min), Dawes et al.[51] suggested low salivation (SFR < 0.3 mL/min). Since our data showed small numbers in cognitive impairment with hyposalivation (n=31), we dichotomized SFR according to the suggestion of Dawes: normal SFR (≥ 0.3mL/min) and low

SFR (< 0.3 mL/min).[51]

Assessment of confounders

According to previous reports, confounders in this study included denture status, socio-demographic factors[37] such as age, sex and education level, behaviors[37,38] such as smoking and drinking, and general health problems [39-41] such as diabetes, hypertension and obesity.

Participants were interviewed face-to-face by trained interviewers for information regarding socio-demographic and behavioral factors. Interviewers were recruited from the survey area and trained before the main survey using structured questionnaires. Socio-demographic factors included education level, age, and sex; health-related behavioral confounders were smoking and alcohol drinking.

Physicians performed a general health assessment and physical examination, and blood samples were obtained at the field survey center. Blood samples were collected in the morning after 8 hours of fasting, and all biochemical markers were analyzed on the same day. Glycated hemoglobin (HbA1c) was measured using ADVIA1650 Autoanalyzer, Bayer, MN, USA. Diabetes was determined if fasting plasma glucose >126 mg/dL or HbA1c ≥ 6.5% or on diabetes medication. Hypertension was diagnosed if systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or on hypertension medication. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2), and obesity was defined as a BMI

of 25.0 kg/m^2 or above, while the normal was BMI less than 25.0 kg/m^2.

Oral examination, including denture status (dentate and denture), was performed by trained dentists.

Statistical analysis

Testing for normality was done using the Kolmogorov-Smirnov test along with a histogram. SFR distribution showed a skew data in both histogram and the Kolmogorov-Smirnov test (Appendix 1). Meanwhile, age distribution showed a reasonable bell-shapein histogram and but the Kolmogorov-Smirnov did not show a normality. However, with large enough sample sizes (> 30 or 40), the violation of the normality assumption should not cause major problems.[52] This implies that we can use a parametric test even when the data are not normally distributed.[52] Additionally, if we have samples consisting of hundreds of observations, we can ignore the distribution of the data.[53] Therefore, parametric tests were used in our study.

Differences in characteristics between cognitive impairment and non-cognitive impairment were compared using bivariate analyses such as Student T-test for continuous variables and chi-square test for categorical variables. Characteristic variables of the participants were described using frequency distributions for categorical variables and means with standard deviations for continuous variables. To compare the adjusted mean of SFR according to cognitive impairment, analysis of covariates (ANCOVA) was applied after controlling for various confounders.

Multivariable logistic regression analysis was used to evaluate the association between SFR and cognitive impairment after controlling for various confounders. The outcome was cognitive impairment, which was binary (no versus yes). Denture status, age, sex, education level, smoking, drinking, diabetes, hypertension, and obesity were considered as confounders since they were associated with cognitive function and/or salivary flow rate.[37,54]

Effect modification of sex and denture status were explored using stratified analysis, because previous studies[55-58] reported the different association of masticatory function and tooth loss with cognitive impairment in sex and denture status.

All analyses were performed using SPSS version 25.0 (SPSS, Inc., Armonk, NY, USA).

3. RESULTS

Participants with cognitive impairment (n=243) with lower total MMSE-KC score showed a higher prevalence of low SFR, higher age, and lower education but less smoking or drinking, hypertension, obesity than those without cognitive impairment (n=406) (Table 1, Supplementary Table 1 and 2). There was no significant difference in denture status, sex, diabetes between participants with and without cognitive impairment.

Participant with normal SFR showed a higher prevalence in non-smoker, alcohol drinker than those with low SFR and hyposalivation ($p<0.05$) (Table 1). Denture status, sex, education level, diabetes, hypertension and obesity did not show the significant difference between normal SFR, low SFR and hyposalivation ($p>0.05$) (Supplementary Table 3).

SFR was significantly higher by 1.6 times in both crude and adjusted value in participants without cognitive impairment compared with those with cognitive impairment (in crude, 0.81 ± 0.04 mL/min for non-cognitive impairment versus 0.50 ± 0.03 mL/min for cognitive impairment, $p < 0.001$; in adjusted, 0.81 ± 0.03 mL/min for non-cognitive impairment versus 0.52 ± 0.04 mL/min for cognitive impairment, $p < 0.001$) (Fig.3).

Participants with low SFR (< 0.3 mL/min) were 1.5 times more likely to

have cognitive impairment than those with normal SFR (odds ratio [OR] = 1.45, confidence interval [CI] = 1.05−2.11) (Table 2). Diabetes showed a significant association with a higher prevalence of cognitive impairment, while higher education, hypertension, and obesity showed a significant association with a lower prevalence of cognitive impairment.

Stratified analyses by sex and denture status showed that the association between cognitive impairment and SFR was modified in females and participants with dentate (Fig.4, Supplementary Table 4). In older women, the association of low SFR with cognitive impairment changed to OR of 1.63 (CI = 1.07−2.50), which was higher by 1.6 times compared with normal SFR. In dentate participants, the association of low SFR with cognitive impairment changed to OR of 1.82 (CI = 1.41−2.90), which was higher to 1.8 times compared with normal SFR. The association of low SFR with cognitive impairment was modified by about 10% higher in women (OR = 1.63 versus 1.50) and about 22% higher in dentate participants (OR = 1.82 versus 1.50).

4. DISCUSSION

This cross-sectional study showed that low unstimulated SFR was significantly associated with a higher prevalence of cognitive impairment adjusted for various confounders in Korean elders. The association was highly modified in women and dentate elders. To the best of our knowledge, this is the first study showing that low unstimulated SFR was independently associated with cognitive impairment after controlling for potential confounders, including denture status, socio-demographic factors, behavioral factors and general health problems.

The association between cognitive impairment and SFR was investigated previously. Ship et al. found the decline of submandibular gland function in people with early-stage dementia compared with healthy individuals.[36] The SFR was positively correlated to the cognitive level in Alzheimer patients, and their SFR decreased over time, opposing a stable direction in the controls.[59] The Danish study demonstrated that the prevalence of salivary gland hypofunction and daytime xerostomia was significantly higher in the cognitive decline group than in the non-cognitive decline group.[35] Our study confirmed the previous findings by demonstrating that elders without cognitive impairment had 1.6 times higher SFR level than those with cognitive impairment.[35,36] and elders with low SFR were more likely to have a risk of cognitive impairment prevalence by 1.5 times higher than those with normal SFR.

This study had four major strengths. Firstly, participants were recruited from the general resident population, not in a nursing home. Secondly, a medical professional evaluated cognitive impairment using the MMSE, the most widely used cognitive impairment screening tool in clinical practice and research. Thirdly, stratification analysis was performed to clarify the modification of the association. Fourthly, the association was adjusted for well-known potential confounders, including denture status, socio-demographic factors, behavioral factors and general health problems. Lastly, this study confirmed the previously reported significant association of diabetes mellitus[60] and education level with cognitive impairment.[41] Therefore, our study was valid enough to test the association of SFR with cognitive impairment.

Hitherto the mechanism of this relationship between cognitive impairment and SFR in human remains still unclear; some pathways on the relationship could be addressed. The salivary function is controlled by the autonomic nervous system and regulated by reflexes, including the afferent neural signal to the salivary centers in the brain and the efferent reflex.[10,13] The chronic and progressive degeneration of the brain in cognitive impairment could alter the perception of the afferent impulses in the salivary centers leading to a decline in parasympathetic output, altering saliva production. Indeed, the downgraded activity of the cholinergic system was related to cognitive impairment.[61] However, this pathway could not change the stimulated SFR.[35] This may be due to the unstimulated SFR being more

affected by the modulation of the salivary nuclei by a complex interaction with higher centers in the brain, including limbic and cortical centers.[10,62] Recent reviews suggested that Alzheimer's disease could affect the insular cortex leading to dysfunction of the autonomic nervous system.[63,64] A Japanese study demonstrated that the stimulation of the posterior area of the insular cortex results in hyperactivity of both saliva and masticatory muscles in rats.[65] Thus, the cognitive impairment may dysregulate the salivary secretion through the autonomic nervous system modulated by the cortical network. Further studies are indicated to clarify the mechanism of this relationship in human.

