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Retrospective analysis of the association between tooth loss and dementia: a population-based matched case-control study

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Objective: To clarify the association between multiple tooth loss and dementia. ***Basic research design***: Case-control study based on the claims data from National Health Insurance Research Database (NHIRD). Patients were divided into two groups: the dementia groups and non-dementia group. For each case patient, one control patient was randomly selected and frequency matched by age (per 5 years) and sex. The case group comprised patients newly diagnosed with dementia, and the index date was the the date of dementia diagnosis, which became the baseline for comorbidity and age calculations. ***Results***: Among the 43,026 individuals, patients with dementia had a significantly higher extraction density at ages 60–69 ($p < 0.0001$) and 70–79 ($p = 0.04$) years compared with control patients. ***Conclusions***: This population-based retrospective study demonstrated an association between tooth loss and dementia. Patients in Taiwan with more tooth extraction experience are likely to have an increased risk of dementia.

Keywords: *Tooth loss; dementia; cognitive impairment*

Introduction

Dementia is a neurocognitive disorder that deteriorates memory, behavior, and cognitive ability. It has physical, psychological, social, and economical effects, not only on patients. but also on their caregivers, families and society. According to the World Health Organization, approximately 50 million people worldwide have dementia, and every year, nearly 10 million new cases are diagnosed. In 2015, the total global societal cost of dementia was estimated to be US$818 billion, equivalent to 1.1% of the global gross domestic product (WHO, 2015).

Although age is the most recognized risk factor for dementia, vascular and psychological diseases, drugs such as antidepressants, and genetic factors are also reported to be associated with the condition (Zen, 2017). Among such factors, oral health has drawn attention because of its relationships with Alzheimer's disease and dementia (Gatz *et al.*, 2006). Suggested underlying mechanisms include poor nutritional status due to impaired masticatory function; periodontal disease–derived inflammatory molecules, bacteria, and bacterial products that promote brain inflammation; and lack of masticatory stimulation (Stein *et al.*, 2007; Okamoto *et al.*, 2010). Additionally, systemic disease may result from pathogenic bacteria among the more than 500 bacterial species harbored in the periodontal pockets (Terezhalmy *et al.*, 1997). In some animal studies, lack of masticatory stimulation has resulted in learning or memory disorder and spatial memory impairment (Yamazaki *et al.*, 2008).

Several community-based surveys have supported the hypothesis that tooth loss is associated with dementia (Okamoto *et al.*, 2010; Takeuchi *et al.*, 2017; Luo *et al.*, 2015). However, research on the association of dementia with tooth loss with a long study period and large sample is limited. In addition, because of differences in the medical environment, patient education, and home-care quality among countries, the tooth care of patients with dementia may vary.

Our study used a population-based design with a large sample size to minimize selection bias and accurately reflect the general population. This case–control study used Taiwan's National Health Insurance Research Database (NHIRD) to test the hypothesis that tooth loss is associated with dementia with a 13-year study period.

Methods

Data source

The National Health Research Institute is a Taiwanese governmental institute that established the NHIRD using de-identified claims data from the National Health Insurance (NHI) program. The NHI is a government program that has provided thorough and comprehensive health care for nearly all residents of Taiwan since 1995. Thus, the NHIRD includes the health care claims data from almost 99% of Taiwanese citizens. The claims data of the NHIRD encompass comprehensive demographic information and

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medical records of diagnoses, examinations, prescriptions, and operations from outpatient, inpatient, and emergency care facilities.

We used data from 1996 to 2013 from the Longitudinal Health Insurance Database 2000, which randomly selected 1 million representative individuals (approximately 4.34% of the NHIRD) with a similar distribution of age and sex (χ^2 = 1.74, degrees of freedom = 1, p = 0.187) to that of the entire population of Taiwan. The medical diagnosis and treatment histories of the individuals were recorded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115-R3).