In our study, the association between SFR and cognitive impairment was modified by sex and denture status. The association of low SFR with cognitive impairment increased by 10% in women, 22% in dentate participants, while the association in men and denture participants lost its significance (Fig.3). Previous studies on cognitive impairment, dementia, and Alzheimer's disease revealed a significantly higher prevalence and incidence rate in women than in men.[55,58,66] Besides, women showed a lower unstimulated SFR than men.[67] Therefore, the association between SFR and cognitive impairment could be increased in women. In contrast, our data showed a non-significant association in men, which was inconsistent with the result of the Danish study.[35] The reason may come from the differences in study design encompassing cognitive impairment assessment (MMSE for ours versus cognitive decline for Danish), age of the population (65 years or

older for ours versus 56 for Danish), and the cut-off point for salivary flow rate (low SFR for ours versus hyposalivation for Danish). Although the sample size of hyposalivation SFR (≤ 0.1 mL/min) in men with cognitive impairment (n=6) and men without cognitive impairment (n=17) was too small, our data also showed that hyposalivation was not associated with cognitive impairment in men (Supplementary Table 3). Regarding the denture status, our data showed a higher prevalence of cognitive impairment in the denture group, which could mask the impact of low SFR on cognitive impairment in the denture group. Our results stratified by denture status supported the previous similar cognitive impairment studies that reported a stronger association of masticatory function with cognitive impairment in the dentate group than in the denture group.[56,57] The mechanism behind the role of the denture in the association between SFR and cognitive impairment is still unknown.

Saliva is a unique fluid that contributes significantly to the maintenance of efficient chewing ability, swallowing activity.[19,68] It also plays a vital role in digestive activity and modulation of microflora.[21] Thus, reduced SFR not only increases the risk of oral health problems[10] but also results in malnutrition due to masticatory difficulty.[69] People with cognitive impairment should be advised to use sugar-free chewing gum routinely and artificial saliva when needed and be monitored for oral fungal infection. As these patients are potential candidates for other oral health diseases,[35,70] aggressive preventive care, including daily care by family members or

caregivers, and short-term regular oral health check-up by a dentist are recommended.

This study has some limitations. Firstly, due to the cross-sectional study design, the direction of causation association between CI and SFR cannot be inferred: whether SFR could be the outcome of cognitive impairment or SFR could influence cognitive function. Secondly, the reproducibility of SFR was not tested. However, unstimulated saliva was collected for five minutes, which was appropriate according to the recommendation (1-6 minutes) from a previous study.[71] Thirdly, iron-deficiency anemia, a disease that could reduce salivation was not considered.[72] Fourthly, antidiabetic agents, which were associated with the risk of CI[73] should be involved in confounders. Last but not least, the effect of currently used medications that alter salivary secretion was not controlled. Mouth rinsing with zinc chloride 0.25% could lead to an increase in SFR.[74] Also, taking cholinesterase inhibitors triggers high production of saliva.[75] In contrast, a wide range of medications can reduce the SFR. Antidepressants[76] can inhibit cholinergic receptors, resulting in xerostomia and decreased SFR. Variety types of antihypertensive medications can decrease the SFR. A study in Italy reported the prevalence of xerostomia at about 8–13% in patients using angiotensin-converting enzyme inhibitors.[77] Calcium channel blockers such as diltiazem, verapamil and nifedipine can cause xerostomia due to their effects on calcium regulation which has an essential role in saliva secretion.[78] Other antihypertensive medications such as alpha 2 adrenergic receptors simulation or beta-blockers

could also reduce the SFR through the effects on central nervous system or beta-adrenergic receptors on the salivary gland.[79] Anticholinergic agents which directly inhibits the salivary secretion via parasympathetic stimulation are commonly prescribed for patients with overative bladder.[80] Dry mouth is a frequent adverse effect in patients who is taking the anticholinergic medication. The antipsychotic drugs, which show the anticholinergic effect, also impairs the salivation.[79]

Future prospective cohort studies that include medication variables related to SFR and cognitive impairment, hypoglycemic agents, and specific antihypertensive medications will infer the causality and estimate unbiased association. Notwithstanding these limitations, our data was sufficient enough to meet the aim of this study.

5. CONCLUSION

The low salivary flow rate was independently associated with cognitive impairment among Korean elders. The relationship was highly modified in females and dentate elders. Salivary flow rate could be a marker for early stage of cognitive impairment. Physicians and dentists should consider salivary flow rate and cognitive impairment as a risk factor between them simultaneously in clinics.

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Table 1. Characteristics of participants by cognitive impairment (n = 649)

Variable	*n*	Cognitive impairment		*P*-value
		No (*n* = 406)	Yes (*n* = 243)	
MMSE-KC score	649	27.0 ± 1.8	19.8 ± 3.3	<0.001
Salivary flow rate (mL/min)				0.004
Normal (≥ 0.3)	414	276 (68.0)	138 (56.8)	
Low (< 0.3)	235	130 (32.0)	105 (43.2)	
Hyposalivation (< 0.1)	97	66 (16.2)	31 (12.8)	
Denture status				0.2
Dentate	378	244 (60.1)	134 (55.1)	
Denture	271	162 (39.9)	109 (44.9)	
Age (year)	649	75.8 ± 5.2	76.8 ± 5.5	0.03
Sex				0.17
Male	211	140 (34.5)	71 (29.2)	
Female	438	266 (65.5)	172 (70.8)	
Education level				<0.001
Junior school or less	495	287 (70.7)	208 (85.6)	
High school or more	154	119 (29.3)	35 (14.4)	
Smoking*				0.02
No	441	262 (64.5)	179 (73.7)	
Yes	208	144 (35.5)	64 (26.3)	
Drinking†				0.001
No	219	118 (29.1)	101 (41.6)	
Yes	430	288 (70.9)	142 (58.4)	
HbA_1C	649	6.05 ± 0.8	6.12 ±0.9	0.1
Diabetes‡				0.09
No	451	292 (71.9)	159 (65.4)	
Yes	198	114 (28.1)	84 (34.6)	
Hypertension#				0.03
No	298	173 (42.6)	125 (51.4)	
Yes	351	233 (57.4)	118 (48.6)	
Obesity♦				0.01
No	362	211 (52.0)	151 (62.1)	
Yes	287	195 (48.0)	92 (37.9)	

Data are presented as numbers (column percentage) for categorical variables and mean± standard deviation for continuous variables.

P-values were obtained by Chi-square test for categorical variables and T-test for continuous variables.

*Smoking: "No" refers to never smoked and "Yes" refers to past and current smoker.

†Alcohol intake: No refers to never drunken, and "Yes" refers to past and current drinker.

‡Diabetes was determined as "Yes" if fasting plasma glucose >126 mg/dL or $HbA_1C \geq 6.5$ % or a history of diabetes.

#Hypertension was determined as "Yes" if systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or taking hypertension medication.

◆Obesity: Body mass index (kg/m^2) ≥ 25.

MMSE-KC: Korean version of Mini-Mental State Examination in the Korean version of the Consortium to Establish a Registry for Alzheimer's disease Assessment Packet (CERAD-K)

Table 2. Adjusted association of salivary flow rate with cognitive impairment (n = 649)

Variables	OR (95% Confidence Interval)	*P*-value
Salivary flow rate (mL/min)		**0.02**
Normal (≥ 0.3)	1	
Low (< 0.3)	1.45 (1.05–2.11)	
Denture status		0.5
Dentate	1	
Denture	1.13 (0.80–1.61)	
Age (year)	1.01 (0.98–1.05)	0.4
Sex		0.4
Male	1	
Female	0.80 (0.50–1.31)	
Education level		**<0.001**
Junior school or less	1	
High school or higher	0.43 (0.27–0.67)	
Smoking*		0.1
No	1	
Yes	0.67 (0.40–1.10)	
Drinking†		0.06
No	1	
Yes	0.71 (0.49–1.01)	
Diabetes‡		**0.02**
No	1	
Yes	1.53 (1.07–2.20)	
Hypertension#		**0.04**
No	1	
Yes	0.69 (0.50–0.97)	
Obesity♦		**0.02**
No	1	
Yes	0.66 (0.46–0.93)	

P-values were obtained by logistic regression adjusted for denture status, age, sex, education level, smoking, drinking, diabetes, hypertension, and obesity.

Bold denotes statistical significance at $p<0.05$.

[*]Smoking: "No" refers to never smoked and "Yes" refers to past and current smoker.

[†]Alcohol intake: No refers to never drunken, and "Yes" refers to past and current drinker.

[‡]Diabetes was determined as "Yes" if fasting plasma glucose >126 mg/dL or $HbA_1C \geq 6.5$ % or history of diabetes.

[#]Hypertension was determined as "Yes" if systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or taking hypertension medication.

[♦]Obesity: Body mass index (kg/m^2) ≥ 25.

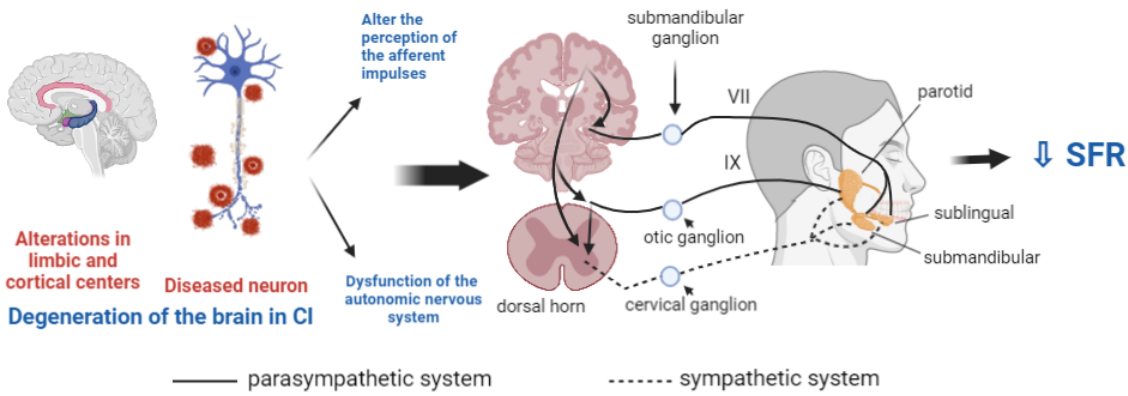

Fig.1. Background of relationship between cognitive impairment and salivary flow rate

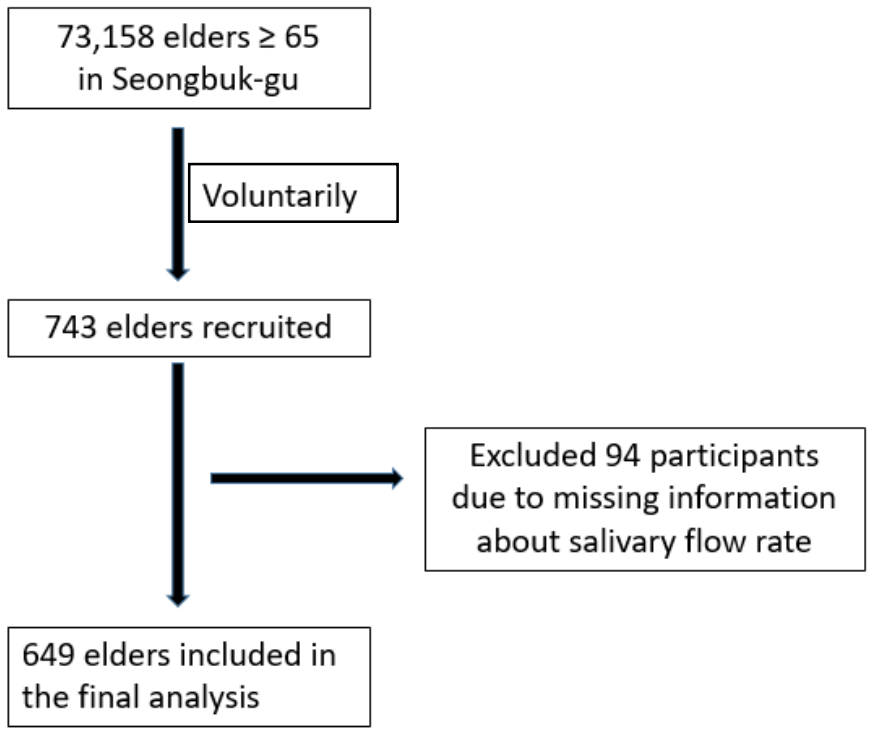

Fig.2. Participants selection flowchart

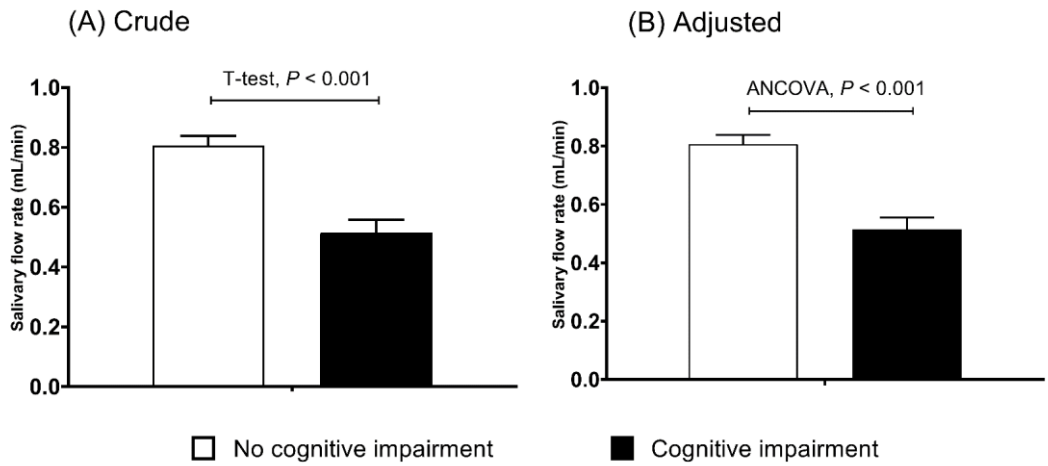

Fig.3. Salivary flow rate (mean ± SE) according to cognitive impairment (*n* = 649).

(A) Crude (0.81 ± 0.04 for cognitive impairment controls versus 0.50 ± 0.03 for cognitive impairment cases); (B) Adjusted (0.81 ± 0.03 for cognitive impairment controls versus 0.52 ± 0.04 for cognitive impairment cases). Bar and whisker are mean and standard error. Adjusted values were from ANCOVA in the general linear model adjusted for denture status, age, sex, education level, smoking, drinking, diabetes, hypertension, and obesity.

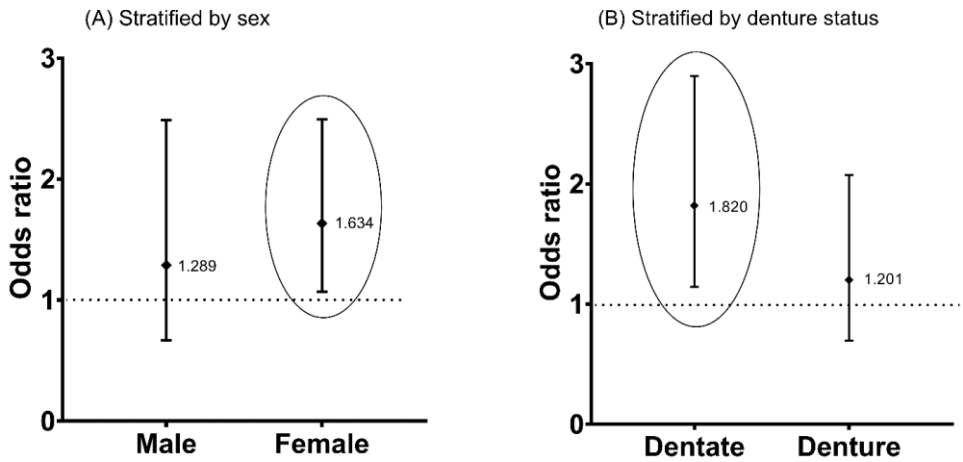

Fig.4. Sex- and denture status-stratified association of salivary flow rate (normal versus low) with cognitive impairment (n = 649).

(A) Sex stratified: Male (Odds ratio [OR] = 1.29, Confident interval [CI]: 0.67–2.5, *P* = 0.45); Female (OR = 1.63, CI: 1.07–2.50, *p* = 0.02); (B) Dental status stratified: Dentate (OR = 1.82, CI: 1.14–2.90, *p* = 0.01); Denture (OR = 1.20, CI: 0.70–2.07, *p* = 0.51). OR were adjusted for denture status, age, sex, education level, smoking, drinking, diabetes, hypertension, and obesity, except for stratified variable in the multivariable logistic regression model. The diamond indicates the OR and a bar indicates 95% CI. The horizontal dotted line is the references as the null of association indicating the OR = 1.