Study population

We conducted a case–control study with two groups: people with and without dementia (cases and controls respectively). The case group comprised patients newly diagnosed (*ICD-9-CM* codes 290, 290.0, 290.1x, 290.2x, 290.3x, 290.4x, 290.8, 290.9, 294.1, 331.0) by a clinical psychiatrist or neurologist between 2000 and 2013. The index date was set as the date of dementia diagnosis and became the baseline for comorbidity and age calculations. For each case, one control was randomly selected and frequency matched by age (per 5 years) and sex. Patients with tooth loss (*ICD-9-OP* codes 92013C, 92014C, 92015C, 92016C) but who had more than seven teeth extracted at one time were excluded to avoid situations such as extractions in cases of trauma, for prosthetic concerns, or from patients with disabilities. Most comorbidities were identified by at least three outpatient visits or one inpatient visit before the index date. These comorbidities were diabetes mellitus (*ICD-9-CM* code 250), hypertension (*ICD-9-CM* codes 401–405), insomnia (*ICD-9-CM* codes 307.41, 307.42, 307.49, 780.50, 780.52, 780.55, 780.56, 780.59), and anxiety (*ICD-9-CM* 300.0–300.3, 300.5–300.9, 309.2–309.4, 309.81, 313.0). Other comorbidities, such as stroke (*ICD-9-CM* codes 430–438) and depression (296.2, 296.3, 300.4, 311.0), were identified by at least one outpatient visit or one inpatient visit before the index date.

Statistical analysis

Demographic characteristics were compared across the two groups using chi-square and t testing for categorical and continuous variables, respectively. Conditional logistic regression with p values was used to estimate the association between tooth loss and dementia. In addition, extraction density was calculated as (total extractions)/(duration) × 100. All statistical analyses were performed using the SAS statistical software package, version 9.4 (SAS Institute Inc., Cary, NC). The significance criterion was set as a two-sided p value of < 0.05.

Results

We included 21,513 (50%) patients with dementia and 21,513 (50%) without (Table 1). Among the participants, 52.8% were female in both groups, and the mean ages were 74.87 and 75.09 years in the non-dementia and dementia groups, respectively. The grouped age, mean age, and sex were similar in the two groups, because of the matching by age and sex. Also, we addressed several comorbidities in this study, namely stroke (p < 0.0001), depression (p < 0.0001), diabetes mellitus (p < 0.0001), hypertension (p < 0.0001), insomnia (p < 0.0001), and anxiety (p < 0.0001) were more prevalent in the dementia group. Table 2 presents the number of teeth extracted before the diagnosis of dementia. During the study period, the highest extraction density in the dementia group was among 80–89 year olds and in the non-dementia groups was among the 70–79 year olds (23.49 per 100 and 21.30 per 100, respectively). Patients with dementia had significantly higher extraction densities at ages 60–69 (p = 0.001) and 70–79 (p = 0.04) years compared with those in the control group.

The extraction number and density of the dementia group were higher than those of the non-dementia group at all age intervals, but statistically significant differences were observed for only the 60–69-year- and 70–79-year-old groups (Figures 1 and 2).

Table 1. Demographic characteristics of patients with and without dementia.

Variable	*Dementia patients*				*p*
	Yes n=21513		*No* n=21513		
	n	*%*	*n*	*%*	
Gender[1]					0.99
Female	11205	52.08	11205	52.08	
Male	10308	47.92	10308	47.92	
Age at baseline, years[1]					0.99
Less than 40	309	1.44	309	1.44	
40-49	429	1.99	429	1.99	
50-59	1288	5.99	1288	5.99	
60-69	3429	15.94	3429	15.94	
70-79	8178	38.01	8178	38.01	
80-89	6853	31.86	6853	31.86	
90-99	1018	4.73	1018	4.73	
Older than 100 years	9	0.04	9	0.04	
Mean (SD)[2]	75.09 (11.50)		74.87 (11.55)		
Comorbidities[1]					
Stroke	13671	63.55	7557	35.13	<.0001
Depression	3151	14.65	823	3.83	<.0001
Diabetes mellitus	8305	38.6	5987	27.83	<.0001
Hypertension	16676	77.52	14180	65.91	<.0001
Insomnia	8304	38.6	5272	24.51	<.0001
Anxiety	7507	34.9	4410	20.5	<.0001

[1]: chi-square test [2]: t test
Abbreviation: SD: standard deviation.

Table 2. Number of extracted teeth 13 years before diagnosed as dementia.

Variable	*Dementia*		*Non-dementia*		*p* [1]
	Total Extraction	*extraction density*[2]	*Total Extraction*	*extraction density*	
Age group (years)					
Less than 40	355	11	282	8.74	0.86
40-49	469	9.92	426	9	0.65
50-59	2254	14.79	2105	13.81	0.94
60-69	8191	20.55	6880	17.26	<.0001
70-79	22158	23.28	20270	21.31	0.04
80-89	19748	23.49	18659	22.18	0.32
90-99	2605	20.27	1815	14.11	0.10

[1] *p* in conditional logistic regression, adjusting for age as a continuous variable and comorbidities.
[2] Extraction density: (total extracts/duration) *100.