SUPPLEMENTARY TABLE 1. Item scores of MMSE-KC by salivary flow rate (n = 649)

Variable	Salivary Flow Rate (ml/min)		P-value
	Normal (≥ 0.3) (n = 414)	Low (< 0.3) (n = 235)	
Orientation in time (5 points)	3.46 ± 1.04	3.16 ± 0.82	< 0.001
Orientation in place (5 points)	3.79 ± 1.51	3.24 ± 1.69	< 0.001
Verbal memory (6 points)	3.94 ± 1.33	3.62 ± 1.16	0.002
Attention/calculation (5 points)	2.39 ± 1.12	2.16 ± 0.81	0.003
Language (5 points)	4.65 ± 0.63	4.66 ± 0.52	0.74
Praxis (3 points)	2.19 ± 0.54	2.10 ± 0.47	0.01
Visuospatial construction (1 point)	0.63 ± 0.48	0.63 ± 0.49	0.94

Data are presented as mean ± standard deviation. P-values were obtained by T-test

MMSE-KC: Korean version of Mini-Mental State Examination in the Korean version of the Consortium to Establish a Registry for Alzheimer's disease Assessment Packet (CERAD-K)

SUPPLEMENTARY TABLE 2. Item scores of MMSE-KC by cognitive impairment (n = 649)

Variable	Cognitive impairment		P-value
	No (n = 406)	Yes (n = 243)	
Orientation in time (5 points)	3.59 ± 0.99	2.94 ± 0.79	< 0.001
Orientation in place (5 points)	4.06 ± 1.22	2.78 ± 1.81	< 0.001
Verbal memory (6 points)	4.16 ± 1.19	3.25 ± 1.22	< 0.001
Attention/calculation (5 points)	2.61 ± 1.10	1.80 ± 0.59	< 0.001
Language (5 points)	4.77 ± 0.45	4.76 ± 0.75	< 0.001
Praxis (3 points)	2.25 ± 0.50	2.00 ± 0.45	< 0.001
Visuospatial construction (1 point)	0.71 ± 0.46	0.51 ± 0.50	< 0.001

Data are presented as mean ± standard deviation. P-values were obtained by T-test

MMSE-KC: Korean version of Mini-Mental State Examination in the Korean version of the Consortium to Establish a Registry for Alzheimer's disease Assessment Packet (CERAD-K)

SUPPLEMENTARY TABLE 3: Salivary flow rate according to the characteristics of participants (n = 649)

Variable	Salivary flow rate			*P*-value
	Hyposalivation (n=97)	Low (n=138)	Normal (n=414)	
Denture status				0.217
Dentate	57 (15.1)	89 (23.5)	232 (61.4)	
Denture	40 (14.8)	49 (18.1)	182 (67.2)	
Sex				0.060
Male	23 (10.9)	41 (19.4)	147 (69.7)	
Female	74 (16.9)	97 (22.1)	267 (61.0)	
Education level				0.080
Junior school or less	82 (16.6)	107 (21.6)	306 (61.8)	
High school or more	15 (9.7)	31 (20.1)	108 (70.1)	
Smoking*				0.031
No	69 (15.6)	105 (23.8)	267 (60.5)	
Yes	28 (13.5)	33 (15.9)	147 (70.7)	
Drinking†				<0.001
No	40 (18.3)	64 (29.2)	115 (52.5)	
Yes	57 (13.3)	74 (17.2)	299 (69.5)	
Diabetes‡				0.703
No	69 (15.3)	92 (20.4)	290 (64.3)	
Yes	28 (14.1)	46 (23.2)	124 (62.6)	
Hypertension#				0.065
No	34 (11.4)	65 (21.8)	199 (66.8)	
Yes	63 (17.9)	73 (20.8)	215 (61.3)	
Obesity♦				0.715
No	51 (14.1)	80 (22.1)	231 (63.8)	
Yes	46 (16.0)	58 (20.2)	183 (63.8)	

Data are presented as numbers (raw percentage) for categorical variables.

P-values were obtained by Chi-square test for categorical variables

*Smoking: "No" refers to never smoked and "Yes" refers to past and current smoker.

†Alcohol intake: No refers to never drunken, and "Yes" refers to past and

current drinker.

‡Diabetes was determined as "Yes" if fasting plasma glucose >126 mg/dL or $HbA_1C \geq 6.5$ % or a history of diabetes.

#Hypertension was determined as "Yes" if systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or taking hypertension medication.

♦Obesity: Body mass index (kg/m^2) ≥ 25.

SUPPLEMENTARY TABLE 4: Association of salivary flow rate with cognitive impairment in men (n=211)

Variable	N	OR (95% Confidence Interval)	
		Crude	Adjusted*
Salivary flow rate(mL/min)			
Normal (≥ 0.3)	147	1	1
Low (0.1 - 0.3)	41	1.90 (0.94 - 3.84)	1.82 (0.85 - 3.92)
Hyposalivation (<0.1)	23	0.78 (0.29 - 2.09)	0.72 (0.25 - 2.04)

*Adjusted for denture status, age, education level, smoking, drinking, diabetes, hypertension, and obesity

-국문 초록-

한국노인에서 타액유출량과 인지장애 위험의 연관성: 단면조사 연구

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부티녹후옹

1. 연구 목적

타액 기능은 인지장애와 관련이 있는 것으로 제안되고 있으나, 타액유출량의 인지장애에 대한 영향력은 아직 명확하게 규명되지 않았다. 따라서, 본 연구의 목적은 한국노인에서 타액유출량과 인지장애의 연관성 여부를 규명하는 데에 있다.

2. 연구 방법

본 단면조사 연구는 지역사회 주민 중 65세 이상 노인 649명을 대상으로 하였다. 종속변수인 인지장애는 Mini-Mental Status Examination을 사용하여 평가되었다. 설명변수인 타액유출량은 비자극성 타액으로 측정되어 이분화되었다. 설명변수의 종속변수에 대한 연관성 보정을 위한 교란 요인으로 의치장착상태, 연령, 성별, 교육수준, 흡연, 음주, 당뇨병, 고혈압, 비만 등이 고려되었다. 보정연관성 (adjusted association)의 평가에는, 다변수 로지스틱 회귀분석(multivariable logistic regression analysis)이

적용되었다. 효과수정(effect modification)의 평가에는, 성별과 의치장착상태에 따른 층화분석(stratified analysis)이 수행되었다.

3. 연구 결과

타액유출량은 비인지장애 노인에서 0.81mL/min이었고, 인지장애 노인에서 0.52mL/min이어서, 비인지장애 노인에서 비인지장애 노인에서 보다 통계적으로 유의하게 높았다 ($p < 0.001$). 저타액유출량의 인지장애에 대한 보정연관성은 보정교차비(adjusted odds ratio: OR)가 1.5이어서 (신뢰 구간 [confidence interval: CI] = 1.05-2.10), 저타액유출량(< 0.3mL/min) 노인에서 정상타액유출량 노인에서 보다 인지장애 가능성은 1.5배 높았다. 타액유출량의 인지장애에 대한 보정연관성은 여성에서 약 10% 더 높았고 (OR = 1.63, CI = 1.07-2.50), 의치비장착 유치악(dentate) 노인에서 약 22% 더 높았다 (OR = 1.82, CI = 1.41- 2.90).

4. 결론

타액유출량은 한국 노인에서 인지장애와 독립적 연관성이 있었고, 이 연관성은 여성과 의치비장착 유치악 노인에서 높았다. 따라서, 저타액유출량은 의과 및 치과 진료 시 인지장애의 위험요소로 반드시 고려되어야 한다.

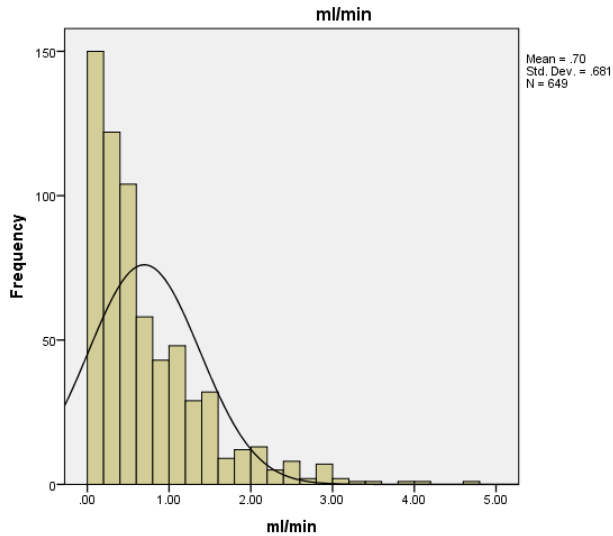
주요어: 노인, 역학, 인지장애, 타액유출량, 한국인

학 번: 2019-27186

APPENDIX

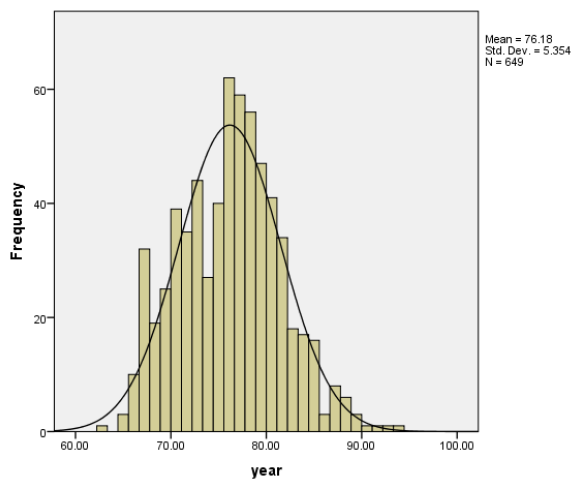
Appendix 1. Distribution of population

1-1 Distribution of salivary flow rate



One-Sample Kolmogorov-Smirnov Test of distribution $p<0.001$

1-2 Distribution of age



One-Sample Kolmogorov-Smirnov Test of distribution $p=0.029$

Appendix 2. Raw data by SPSS statistic

2-1 Raw data by SPSS statistic for Table 1

Table 1: Characteristics of participants by cognitive impairment (n = 649)