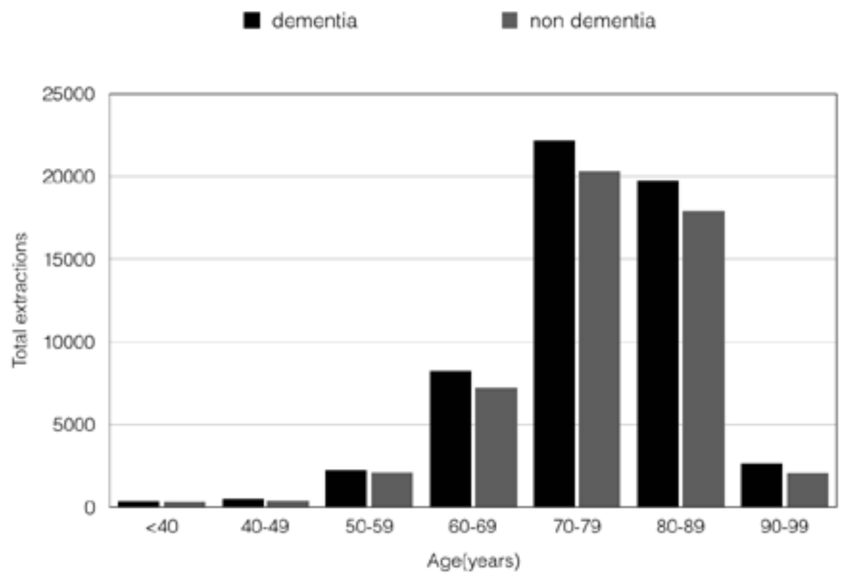

Figure 1. *The extraction number among dementia and non-dementia group in different ages at 10-year interval.*

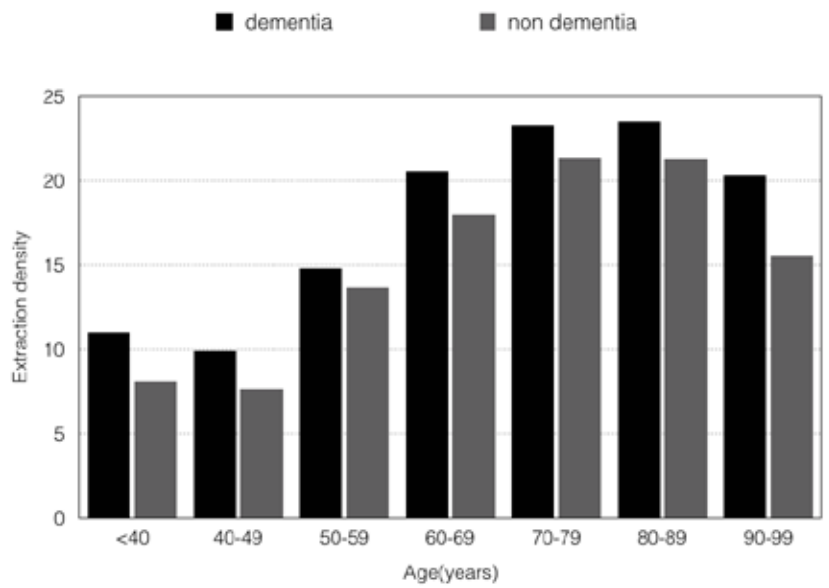

Figure 2. *The extraction density among dementia and non-dementia group in different ages at 10-year interval.*

In Figure 3, the horizontal axis represents time in 1-year intervals, with the 0 on the horizontal axis representing the year dementia was diagnosed. The line charts with the vertical axes on the right side illustrate the number of extractions per patient per year until dementia diagnosis, whereas the bar chart with the vertical axis on the left side depicts the number of patients diagnosed each year as having dementia. The increasing trend in the line chart indicates that tooth loss increased as the time of dementia diagnoses approached closer.

Discussion

Earlier studies that have investigated the association of tooth loss with dementia have observed results consistent with our study. Stein et al. (2007) investigated the association between the history of oral disease and the development of dementia and revealed an increasing risk of dementia among people with fewer teeth. Okamoto et al. (2007) used a community-based survey to discover that a decrease in the number of remaining teeth had significant relationships with low Mini-Mental State Examination scores and with a high risk of mild memory impairment. Studies by Takeuchi et al. (2017) and Luo et al. (2015) also related fewer remaining teeth to dementia.