2-1-1 T-test

2-1-1-1 MMSE-KC score

Group Statistics

	cognitive_impair	N	Mean	Std. Deviation	Std. Error Mean
MMSE_total	.00	406	27.044	1.8279	.0907
	1.00	243	19.802	3.2857	.2108

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
MMSE_total	Equal variances assumed	51.904	.000	36.065	647	.000	7.2419	.2008	6.8476	7.6362
	Equal variances not assumed			31.559	333.132	.000	7.2419	.2295	6.7905	7.6933

2-1-1-2 Age

Group Statistics

	cognitive_impair	N	Mean	Std. Deviation	Std. Error Mean
age	.00	406	75.8208	5.24522	.26032
	1.00	243	76.7717	5.49017	.35219

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
age	Equal variances assumed	.153	.696	-2.196	647	.028	-.95091	.43296	-1.80109	-.10074
	Equal variances not assumed			-2.171	491.064	.030	-.95091	.43796	-1.81141	-.09042

2-1-1-3 HbA1C

Group Statistics

	cognitive_impair	N	Mean	Std. Deviation	Std. Error Mean
HbA1c	.00	406	6.054	.8469	.0420
	1.00	243	6.168	.9118	.0585

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
HbA1c	Equal variances assumed	2.895	.089	-1.605	647	.109	-.1135	.0707	-.2523	.0254
	Equal variances not assumed			-1.575	479.978	.116	-.1135	.0720	-.2550	.0281

2-1-2 Chi-square test

2-1-2-1 Salivary flow rate

SFR_3G * cognitive_impair Crosstabulation

			cognitive_impair		
			.00	1.00	Total
SFR_3G	1.00	Count	66	31	97
		Expected Count	60.7	36.3	97.0
		% within SFR_3G	68.0%	32.0%	100.0%
		% within cognitive_impair	16.3%	12.8%	14.9%
		% of Total	10.2%	4.8%	14.9%
	2.00	Count	64	74	138
		Expected Count	86.3	51.7	138.0
		% within SFR_3G	46.4%	53.6%	100.0%
		% within cognitive_impair	15.8%	30.5%	21.3%
		% of Total	9.9%	11.4%	21.3%
	3.00	Count	276	138	414
		Expected Count	259.0	155.0	414.0
		% within SFR_3G	66.7%	33.3%	100.0%
		% within cognitive_impair	68.0%	56.8%	63.8%
		% of Total	42.5%	21.3%	63.8%
Total		Count	406	243	649
		Expected Count	406.0	243.0	649.0
		% within SFR_3G	62.6%	37.4%	100.0%
		% within cognitive_impair	100.0%	100.0%	100.0%
		% of Total	62.6%	37.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	19.655[a]	2	.000
Likelihood Ratio	19.156	2	.000
Linear-by-Linear Association	1.636	1	.201
N of Valid Cases	649		

2-1-2-2 Denture status

denture_status * cognitive_impair Crosstabulation

			cognitive_impair		
			.00	1.00	Total
denture_status	.00	Count	244	134	378
		Expected Count	236.5	141.5	378.0
		% within denture_status	64.6%	35.4%	100.0%
		% within cognitive_impair	60.1%	55.1%	58.2%
		% of Total	37.6%	20.6%	58.2%
	1.00	Count	82	53	135
		Expected Count	84.5	50.5	135.0
		% within denture_status	60.7%	39.3%	100.0%
		% within cognitive_impair	20.2%	21.8%	20.8%
		% of Total	12.6%	8.2%	20.8%
	2.00	Count	80	56	136
		Expected Count	85.1	50.9	136.0
		% within denture_status	58.8%	41.2%	100.0%
		% within cognitive_impair	19.7%	23.0%	21.0%
		% of Total	12.3%	8.6%	21.0%
Total		Count	406	243	649
		Expected Count	406.0	243.0	649.0
		% within denture_status	62.6%	37.4%	100.0%
		% within cognitive_impair	100.0%	100.0%	100.0%
		% of Total	62.6%	37.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	1.641[a]	2	.440
Likelihood Ratio	1.634	2	.442
Linear-by-Linear Association	1.600	1	.206
N of Valid Cases	649		

2-1-2-3 Sex

sex * cognitive_impair Crosstabulation

			cognitive_impair		
			.00	1.00	Total
sex	1	Count	140	71	211
		Expected Count	132.0	79.0	211.0
		% within sex	66.4%	33.6%	100.0%
		% within cognitive_impair	34.5%	29.2%	32.5%
		% of Total	21.6%	10.9%	32.5%
	2	Count	266	172	438
		Expected Count	274.0	164.0	438.0
		% within sex	60.7%	39.3%	100.0%
		% within cognitive_impair	65.5%	70.8%	67.5%
		% of Total	41.0%	26.5%	67.5%
Total		Count	406	243	649
		Expected Count	406.0	243.0	649.0
		% within sex	62.6%	37.4%	100.0%
		% within cognitive_impair	100.0%	100.0%	100.0%
		% of Total	62.6%	37.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.920[a]	1	.166		
Continuity Correction[b]	1.688	1	.194		
Likelihood Ratio	1.936	1	.164		
Fisher's Exact Test				.194	.097
Linear-by-Linear Association	1.917	1	.166		
N of Valid Cases	649				

2-1-2-4 Education level

Edu_2G * cognitive_impair Crosstabulation

			cognitive_impair		
			.00	1.00	Total
Edu_2G	.00	Count	287	208	495
		Expected Count	309.7	185.3	495.0
		% within Edu_2G	58.0%	42.0%	100.0%
		% within cognitive_impair	70.7%	85.6%	76.3%
		% of Total	44.2%	32.0%	76.3%
	1.00	Count	119	35	154
		Expected Count	96.3	57.7	154.0
		% within Edu_2G	77.3%	22.7%	100.0%
		% within cognitive_impair	29.3%	14.4%	23.7%
		% of Total	18.3%	5.4%	23.7%
Total		Count	406	243	649
		Expected Count	406.0	243.0	649.0
		% within Edu_2G	62.6%	37.4%	100.0%
		% within cognitive_impair	100.0%	100.0%	100.0%
		% of Total	62.6%	37.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	18.665[a]	1	.000		
Continuity Correction[b]	17.851	1	.000		
Likelihood Ratio	19.696	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	18.637	1	.000		
N of Valid Cases	649				

2-1-2-5 Smoking

Smk_2G * cognitive_impair Crosstabulation

			cognitive_impair		
			.00	1.00	Total
Smk_2G	.00	Count	262	179	441
		Expected Count	275.9	165.1	441.0
		% within Smk_2G	59.4%	40.6%	100.0%
		% within cognitive_impair	64.5%	73.7%	68.0%
		% of Total	40.4%	27.6%	68.0%
	1.00	Count	144	64	208
		Expected Count	130.1	77.9	208.0
		% within Smk_2G	69.2%	30.8%	100.0%
		% within cognitive_impair	35.5%	26.3%	32.0%
		% of Total	22.2%	9.9%	32.0%
Total		Count	406	243	649
		Expected Count	406.0	243.0	649.0
		% within Smk_2G	62.6%	37.4%	100.0%
		% within cognitive_impair	100.0%	100.0%	100.0%
		% of Total	62.6%	37.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	5.819[a]	1	.016		
Continuity Correction[b]	5.408	1	.020		
Likelihood Ratio	5.912	1	.015		
Fisher's Exact Test				.019	.010
Linear-by-Linear Association	5.810	1	.016		
N of Valid Cases	649				