Instead of using remaining teeth as a measure of oral condition, as in most previous studies, we used the number of extracted teeth and extraction density. The number of remaining teeth reflects the long-term oral condition but may not reflect instantaneous changes. However, the number of extracted teeth and extraction density before the diagnosis of dementia may reflect contemporaneous changes. In our study, information on the condition of the remaining teeth was not available. We assumed that a high number of extracted teeth implies poor oral health and few remaining teeth; this was in agreement with our clinical findings.

Lee et al. (2015) investigated the reasons for permanent tooth extraction in Taiwan using NHIRD data. Dental caries and periodontal disease were the most common causes. Both dental caries and periodontal disease indicate poor oral health. Periodontitis is characterized by inflammation and caries can cause inflammation.

The major aspect of the cognition function is influenced by multiple factors; of these, aging has a crucial role. However, it is difficult to distinguish between normal and pathological aging because both share similar mechanisms and risks factors. The term “inflammaging” is defined as aging associated with increased circulatory proinflammatory molecule concentrations. Poor oral health increases proinflammatory biomarker concentration, which precedes the risk of dementia. Increases in proinflammatory molecule concentration are influenced by nutrition, which may result from more extracted teeth impairing masticatory function and consequent changes diet. Moreover, socioeconomic status can influence the number of extracted teeth via mechanisms such as access to medical resources, perceptions of health care, dietary patterns and personal lifestyles.

The role of inflammation in the pathogenesis of dementia has been suggested by several studies. The chronic inflammatory state of the periodontal tissue may participate in the positively reinforced cascade that begins from the glial cells in the brain through the collaborative production of proinflammatory cytokines, such as C-reactive protein, tumor necrosis factor-alpha and interleukins 1 and 6. These in turn stimulate the glial cells

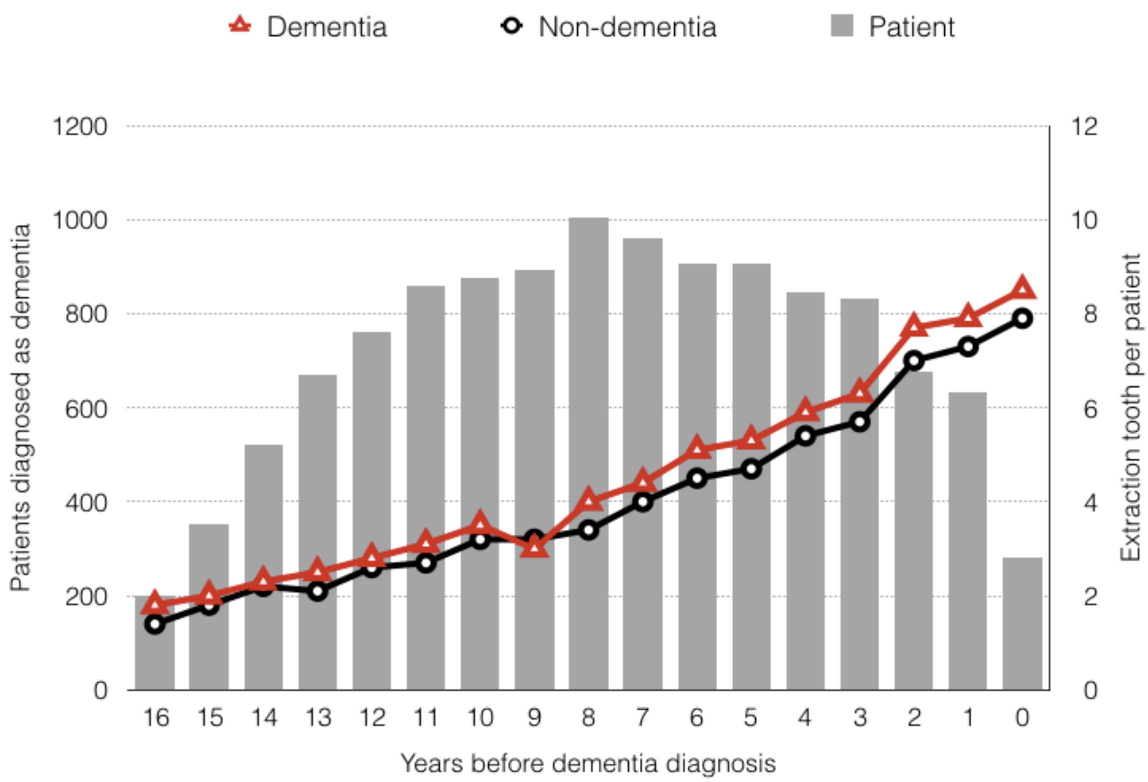

Figure 3. *Line charts with vertical axis on right side: the number of extraction per patient every year until diagnosed as dementia. Bar chart with the vertical axis on left side: the number of patients diagnosed as dementia in each year*