2-1-2-6 Drinking

Alc_2G * cognitive_impair Crosstabulation

			cognitive_impair		
			.00	1.00	Total
Alc_2G	.00	Count	118	101	219
		Expected Count	137.0	82.0	219.0
		% within Alc_2G	53.9%	46.1%	100.0%
		% within cognitive_impair	29.1%	41.6%	33.7%
		% of Total	18.2%	15.6%	33.7%
	1.00	Count	288	142	430
		Expected Count	269.0	161.0	430.0
		% within Alc_2G	67.0%	33.0%	100.0%
		% within cognitive_impair	70.9%	58.4%	66.3%
		% of Total	44.4%	21.9%	66.3%
Total		Count	406	243	649
		Expected Count	406.0	243.0	649.0
		% within Alc_2G	62.6%	37.4%	100.0%
		% within cognitive_impair	100.0%	100.0%	100.0%
		% of Total	62.6%	37.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	10.623[a]	1	.001		
Continuity Correction[b]	10.072	1	.002		
Likelihood Ratio	10.512	1	.001		
Fisher's Exact Test				.001	.001
Linear-by-Linear Association	10.607	1	.001		
N of Valid Cases	649				

2-1-2-7 Diabetes

Diabetes_2G * cognitive_impair Crosstabulation

			cognitive_impair		
			.00	1.00	Total
Diabetes_2G	.00	Count	292	159	451
		Expected Count	282.1	168.9	451.0
		% within Diabetes_2G	64.7%	35.3%	100.0%
		% within cognitive_impair	71.9%	65.4%	69.5%
		% of Total	45.0%	24.5%	69.5%
	1.00	Count	114	84	198
		Expected Count	123.9	74.1	198.0
		% within Diabetes_2G	57.6%	42.4%	100.0%
		% within cognitive_impair	28.1%	34.6%	30.5%
		% of Total	17.6%	12.9%	30.5%
Total		Count	406	243	649
		Expected Count	406.0	243.0	649.0
		% within Diabetes_2G	62.6%	37.4%	100.0%
		% within cognitive_impair	100.0%	100.0%	100.0%
		% of Total	62.6%	37.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.019[a]	1	.082		
Continuity Correction[b]	2.721	1	.099		
Likelihood Ratio	2.994	1	.084		
Fisher's Exact Test				.094	.050
Linear-by-Linear Association	3.015	1	.083		
N of Valid Cases	649				

2-1-2-8 Hypertension

HypT_2G * cognitive_impair Crosstabulation

			cognitive_impair		
			.00	1.00	Total
HypT_2G	.00	Count	173	125	298
		Expected Count	186.4	111.6	298.0
		% within HypT_2G	58.1%	41.9%	100.0%
		% within cognitive_impair	42.6%	51.4%	45.9%
		% of Total	26.7%	19.3%	45.9%
	1.00	Count	233	118	351
		Expected Count	219.6	131.4	351.0
		% within HypT_2G	66.4%	33.6%	100.0%
		% within cognitive_impair	57.4%	48.6%	54.1%
		% of Total	35.9%	18.2%	54.1%
Total		Count	406	243	649
		Expected Count	406.0	243.0	649.0
		% within HypT_2G	62.6%	37.4%	100.0%
		% within cognitive_impair	100.0%	100.0%	100.0%
		% of Total	62.6%	37.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.772[a]	1	.029		
Continuity Correction[b]	4.423	1	.035		
Likelihood Ratio	4.768	1	.029		
Fisher's Exact Test				.034	.018
Linear-by-Linear Association	4.765	1	.029		
N of Valid Cases	649				

2-1-2-9 Obesity

obesity * cognitive_impair Crosstabulation

			cognitive_impair		
			.00	1.00	Total
obesity	0	Count	211	151	362
		Expected Count	226.5	135.5	362.0
		% within obesity	58.3%	41.7%	100.0%
		% within cognitive_impair	52.0%	62.1%	55.8%
		% of Total	32.5%	23.3%	55.8%
	1	Count	195	92	287
		Expected Count	179.5	107.5	287.0
		% within obesity	67.9%	32.1%	100.0%
		% within cognitive_impair	48.0%	37.9%	44.2%
		% of Total	30.0%	14.2%	44.2%
Total		Count	406	243	649
		Expected Count	406.0	243.0	649.0
		% within obesity	62.6%	37.4%	100.0%
		% within cognitive_impair	100.0%	100.0%	100.0%
		% of Total	62.6%	37.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6.374[a]	1	.012		
Continuity Correction[b]	5.968	1	.015		
Likelihood Ratio	6.413	1	.011		
Fisher's Exact Test				.014	.007
Linear-by-Linear Association	6.364	1	.012		
N of Valid Cases	649				

2-2 Raw data by SPSS statistic for Table 2

Table 2: Adjusted association of salivary flow rate with cognitive impairment (n = 649)

Adjusted odds ratio

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	SFR_2G(1)	.398	.177	5.063	1	.024	1.449	1.053	2.107
	denture_status_2G	.123	.180	.468	1	.494	1.131	.795	1.608
	age	.015	.017	.811	1	.368	1.015	.983	1.048
	sex	-.233	.256	.826	1	.363	.792	.480	1.309
	Edu_2G	-.847	.227	13.917	1	.000	.428	.275	.669
	Smk_2G	-.406	.258	2.482	1	.115	.666	.402	1.104
	Alc_2G	-.346	.184	3.532	1	.060	.707	.493	1.015
	Diabetes_2G	.427	.184	5.371	1	.020	1.533	1.068	2.200
	HypT_2G	-.364	.172	4.467	1	.035	.695	.496	.974
	obesity	-.421	.177	5.695	1	.017	.656	.464	.928
	Constant	-.688	1.409	.239	1	.625	.502		

a. Variable(s) entered on step 1: SFR_2G, denture_status_2G, age, sex, Edu_2G, Smk_2G, Alc_2G, Diabetes_2G, HypT_2G, obesity.

2-3 Raw data by SPSS statistic for Figure 3

Figure 3: Salivary flow rate (mean ± SE) according to cognitive impairment (n = 649)

2-3-1. Crude value

Group Statistics

	cognitive_impair	N	Mean	Std. Deviation	Std. Error Mean
sal_Flow	.00	406	.8141	.76474	.03795
	1.00	243	.5009	.44734	.02870

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
sal_Flow	Equal variances assumed	55.256	.000	5.816	647	.000	.31326	.05386	.20750	.41902
	Equal variances not assumed			6.584	646.707	.000	.31326	.04758	.21983	.40669

2-3-2. Adjusted value

Estimates

Dependent Variable: sal_Flow

MMSE 24	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
.00	.806[a]	.033	.740	.871
1.00	.515[a]	.043	.430	.600

a. Covariates appearing in the model are evaluated at the following values: denture_status = .6271, age = 76.1769, sex = 1.67, Edu_2G = .2373, Smk_2G = .3205, Alc_2G = .6626, Diabetes_2G = .3051, HypT_2G = .5408, obesity = .44.

Pairwise Comparisons

Dependent Variable: sal_Flow

(I) MMSE 24	(J) MMSE 24	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
.00	1.00	.291*	.056	.000	.182	.400
1.00	.00	-.291*	.056	.000	-.400	-.182

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Univariate Tests

Dependent Variable: sal_Flow

	Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Contrast	11.964	1	11.964	27.445	.000	.041
Error	278.125	638	.436			

The F tests the effect of MMSE 24. This test is based on the linearly independent pairwise comparisons among the estimated marginal means.

2-4 Raw data by SPSS statistic for Figure 4

Figure 4. Sex and denture status stratified association of salivary flow rate (normal versus low) with cognitive impairment (n = 649).

2-4-1. Stratification by sex (n=649)

2-4-1-1. Stratification by males (n=211)

Variables in the Equation[a]

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[b]	SFR_2G(1)	.254	.335	.574	1	.449	1.289	.668	2.488
	denture_status_2G	-.133	.324	.170	1	.680	.875	.464	1.651
	age	-.013	.028	.211	1	.646	.987	.934	1.044
	Edu_2G	-.565	.324	3.051	1	.081	.568	.301	1.071
	Smk_2G	-.371	.366	1.025	1	.311	.690	.337	1.415
	Alc_2G	-.715	.391	3.350	1	.067	.489	.227	1.052
	Diabetes_2G	.460	.325	2.005	1	.157	1.585	.838	2.996
	HypT_2G	-.163	.308	.279	1	.598	.850	.465	1.554
	obesity	.214	.324	.434	1	.510	1.238	.656	2.337
	Constant	1.215	2.251	.291	1	.589	3.371		

a. sex = 1

b. Variable(s) entered on step 1: SFR_2G, denture_status_2G, age, Edu_2G, Smk_2G, Alc_2G, Diabetes_2G, HypT_2G, obesity.