to produce pathologic protein molecules, such as P-tau and amyloid beta peptides 1–42, which eventually cause nerve cell damage. Periodontitis, is theorized to cause a chronic inflammatory state and generate proinflammatory mediators that infiltrate the nervous system from the oral cavity via the blood–brain barrier, or possibly, contribute to the positively reinforced cascade and lead to the amplification of inflammatory molecules in the central nervous system (Pallavi *et al*., 2017).

Tooth loss may impair the masticatory function and alter nutritional habits. Diets low in antioxidants and vitamins B and E and high in unsaturated fats may increase dementia risk.

A plausible pathway has been suggested in which the impaired masticatory function and continuous tooth loss affect cortical remapping and lead to dementia by impairing the functional neuronal connections between the sensory receptors in the periodontal ligaments and sensory cortex (Jou, 2012).

When a tooth is extracted, the patient is deprived of sensory information input (Kondo *et al*., 1994), and the neuromuscular reflexes of the masticatory muscles and joints are also impaired. As a consequence, sensory and motor cortical remapping occur, and all the related functional connections must undergo cortical reorganization (Jou, 2012). If tooth loss is repetitive, as the affected connections grow, larger cortical areas become involved in the remapping process. If the process is not properly matured, this continuous cortical rewiring and rebuilding of neural pathways may result in a series of non-ideal or over-detoured connections. Long-term and regular use of these non-ideal connections is likely to result in abnormal levels of burden and produce excessive beta–amyloid, causing synaptic and extrasynaptic dysfunction (Bordji *et al*., 2011; Gladding and Raymond, 2011).

Socioeconomic status is believed to affect patient perceptions of health care. Poor oral hygiene leads is a risk factor for periodontal disease, and low access to care may result in tooth loss. These factors may in turn contribute to dementia through the progression of the inflammatory state or through the impaired masticatory function and nutrition. Moreover, the socioeconomic status considerably influences lifestyle and dietary patterns (e.g., high-calorie and low-fiber diets, overeating and low antioxidant consumption). A sedentary lifestyle and emotional stress have also been reported as key factors for pathological decline in cognitive function. (Vauzour *et al*., 2017)

Dementia was also associated with a higher extraction density among individuals aged 60–79 years, despite the average age of dementia diagnosis being 75 years. This finding is inconsistent with the assumption that cognition decline with normal aging would be faster when there are more teeth extracted. In our study, tooth extraction per patient increased every year toward the index date. This increasing trend of tooth extraction suggests that slow progression of periodontal disease leads to declining masticatory function. However, early symptoms of dementia before diagnosis may also affect oral hygiene ability and contribute to tooth loss and may contribute to reverse causality in the relationship between tooth extraction and dementia.

The major strengths of our study are the long study period and large sample, based on a nationwide population-based database. The NHIRD data provide a large sample and high statistical power for identifying associations. In addition, rather than exploring the current oral condition, we examined the number of teeth extracted in the previous 10 years, before dementia diagnosis. This approach also minimized bias due to poor oral hygiene in patients with dementia, which would increase the number of teeth extracted.

Several limitations of this study warrant consideration. First, data on socioeconomic status were lacking. Nevertheless, because more than 99% of Taiwanese inhabitants are enrolled in the NHI program, the economic status may be less of a barrier to medical care. Thus, the possibility of selection bias is unlikely. Second, the diagnosis of dementia largely depended on administrative claims data reported by physicians, which may be less accurate than standardized research interviews. Misclassification bias was minimized because the Bureau of NHI routinely collected charts from hospitals and clinics to prevent miscoding. Finally, the NHIRD could not provide information on some other risk factors for dementia, such as lifestyle and family history. Nevertheless, we partly adjusted for confounding by matching the gender, age and residence of the control group. The residual confounding by socioeconomic status, lifestyle, and family history remains a major limitation in this study. There exist other possible explanations for the positive findings in this study, and these warrant further research.

Conclusion

In conclusion, this population-based retrospective study demonstrated an association between tooth loss and dementia. Taiwanese patients who had more teeth extracted had a greater risk of dementia.

Acknowledgement

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