2-4-1-2. Stratification by males (n=438)

Variables in the Equation[a]

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[b]	SFR_2G(1)	.491	.216	5.166	1	.023	1.634	1.070	2.495
	denture_status_2G	.215	.222	.939	1	.333	1.240	.802	1.917
	age	.033	.021	2.455	1	.117	1.034	.992	1.078
	Edu_2G	-1.187	.346	11.738	1	.001	.305	.155	.602
	Smk_2G	-.466	.378	1.523	1	.217	.627	.299	1.315
	Alc_2G	-.171	.220	.603	1	.437	.843	.548	1.297
	Diabetes_2G	.353	.231	2.327	1	.127	1.423	.904	2.238
	HypT_2G	-.451	.214	4.445	1	.035	.637	.419	.969
	obesity	-.745	.214	12.149	1	.000	.475	.312	.722
	Constant	-2.479	1.647	2.265	1	.132	.084		

a. sex = 2

b. Variable(s) entered on step 1: SFR_2G, denture_status_2G, age, Edu_2G, Smk_2G, Alc_2G, Diabetes_2G, HypT_2G, obesity.

2-4-2. Stratification by denture status (n=649)

2-4-2-1. Stratification by dentate (n=378)

Variables in the Equation[a]

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[b]	SFR_2G(1)	.599	.237	6.368	1	.012	1.820	1.143	2.897
	age	.056	.024	5.461	1	.019	1.057	1.009	1.108
	sex	-.545	.353	2.381	1	.123	.580	.290	1.159
	Edu_2G	-1.192	.310	14.820	1	.000	.304	.166	.557
	Smk_2G	-.414	.358	1.338	1	.247	.661	.327	1.333
	Alc_2G	-.189	.259	.529	1	.467	.828	.498	1.377
	Diabetes_2G	.320	.258	1.532	1	.216	1.377	.830	2.285
	HypT_2G	-.571	.232	6.063	1	.014	.565	.358	.890
	obesity	-.244	.235	1.073	1	.300	.784	.494	1.243
	Constant	-3.295	2.031	2.633	1	.105	.037		

a. denture_status = .00

b. Variable(s) entered on step 1: SFR_2G, age, sex, Edu_2G, Smk_2G, Alc_2G, Diabetes_2G, HypT_2G, obesity.

2-4-2-2. Stratification by denture (n=271)

Variables in the Equation[a]

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[b]	SFR_2G(1)	.183	.279	.430	1	.512	1.201	.695	2.075
	age	-.030	.024	1.558	1	.212	.970	.925	1.017
	sex	.172	.391	.194	1	.659	1.188	.552	2.554
	Edu_2G	-.341	.354	.932	1	.334	.711	.356	1.421
	Smk_2G	-.395	.390	1.025	1	.311	.674	.314	1.447
	Alc_2G	-.553	.277	3.985	1	.046	.575	.334	.990
	Diabetes_2G	.574	.275	4.359	1	.037	1.776	1.036	3.046
	HypT_2G	.033	.271	.015	1	.904	1.033	.607	1.759
	obesity	-.695	.280	6.175	1	.013	.499	.288	.863
	Constant	2.203	2.104	1.096	1	.295	9.049		

a. denture_status_2G = 1.00

b. Variable(s) entered on step 1: SFR_2G, age, sex, Edu_2G, Smk_2G, Alc_2G, Diabetes_2G, HypT_2G, obesity.

2-5 Raw data by SPSS statistic for Supplementary Table 1

Supplementary Table 1. Item scores of MMSE-KC by salivary flow rate (n = 649)

Group Statistics

	SFR_2g	N	Mean	Std. Deviation	Std. Error Mean
MMSE_time	.00	414	3.4565	1.03769	.05100
	1.00	235	3.1617	.82134	.05358
MMSE_place	.00	414	3.7850	1.51175	.07430
	1.00	235	3.2383	1.69041	.11027
MMSE_memo	.00	414	3.9420	1.32823	.06528
	1.00	235	3.6170	1.15753	.07551
MMSE_att	.00	414	2.3913	1.11626	.05486
	1.00	235	2.1617	.81086	.05289
MMSE_lang	.00	414	4.6473	.63496	.03121
	1.00	235	4.6638	.52478	.03423
MMSE_praxis	.00	414	2.1932	.53575	.02633
	1.00	235	2.0979	.40693	.02655
MMSE_vis	.00	414	.6329	.48261	.02372
	1.00	235	.6298	.48389	.03157

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
MMSE_time	Equal variances assumed	49.315	.000	3.740	647	.000	.29482	.07882	.14004	.44960
	Equal variances not assumed			3.986	580.245	.000	.29482	.07397	.14954	.44010
MMSE_place	Equal variances assumed	9.184	.003	4.240	647	.000	.54673	.12894	.29353	.79992
	Equal variances not assumed			4.112	442.966	.000	.54673	.13297	.28540	.80805
MMSE_memo	Equal variances assumed	1.827	.177	3.135	647	.002	.32501	.10366	.12146	.52855
	Equal variances not assumed			3.256	542.722	.001	.32501	.09981	.12894	.52108
MMSE_att	Equal variances assumed	41.115	.000	2.766	647	.006	.22960	.08302	.06658	.39262
	Equal variances not assumed			3.013	608.958	.003	.22960	.07621	.07994	.37926
MMSE_lang	Equal variances assumed	1.284	.258	-.338	647	.736	-.01649	.04880	-.11231	.07933
	Equal variances not assumed			-.356	563.878	.722	-.01649	.04632	-.10747	.07450
MMSE_praxis	Equal variances assumed	35.163	.000	2.368	647	.018	.09536	.04027	.01629	.17444
	Equal variances not assumed			2.551	594.764	.011	.09536	.03739	.02193	.16880
MMSE_vis	Equal variances assumed	.024	.877	.078	647	.938	.00306	.03946	-.07441	.08054
	Equal variances not assumed			.078	485.205	.938	.00306	.03948	-.07452	.08064

2-6 Raw data by SPSS statistic for Supplementary Table 2

Supplementary Table 2. Item scores of MMSE-KC by cognitive impairment (n = 649)

Group Statistics

	cognitive_impair	N	Mean	Std. Deviation	Std. Error Mean
MMSE_time	.00	406	3.5936	.99125	.04919
	1.00	243	2.9424	.79563	.05104
MMSE_place	.00	406	4.0690	1.22532	.06081
	1.00	243	2.7819	1.81527	.11645
MMSE_memo	.00	406	4.1675	1.18906	.05901
	1.00	243	3.2510	1.21575	.07799
MMSE_att	.00	406	2.6108	1.10276	.05473
	1.00	243	1.8025	.59097	.03791
MMSE_lang	.00	406	4.7685	.44510	.02209
	1.00	243	4.4609	.75070	.04816
MMSE_praxis	.00	406	2.2512	.49783	.02471
	1.00	243	2.0041	.44996	.02886
MMSE_vis	.00	406	.7069	.45575	.02262
	1.00	243	.5062	.50099	.03214

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
MMSE_time	Equal variances assumed	105.493	.000	8.699	647	.000	.65121	.07486	.50422	.79820
	Equal variances not assumed			9.186	594.114	.000	.65121	.07089	.51199	.79043
MMSE_place	Equal variances assumed	100.126	.000	10.767	647	.000	1.28707	.11954	1.05234	1.52181
	Equal variances not assumed			9.797	375.309	.000	1.28707	.13137	1.02876	1.54539
MMSE_memo	Equal variances assumed	.300	.584	9.423	647	.000	.91646	.09726	.72548	1.10743
	Equal variances not assumed			9.371	500.415	.000	.91646	.09780	.72431	1.10861
MMSE_att	Equal variances assumed	136.971	.000	10.554	647	.000	.80837	.07660	.65796	.95877
	Equal variances not assumed			12.142	640.223	.000	.80837	.06658	.67763	.93910
MMSE_lang	Equal variances assumed	81.293	.000	6.554	647	.000	.30757	.04693	.21541	.39972
	Equal variances not assumed			5.805	345.415	.000	.30757	.05298	.20336	.41178
MMSE_praxis	Equal variances assumed	76.759	.000	6.341	647	.000	.24712	.03897	.17059	.32364
	Equal variances not assumed			6.504	550.075	.000	.24712	.03799	.17248	.32175
MMSE_vis	Equal variances assumed	49.928	.000	5.230	647	.000	.20072	.03838	.12536	.27608
	Equal variances not assumed			5.107	471.914	.000	.20072	.03930	.12350	.27795

2-7 Raw data by SPSS statistic for Supplementary Table 3

Supplementary Table 3. Salivary flow rate according to the characteristics of participants (n = 649)

2-7-1 Denture status

denture_status_2G * SFR_3G

Crosstab

			SFR_3G			
			1.00	2.00	3.00	Total
denture_status_2G	.00	Count	57	89	232	378
		% within denture_status_2G	15.1%	23.5%	61.4%	100.0%
	1.00	Count	40	49	182	271
		% within denture_status_2G	14.8%	18.1%	67.2%	100.0%
Total		Count	97	138	414	649
		% within denture_status_2G	14.9%	21.3%	63.8%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	3.054[a]	2	.217
Likelihood Ratio	3.089	2	.213
Linear-by-Linear Association	1.069	1	.301
N of Valid Cases	649		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 40.50.

2-7-2 Sex

sex * SFR_3G

Crosstab

			SFR_3G			
			1.00	2.00	3.00	Total
sex	1	Count	23	41	147	211
		% within sex	10.9%	19.4%	69.7%	100.0%
	2	Count	74	97	267	438
		% within sex	16.9%	22.1%	61.0%	100.0%
Total		Count	97	138	414	649
		% within sex	14.9%	21.3%	63.8%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	5.611[a]	2	.060
Likelihood Ratio	5.790	2	.055
Linear-by-Linear Association	5.601	1	.018
N of Valid Cases	649		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 31.54.

2-7-3 Education level

Edu_2G * SFR_3G

Crosstab

			SFR_3G			
			1.00	2.00	3.00	Total
Edu_2G	.00	Count	82	107	306	495
		% within Edu_2G	16.6%	21.6%	61.8%	100.0%
	1.00	Count	15	31	108	154
		% within Edu_2G	9.7%	20.1%	70.1%	100.0%
Total		Count	97	138	414	649
		% within Edu_2G	14.9%	21.3%	63.8%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	5.055[a]	2	.080
Likelihood Ratio	5.396	2	.067
Linear-by-Linear Association	4.897	1	.027
N of Valid Cases	649		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 23.02.

2-7-4 Smoking

Smk_2G * SFR_3G

Crosstab

			SFR_3G			
			1.00	2.00	3.00	Total
Smk_2G	.00	Count	69	105	267	441
		% within Smk_2G	15.6%	23.8%	60.5%	100.0%
	1.00	Count	28	33	147	208
		% within Smk_2G	13.5%	15.9%	70.7%	100.0%
Total		Count	97	138	414	649
		% within Smk_2G	14.9%	21.3%	63.8%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	6.919[a]	2	.031
Likelihood Ratio	7.115	2	.029
Linear-by-Linear Association	3.899	1	.048
N of Valid Cases	649		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 31.09.

2-7-5 Drinking

Alc_2G * SFR_3G

Crosstab

			SFR_3G			
			1.00	2.00	3.00	Total
Alc_2G	.00	Count	40	64	115	219
		% within Alc_2G	18.3%	29.2%	52.5%	100.0%
	1.00	Count	57	74	299	430
		% within Alc_2G	13.3%	17.2%	69.5%	100.0%
Total		Count	97	138	414	649
		% within Alc_2G	14.9%	21.3%	63.8%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	18.878[a]	2	.000
Likelihood Ratio	18.567	2	.000
Linear-by-Linear Association	12.815	1	.000
N of Valid Cases	649		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 32.73.

2-7-6 Diabetes

Diabetes_2G * SFR_3G

Crosstab

			SFR_3G			
			1.00	2.00	3.00	Total
Diabetes_2G	.00	Count	69	92	290	451
		% within Diabetes_2G	15.3%	20.4%	64.3%	100.0%
	1.00	Count	28	46	124	198
		% within Diabetes_2G	14.1%	23.2%	62.6%	100.0%
Total		Count	97	138	414	649
		% within Diabetes_2G	14.9%	21.3%	63.8%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.703[a]	2	.703
Likelihood Ratio	.696	2	.706
Linear-by-Linear Association	.007	1	.935
N of Valid Cases	649		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 29.59.

2-7-7 Hypertension

HypT_2G * SFR_3G

Crosstab

			SFR_3G			
			1.00	2.00	3.00	Total
HypT_2G	.00	Count	34	65	199	298
		% within HypT_2G	11.4%	21.8%	66.8%	100.0%
	1.00	Count	63	73	215	351
		% within HypT_2G	17.9%	20.8%	61.3%	100.0%
Total		Count	97	138	414	649
		% within HypT_2G	14.9%	21.3%	63.8%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	5.460[a]	2	.065
Likelihood Ratio	5.554	2	.062
Linear-by-Linear Association	4.268	1	.039
N of Valid Cases	649		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 44.54.

2-7-8 Obesity

obesity * SFR_3G

Crosstab

			SFR_3G			
			1.00	2.00	3.00	Total
obesity	0	Count	51	80	231	362
		% within obesity	14.1%	22.1%	63.8%	100.0%
	1	Count	46	58	183	287
		% within obesity	16.0%	20.2%	63.8%	100.0%
Total		Count	97	138	414	649
		% within obesity	14.9%	21.3%	63.8%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.672[a]	2	.715
Likelihood Ratio	.671	2	.715
Linear-by-Linear Association	.115	1	.734
N of Valid Cases	649		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 42.90.

2-8 Raw data by SPSS statistic for Supplementary Table 4

Supplementary Table 4: Association of salivary flow rate with cognitive impairment in men (n=211)

2-8-1 Crude value

Variables in the Equation[a]

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[b]	SFR_3G			3.834	2	.147			
	SFR_3G(1)	-.255	.507	.253	1	.615	.775	.287	2.094
	SFR_3G(2)	.640	.360	3.156	1	.076	1.896	.936	3.841
	Constant	-.786	.178	19.550	1	.000	.455		

a. sex = 1

b. Variable(s) entered on step 1: SFR_3G.

2-8-2 Adjusted value

Variables in the Equation[a]

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[b]	SFR_3G			3.098	2	.212			
	SFR_3G(1)	-.329	.531	.385	1	.535	.719	.254	2.037
	SFR_3G(2)	.601	.391	2.357	1	.125	1.823	.847	3.924
	age	-.012	.028	.165	1	.685	.989	.935	1.045
	Edu_2G	-.639	.328	3.805	1	.051	.528	.278	1.003
	Smk_2G	-.350	.363	.928	1	.335	.705	.346	1.436
	Alc_2G	-.611	.391	2.435	1	.119	.543	.252	1.169
	Diabetes_2G	.499	.328	2.319	1	.128	1.647	.867	3.130
	HypT_2G	-.122	.310	.155	1	.694	.885	.482	1.626
	obesity	.191	.324	.346	1	.556	1.210	.641	2.286
	Constant	.927	2.269	.167	1	.683	2.526		

a. sex = 1

b. Variable(s) entered on step 1: SFR_3G, age, Edu_2G, Smk_2G, Alc_2G, Diabetes_2G, HypT_2G, obesity.

Appendix 3: Strengthening the Reporting of Observational studies (STROBE) in Epidemiology guideline

STROBE Statement - Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes. In Abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes. In Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes. In Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes. In Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Yes. In Method
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes. In Method
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes. In Method and Figure 2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes. In Method
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes. In Method
Bias	9	Describe any efforts to address potential sources of bias	Yes. In Method
Study size	10	Explain how the study size was arrived at	Yes. In Method
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes. In Method
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes. In Method
		(*b*) Describe any methods used to examine subgroups and interactions	Yes. In Method
		(*c*) Explain how missing data were addressed	Yes. In Method
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Yes. In Method
		(*e*) Describe any sensitivity analyses	Yes. In Method
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes. In Method
		(b) Give reasons for non-participation at each stage	Yes. In Method

		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes. In Results and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Yes. In Method
Outcome data	15*	Report numbers of outcome events or summary measures	Yes. In Results and Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes. In Results, Table 2 and Figure 3
		(*b*) Report category boundaries when continuous variables were categorized	Yes. In Results and Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done - (e.g.) analyses of subgroups and interactions, and sensitivity analyses	Yes. In Results and Figure 4
Discussion			
Key results	18	Summarize key results with reference to study objectives	Yes. In Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes. In Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes. In Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes. In Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes