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Dental scaling and lower risk of spontaneous intracranial hemorrhage

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ABSTRACT

Background: —Spontaneous intracranial hemorrhage (ICH) has high fatality while has few proven treatments. We aim at investigating the association between dental scaling (DS) and the risk of ICH.

Methods: —In this cohort study, two cohorts were matched by propensity score based on potential confounders. Data from ICH between January 2008 and December 2014 in Taiwan were analyzed. The subjects underwent DS at least 6 times between January 1, 2002, and December 31, 2007, while the matched controls did not undergo any DS during the same period. Cumulative incidences and hazard ratios (HRs) were calculated after adjusting for competing confounders.

Results: —Each cohort consisted of 681,126 subjects. Compared with the non-DS cohort, the regular-DS cohort had a significantly lower incidence of ICH (0.8% vs 1.2%; $P < 0.0001$), and the adjusted hazards ratio (aHR) of 7-year ICH was 0.61 (95% confidence interval, CI, 0.59–0.63; $P < 0.0001$). The 30–39-year age group of the regular-DS cohort had the lowest HR (0.57; 95% CI, 0.52–0.61; $P < 0.0001$) of 7-year ICH when compared with similar controls. Compared with the controls, the regular-DS cohort also had significantly lower HR (0.82; 95% CI, 0.81–0.82; $P < 0.0001$) of 7-year hypertension. Compared with those without DS, the lowest risk of intracerebral hemorrhage was observed in the male participants with regular DS (0.43; 95% CI, 0.40–0.47; $P < 0.0001$).

Conclusions: —Regular DS was consistently associated with lower ICH risk in subjects aged 30–59 years, which may benefit from the decreased HBP risk. DS had a potential role in the prophylaxis for ICH, a condition with a high disability or mortality.

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1. Introduction

In 2013, cerebrovascular disease ranked as the second most common cause of disability-adjusted life-years worldwide [1]. According to the report of the Global Burden of Disease Study 2016, 2.84 million deaths were caused by spontaneous intracranial Hemorrhage (ICH), including intracerebral Hemorrhage (ICBH), subarachnoid Hemorrhage (SAH), and intraventricular Hemorrhage (IVH) [2]. Although modern medicine continues to improve, a systematic epidemiological review reported that the worldwide burden of ICH in age-standardized rates has only slightly decreased by 14% from 1990 to 2016 [3]. Case fatality of ICH at 1 month is 40% and increases to 54% at one year [4]. Survivors of ICH usually have varying degrees of disability, and cognitive impairment, which in turn lead to the loss of many years of productive life.

Apart from SAH, there are few proven treatments for ICH [5]. Therefore, prevention is particularly important. ICH usually has "primary" or "secondary" aetiologies. Over 80% of primary ICH is related to hypertension. Modifiable risk factors for ICH and SAH include smoking, hypertension, and excess alcohol intake [5,6]. These factors are significantly associated with ICH. Cumulative evidence has shown that gut microbiota dysbiosis contributes to the development of hypertension [7–9]. Since hypertension is an important precipitating factor for ICH, it seems plausible that there may be an inherent relationship between gut microbiota dysbiosis and ICH. Like gut microbiota propagates in the gastrointestinal tract, the oral cavity harbors plenty of diverse microbiota. Studies have shown that certain species of oral microbiota play a role in the development of cerebrovascular diseases. Stimulation by the antigen of *Porphyromonas gingivitis*, harbored in the oral cavity, exacerbates systemic T-cell activation, which translates into increased vascular inflammation [10]. Furthermore, oral *Streptococcus mutans* that encode Cnm, a collagen-binding protein, have been reported to be associated with ICBH [11]. A previous case-controlled study indicated that maintaining periodontal hygiene can help reduce the incidence of ischemic stroke [12].

However, no large-scale clinical findings have been reported regarding the correlation between oral microbiota and cerebrovascular disease. Dental scaling (DS) is a widely used measure of dental prophylaxis, which abates the overload of dental plaques and, thus, decreases the prevalence of periodontal diseases. DS is covered by health insurance in Taiwan. In this study, we aimed to investigate the relationship between oral microbiota and ICH by investigating the correlation between DS and the incidence of ICH.

2. Methods

2.1. Study cohort

Two cohorts were included: the regular-DS cohort included participants who underwent regular DS (Procedure code 91004C) at least 6 times between January 1, 2002, and December 31, 2007 (cases); and the non-DS cohort included those who did not undergo any

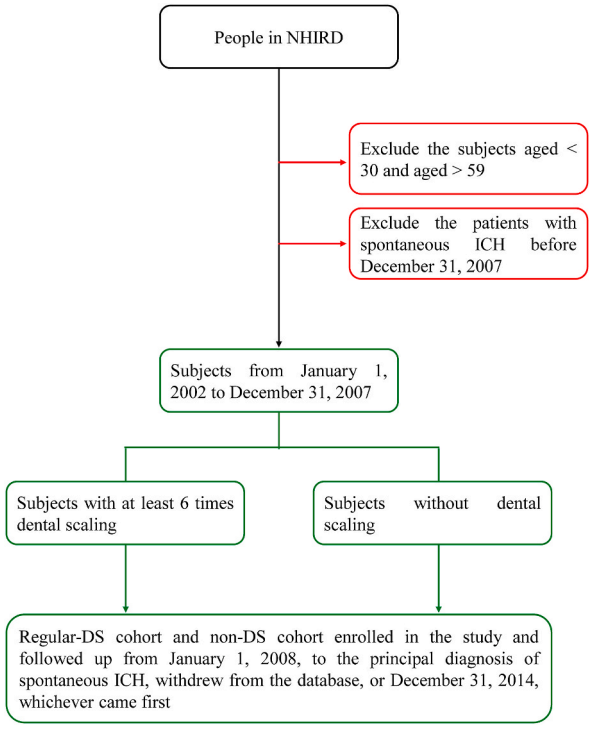

Fig. 1. Flowchart of patient enrolment in the study. NHIRD, National Health Insurance Research Database; ICH, intracranial Hemorrhage; DS, dental scaling.

DS during the same period (controls). The selection of the study cohort was shown in Fig. 1.

Because of the relatively low incidence of ICH (ICD-9-CM codes 430–432) in young people and a relatively high incidence of dental disease in elderly people, we excluded the subjects younger than 30 years or older than 59 years as of 2001. To avoid overestimating the risk of ICH, this study only enrolled subjects without ICH before December 31, 2007, which was assigned as the index date for each patient. The subjects in the regular-DS and non-DS cohorts were matched by propensity score matching method based on potential confounders. Database and the confounders were introduced in the Supplementary Methods.

To perform an in-depth investigation of the risk of ICH between these two cohorts, the regular-DS cohort was further subdivided into two case cohorts: those who underwent DS 6–9 times (case-1), and those who underwent DS at least 10 times (case-2). The association between DS and the risk of ICH was also further depicted according to the location of hemorrhages such as ICBH, SAH, and IVH.

2.2. Outcomes

The main outcome was a principal diagnosis of ICH. Each patient was followed up from January 1, 2008, to the following three events, whichever was the earliest: (1) a principal diagnosis of ICH; (2) censored for death, lost to follow-up, or withdrew from the database; and (3) December 31, 2014.

2.3. Statistics

We compared the characteristics of socio-demographics, comorbidities, and antiplatelet agents or anticoagulants between the regular-DS and non-DS cohorts by χ^2 test. Univariate analyses, multivariable analyses, and stratified analyses were carried out with Cox-proportional hazard models to estimate the hazard ratios (HR) and 95% confidence interval (CI) for the association between DS and ICH with the non-DS cohort as the reference. This study adjusted the multivariable analyses for potential confounders including age, sex, monthly income, geographical location, urbanization level of the patient's residence, comorbidities, and antiplatelet agents or anticoagulants. The stratified analyses of the association between DS and ICH included three parts: firstly, the association was assessed in each of two subgroups of the regular-DS cohort using the non-DS cohort as the reference, and those associations were further examined in different age groups; secondly, the association was further assessed by the stratification of sex and the location of ICH; thirdly, it was assessed in the HTN comorbidity group and non-HTN comorbidity group. Additionally, we measured the association between DS and HTN after the index date in the case and control cohorts without HTN and further analyzed the association according to the age groups.

Statistical analyses were performed using SAS software for Windows (version 9.2, SAS Institute, Cary, NC, USA) and R for Windows (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria). A P value below 0.05 was regarded as statistically significant.

2.4. Study approval

The Institutional Review Board of XX XX University approved our study and waived the need for informed consent (TMU-

Table 1
Socio-demographic characteristics of the case and control cohorts.

Variables		Case cohort (n = 681,126)	Control cohort (n = 681,126)	P value
Age, No. (%), y				0.970
	30–39	265,656 (39.0)	265,562 (39.0)	
	40–49	264,214 (38.8)	264,193 (38.8)	
	50–59	151,256 (22.2)	151,371 (22.2)	
Sex, No. (%)				0.299
	Male	322,530 (47.4)	321,924 (47.3)	
	Female	358,596 (52.6)	359,202 (52.7)	
Monthly insured income, No. (%)				0.738
	≤NT$15,840	115,094 (16.9)	114,804 (16.9)	
	NT$15,841–25,000	231,067 (33.9)	231,399 (34.0)	
	≥NT$25,001	334,965 (49.2)	334,923 (49.2)	
Geographical region, No. (%)				0.945
	Northern	338,431 (49.7)	338,459 (49.7)	
	Central	166,356 (24.4)	166,165 (24.4)	
	Southern	167,973 (24.7)	168,183 (24.7)	
	Eastern	8366 (1.2)	8319 (1.2)	
Urbanization level, No. (%)				0.987
	1 (most urbanized)	200,297 (29.4)	200,209 (29.4)	
	2	118,094 (17.3)	118,398 (17.4)	
	3	38,809 (5.7)	38,864 (5.7)	
	4	45,332 (6.7)	45,386 (6.7)	
	5	3855 (0.6)	3804 (0.6)	
	6	9243 (1.4)	9241 (1.4)	
	7	265,496 (39.0)	265,224 (38.9)	

Table 2
Risk of spontaneous intracranial hemorrhage between the case and control cohorts stratified by age groups and the location of hemorrhage stroke.

	Case cohort (n = 681,126)	Age of case cohort, mean (SD), y	Control cohort (n = 681,126)	Age of control cohort, mean (SD), y	HR (95% CI)	P value	Adjusted HR (95% CI)*	P value
Case-control, No. (%)	5123 (0.8)	46.5 (7.8)	8358 (1.2)	46.3 (7.8)	0.61 (0.59,0.63)	<0.0001	0.61 (0.59,0.63)	<0.0001
Case1-control	4674 (0.8)	46.5 (7.8)	8358 (1.2)	46.3 (7.8)	0.61 (0.59,0.63)	<0.0001	0.61 (0.59,0.64)	<0.0001
Case2-control	449 (0.8)	47.3 (7.5)	8358 (1.2)	46.3 (7.8)	0.63 (0.57,0.69)	<0.0001	0.58 (0.53,0.64)	<0.0001
Age 30–39 years, No. (%)	1066 (0.4)	35.0 (2.8)	1875 (0.7)	35.2 (2.8)	0.57 (0.53,0.61)	<0.0001	0.57 (0.52,0.61)	<0.0001
Case1-control	989 (0.4)	35.0 (2.8)	1875 (0.7)	35.2 (2.8)	0.57 (0.53,0.62)	<0.0001	0.57 (0.53,0.62)	<0.0001
Case2-control	77 (0.4)	35.3 (2.8)	1875 (0.7)	35.2 (2.8)	0.54 (0.43,0.68)	<0.0001	0.50 (0.40,0.63)	<0.0001
Age 40–49 years, No. (%)	1994 (0.8)	44.8 (2.9)	3322 (1.3)	44.9 (2.8)	0.60 (0.57,0.63)	<0.0001	0.60 (0.57,0.63)	<0.0001
Case1-control	1820 (0.8)	44.8 (2.9)	3322 (1.3)	44.9 (2.8)	0.60 (0.57,0.63)	<0.0001	0.60 (0.57,0.64)	<0.0001
Case2-control	174 (0.7)	44.9 (2.7)	3322 (1.3)	44.9 (2.8)	0.59 (0.51,0.69)	<0.0001	0.57 (0.49,0.66)	<0.0001
Age 50–59 years, No. (%)	2063 (1.4)	54.2 (2.9)	3161 (2.1)	54.3 (3.0)	0.65 (0.62,0.69)	<0.0001	0.65 (0.62,0.69)	<0.0001
Case1-control	1865 (1.4)	54.2 (2.9)	3161 (2.1)	54.3 (3.0)	0.65 (0.61,0.69)	<0.0001	0.66 (0.62,0.69)	<0.0001
Case2-control	198 (1.4)	54.2 (2.9)	3161 (2.1)	54.3 (3.0)	0.65 (0.56,0.75)	<0.0001	0.63 (0.55,0.73)	<0.0001
ICBH case-control	1566 (0.2)	46.8 (7.9)	3081 (0.5)	46.5 (7.7)	0.51 (0.48,0.54)	<0.0001	0.51 (0.48,0.54)	<0.0001
Age 30–39 years	301 (0.1)	34.7 (2.9)	645 (0.2)	35.1 (2.8)	0.47 (0.41,0.53)	<0.0001	0.46 (0.41,0.53)	<0.0001
Age 40–49 years	608 (0.2)	44.8 (2.9)	1244 (0.5)	44.9 (2.8)	0.49 (0.44,0.54)	<0.0001	0.49 (0.44,0.54)	<0.0001
Age 50–59 years	657 (0.4)	54.3 (3.0)	1192 (0.8)	54.2 (3.0)	0.55 (0.50,0.60)	<0.0001	0.55 (0.50,0.61)	<0.0001
SAH case-control	695 (0.1)	45.4 (7.5)	764 (0.1)	45.6 (7.8)	0.91 (0.82,1.00)	0.0658	0.91 (0.82,1.00)	0.0701
Age 30–39 years	167 (0.1)	35.1 (2.7)	183 (0.1)	34.9 (2.8)	0.91 (0.74,1.10)	0.3850	0.91 (0.74,1.10)	0.3660
Age 40–49 years	300 (0.1)	44.6 (2.8)	325 (0.1)	44.9 (2.9)	0.92 (0.79,1.10)	0.3050	0.92 (0.79,1.10)	0.3040
Age 50–59 years	228 (0.2)	53.8 (3.0)	256 (0.2)	54.2 (3.0)	0.89 (0.74,1.10)	0.1960	0.89 (0.75,1.10)	0.2120
IVH case-control	2197 (0.3)	46.7 (7.9)	3313 (0.5)	46.6 (8.0)	0.66 (0.63,0.70)	<0.0001	0.66 (0.63,0.70)	<0.0001
Age 30–39 years	462 (0.2)	35.1 (2.8)	747 (0.3)	35.2 (2.8)	0.62 (0.55,0.69)	<0.0001	0.61 (0.55,0.69)	<0.0001
Age 40–49 years	816 (0.3)	44.8 (2.9)	1252 (0.5)	45.0 (2.8)	0.65 (0.59,0.71)	<0.0001	0.65 (0.59,0.71)	<0.0001
Age 50–59 years	919 (0.6)	54.3 (2.9)	1314 (0.9)	54.5 (3.0)	0.70 (0.64,0.76)	<0.0001	0.70 (0.64,0.76)	<0.0001
Mix case-control	665 (0.1)	46.5 (7.5)	1200 (0.2)	45.5 (7.6)	0.55 (0.50,0.61)	<0.0001	0.55 (0.50,0.61)	<0.0001
Age 30–39 years	136 (0.1)	35.5 (2.8)	300 (0.1)	35.4 (2.6)	0.45 (0.37,0.55)	<0.0001	0.45 (0.37,0.55)	<0.0001
Age 40–49 years	270 (0.1)	44.8 (2.8)	501 (0.2)	44.8 (2.8)	0.54 (0.46,0.62)	<0.0001	0.54 (0.46,0.62)	<0.0001
Age 50–59 years	259 (0.2)	54.0 (2.8)	399 (0.3)	54.1 (2.9)	0.65 (0.55,0.76)	<0.0001	0.65 (0.55,0.76)	<0.0001

HR, hazard ratio; CI, confidence interval; ICBH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; Mix, more than one type of ICH, including ICBH, SAH, and IVH; Case1 cohort: 6–9 episodes of dental scaling; Case2 cohort: ≥10 episodes of dental scaling.
*Adjusted by age, sex, monthly income, geographical location, and urbanization level of the patient's residence, comorbidities, and antiplatelet agents and anticoagulants.

N201712044). No identifiable personal information such as name, ID card number, etc., was collected in this study.

3. Results

3.1. Socio-demographic characteristics of the case and control cohorts

A total of 681,126 case-patients (623,020 in case-1 and 58,106 in case-2) in the regular-DS cohort and 681,126 controls in the non-DS cohort were included in this study (Supplementary Table 1). The detailed socio-demographic characteristics of the case and control cohorts are summarized in Table 1. After propensity score matching, no significant differences were found in terms of age (P = 0.970), sex (P = 0.299), monthly income (P = 0.738), geographical region (P = 0.945), and urbanization level (P = 0.987).

3.2. Comorbidities and antiplatelet agents or anticoagulants between the case and control cohorts

The comorbidities and antiplatelet agents or anticoagulants of the case and control cohorts are summarized in Supplementary Table 2. Similar to the socio-demographic characteristics, the differences in most comorbidities, except HTN and DM, were not significantly different between the two cohorts. Regarding antiplatelet agents, no significant differences were found between dipyridamole and aspirin. The subjects in the regular-DS cohort were less likely to have HTN and DM, and more likely to take clopidogrel, ticlopidine, heparin, and warfarin than those in the non-DS cohort.

Table 3
Risk of spontaneous intracranial hemorrhage between the case and control cohorts stratified by sex and the location of hemorrhage stroke.

	Case cohort (n = 681,126)	Age of case cohort, mean (SD), y	Control cohort (n = 681,126)	Age of control cohort, mean (SD), y	HR (95% CI)	P value	Adjusted HR (95% CI)*	P value
Male, No. (%)	2806 (0.9)	46.5 (7.8)	5384 (1.7)	46.0 (7.8)	0.52 (0.49,0.54)	<0.0001	0.52 (0.50,0.54)	<0.0001
Case1-control	2534 (0.9)	46.4 (7.8)	5384 (1.7)	46.0 (7.8)	0.52 (0.49,0.54)	<0.0001	0.52 (0.50,0.54)	<0.0001
Case2-control	272 (0.9)	47.3 (7.4)	5384 (1.7)	46.0 (7.8)	0.53 (0.47,0.60)	<0.0001	0.51 (0.45,0.58)	<0.0001
Female, No. (%)	2317 (0.6)	46.6 (7.8)	2974 (0.8)	46.8 (7.8)	0.78 (0.74,0.82)	<0.0001	0.78 (0.74,0.83)	<0.0001
Case1-control	2140 (0.6)	46.6 (7.8)	2974 (0.8)	46.8 (7.8)	0.78 (0.74,0.82)	<0.0001	0.79 (0.74,0.83)	<0.0001
Case2-control	177 (0.6)	47.4 (7.5)	2974 (0.8)	46.8 (7.8)	0.77 (0.66,0.90)	0.0009	0.75 (0.64,0.87)	0.0002
ICBH case-control								
Male	914 (0.3)	46.4 (7.8)	2116 (0.7)	46.2 (7.7)	0.43 (0.40,0.46)	<0.0001	0.43 (0.40,0.47)	<0.0001
Female	652 (0.2)	47.4 (7.9)	965 (0.3)	47.1 (7.6)	0.68 (0.61,0.75)	<0.0001	0.68 (0.62,0.75)	<0.0001
SAH case-control								
Male	312 (0.1)	46.2 (7.6)	389 (0.1)	44.8 (8.0)	0.80 (0.69,0.93)	0.0030	0.80 (0.69,0.93)	0.0031
Female	383 (0.1)	44.7 (7.4)	375 (0.1)	46.4 (7.5)	1.00 (0.89,1.20)	0.7610	1.00 (0.89,1.20)	0.7400
IVH case-control								
Male	1220 (0.4)	46.7 (8.0)	2108 (0.7)	46.3 (7.9)	0.57 (0.54,0.62)	<0.0001	0.57 (0.54,0.62)	<0.0001
Female	977 (0.3)	46.8 (7.8)	1205 (0.3)	47.0 (8.1)	0.81 (0.75,0.88)	<0.0001	0.82 (0.75,0.89)	<0.0001
Mix case-control								
Male	1220 (0.4)	46.7 (8.0)	2108 (0.7)	46.3 (7.9)	0.57 (0.54,0.62)	<0.0001	0.57 (0.54,0.62)	<0.0001
Female	977 (0.3)	46.8 (7.8)	1205 (0.3)	47.0 (8.1)	0.81 (0.75,0.88)	<0.0001	0.82 (0.75,0.89)	<0.0001

HR, hazard ratio; CI, confidence interval; ICBH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; Mix, more than one type of ICH, including ICBH, SAH, and IVH; Case1 cohort: 6–9 episodes of dental scaling; Case2 cohort: ≥10 episodes of dental scaling.
*Adjusted by age group, monthly income, geographical location, and urbanization level of the patient's residence, comorbidities, and antiplatelet agents and anticoagulants.

3.3. Regular DS reduced the risk of ICH

Table 2 summarizes the associations between ICH and DS in the case and control cohorts, stratified by the frequency of DS and age. Compared with those in the control cohort, the subjects in the case-cohort were less likely to have ICH (adjusted HR [aHR] = 0.61, 95% CI: 0.59–0.63), especially those who underwent DS at least 10 times (case-2 cohort) (aHR = 0.58, 95% CI: 0.53–0.64). A lower risk of ICH was also observed in the case-1 cohort (aHR = 0.61, 95% CI: 0.59–0.64). Concerning different age groups, the subjects in the 30–39-year age group in the case-cohort had the lowest risk of ICH (aHR = 0.57, 95% CI: 0.52–0.61), especially those in the case-2 cohort (aHR = 0.50, 95% CI: 0.40–0.63), and the protective effect of DS on ICH declined with age. Stratified by the location of hemorrhage, the lowest risk of ICH was observed in the subgroup of ICBH (aHR = 0.51, 95% CI: 0.48–0.54), especially those in the age 30–39 cohort (aHR = 0.46, 95% CI: 0.41–0.53) (Table 2). Stratified by sex, a lower risk of ICH was observed in the male cohort (aHR = 0.52, 95% CI: 0.50–0.54) (Table 3). In the subgroup of ICBH, the lowest risk was observed in the male cohort (aHR = 0.43, 95% CI: 0.40–0.47) (Table 3). The results of Kaplan-Meier analyses in Fig. 2A–D and Supplementary Table 3, and Supplementary Figure 1 present the significant differences in the ICH-free survival curves of the case subgroups and the control cohort for all age groups (all $P < 0.001$).

3.4. Regular DS reduced the risk of ICH, independent of HTN

The associations between DS and ICH stratified according to HTN comorbidity are summarized in Supplementary Table 4. In subjects with HTN (aHR = 0.61, 95% CI: 0.58–0.64), the association between DS and lower risk of ICH was similar to that in subjects without HTN (aHR = 0.61, 95% CI: 0.59–0.64). In those with HTN, the case subjects in the age group of 30–39 years had the lowest risk of ICH (aHR = 0.50, 95% CI: 0.43–0.58). However, the salutary effect of DS declined with age. Like those with HTN, in those without HTN, the case subjects in the 30–39-year group also had the greatest difference in the risk of ICH (aHR = 0.59, 95% CI: 0.54–0.64). However, it appears that age had no significant role in the beneficial effects of DS on ICH in the cohort without HTN. The results of

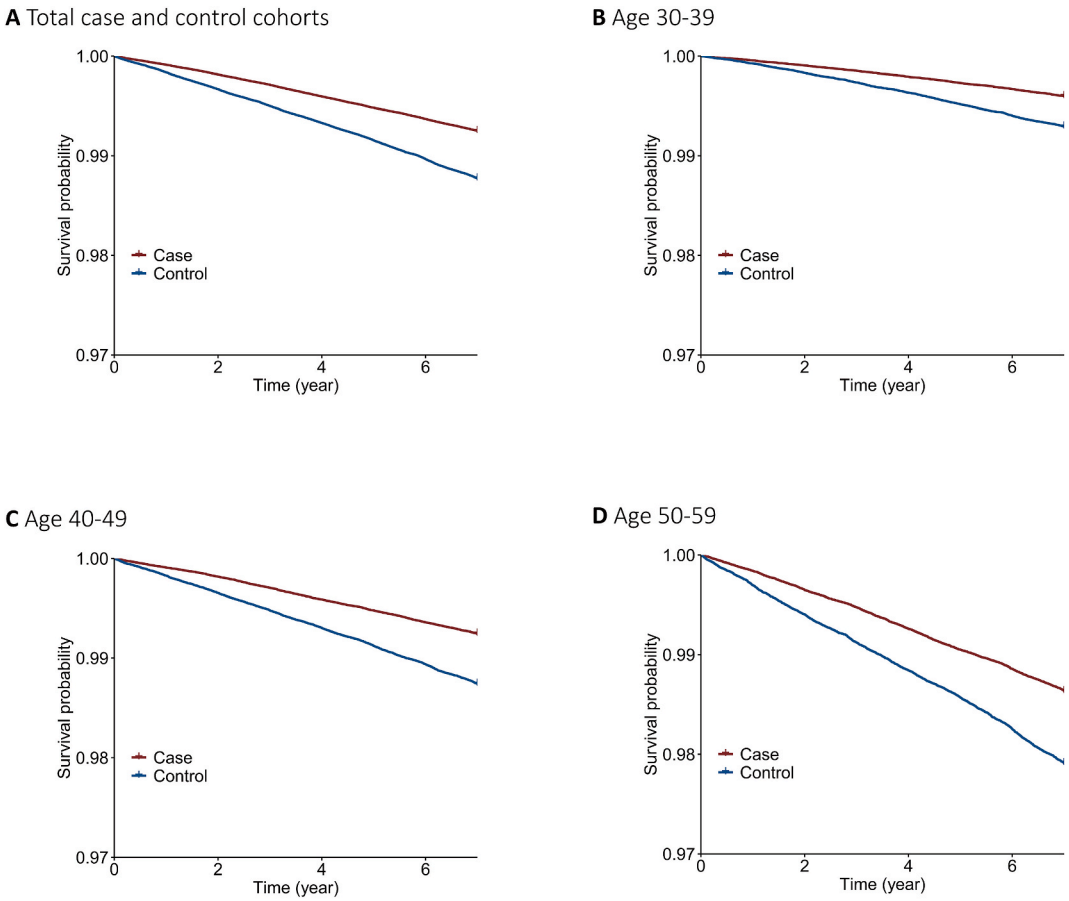

Fig. 2. Kaplan–Meier Estimates of ICH-free survival at 6 years in the subjects with DS (case-cohort) or without DS (control cohort). The figure shows the probability of ICH at 6 years in subjects who underwent regular DS, as compared with those who did not. Panel A: the total case and control cohorts; Panel B: subjects aged 30–39 years; Panel C: subjects aged 40–49 years; Panel D: subjects aged 50–59 years. ICH, Intracranial Hemorrhage; DS, dental scaling.

Kaplan–Meier analyses in Supplementary Figure 2 demonstrate the significant differences observed in the ICH-free survival curves of the case and control cohorts and with and without HTN (all $P < 0.001$).

3.5. Regular DS reduced the risk of HTN

Supplementary Table 5 demonstrates the relationship between DS and the development of HTN after the index date in the subjects without HTN in both the case and control cohorts. Compared with those in the control cohort without HTN, the case subjects without HTN with regular DS were less likely to develop HTN (aHR = 0.82, 95% CI: 0.81–0.82), especially those who underwent DS at least 10 times (case-2 cohort) (aHR = 0.80, 95% CI: 0.78–0.82). The lower risk of HTN was also observed in the case-1 cohort (aHR = 0.82, 95% CI: 0.81–0.82). Concerning different age groups, the results demonstrate that the case patients aged 40–49 years had the greatest difference in the risk of HTN (both aHR = 0.81, 95% CI: 0.80–0.82). The results of Kaplan–Meier analyses in Fig. 3A–D, Supplementary Table 6, and Supplementary Figure 3 summarize the significant differences observed in the HTN-free survival curves of the case subgroups and control cohort in all age groups (all $P < 0.001$).

4. Discussion

This study was performed based on the data from NHIRD. Since Taiwan's health insurance system subsidizes DS every six months, those who care about their oral hygiene will be arranged for regular DS. In 2012, Chen ZY et al. [13] first reported that the action of DS would significantly reduce the incidence of future cardiovascular disease. In 2013, the association between DS and atrial fibrillation [14], and infective endocarditis [15] was discussed. According to the results, DS can reduce the incidences of atrial fibrillation and endocarditis. In 2015, Chen PC et al. [16] adopted a case-crossover design to discuss the relationship between DS and infective endocarditis. Although no statistically significant result was found, the previous findings cannot be overturned. In 2019, using sampling data from NHIRD, Huang JL et al. [17] also reported that intensive periodontal treatment has a positive impact on ICH events.

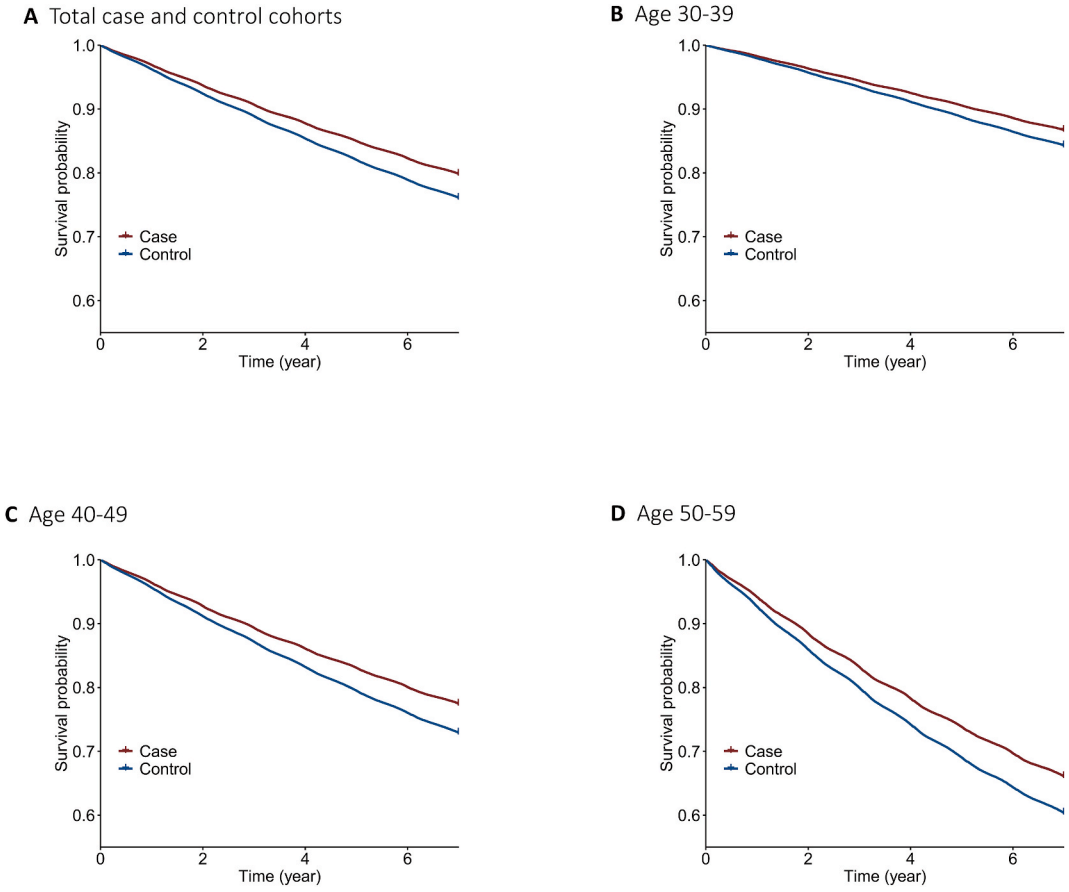

Fig. 3. Kaplan–Meier estimates of HTN-free survival at 6 years after the index date in the case and control cohorts without HTN. The probability of HTN at 6 years after the index date in subjects without HTN who underwent regular DS (case-cohort), as compared with those who did not undergo DS (control cohort). Panel A: total case and control cohorts; Panel B: subjects aged 30–39 years; Panel C: subjects aged 40–49 years; Panel D: subjects aged 50–59 years. HTN, hypertension; DS, dental scaling.

Since DS is widely accepted, this study, therefore, proposes that the more people who care about their oral hygiene, the lower the incidence of ICH, reminding the public cannot neglect the good habit of regular DS.

The most unique finding in this large-scale study was that DS was associated with lower ICH risk, which indicates that DS may serve as a life-saving measure. DS reduces dental plaque and decreases the load of oral microbiota, which further leads to a reduced incidence of gingivitis. Therefore, the correlation between DS and ICH risk mirrors the association between oral microbiota and ICH to some extent. The intrinsic relationship between cerebrovascular disease and oral microbiota merits further study. In recent years, gut microbiota has become one of the most rapidly researched topics. Several studies have suggested that gut microbiota is associated with hypertension, which is one of the key risk factors for ICH. In contrast, oral microbiota is less studied and its correlation with hypertension and ICH remains unclear.

Furthermore, we found that the more the frequency of DS, the more significant the difference in ICH risk. In other words, there is a "dose-dependent relationship" regarding the beneficial effect of DS on ICH (Table 2). This dose-dependent relationship further verifies the correlation between DS and lower ICH risk. From Tables 2 and it can also be seen that all subgroups of different ages can benefit from DS; however, the subgroup of age 30–39 years achieves the most obvious benefit. Additionally, the dose-dependent relationship in the subgroup of age 30–39 years is the most significant; in this age group, the case-1 subgroup had aHR of 0.59, while the case-2 subgroup had 0.51. Due to the high mortality and disability rate of ICH, a considerable number of patients will lose their ability to work even after recovery. Therefore, the benefits achieved in the lower age subgroup from DS will undoubtedly have greater family and social significance. SAH is more common in women [6]. However, the protective effect of DS for SAH is solely observed in the male cohort. More than that, in the male cohort, the risk of ICBH in DS cohorts was less than half of the risk among the controls (Table 3). The cause of sex difference remains unclear.

We also found that the salutary effect of DS on ICH was regardless of the presence of HTN (Supplementary Table 4). In other words, the subjects benefitted from DS both with and without concomitant HTN. When stratified by age, it was noted that the age group of 30–39 years with concomitant HTN benefited the most from DS. Furthermore, the salutary effects decreased with age, which suggests that in those with HTN, DS should be started as soon as possible. In those without HTN, age stratification had little protective effect on DS, but all the subgroups stratified by age benefitted from DS (Supplementary Table 4).

Additionally, there was a correlation between DS and the reduced incidence of HTN (Supplementary Table 5). The salutary effect of DS on HTN was also dose-dependent. The higher the frequency of DS, the more obvious the reduction in HTN incidence. Age stratification had little effect on the correlation between DS and a lower incidence of HTN. The incidence of HTN decreased with increasing DS in all age groups. Since HTN is an important risk factor for ICH, it seems reasonable that the salutary effect of DS on ICH may be achieved through lowered HTN, at least partly. In other words, DS reduces the development of HTN, which, in turn, reduces the incidence of ICH.

5. Limitations

First, there is no ICD-9-CM code for IVH, primary ICH, or secondary ICH. Therefore, we could not further evaluate the location or etiology of ICH.

Second, subarachnoid hemorrhage is more likely to occur in people with autosomal dominant polycystic kidney disease (ADPKD) [6,18]. However, due to the limitations of NHIRD, the influence of family factors and genetic factors on ICH could not be clarified.

Third, some known factors, such as the ratio of apolipoprotein B/A1, diet, and waist-to-hip ratio, are associated with both ICH and ischemic stroke [19]. However, these factors were not included in the database and, therefore, we could not adjust the HR for these confounding factors.

Fourth, smoking and drinking are known risk factors for ICH. While smoking and drinking habits are recorded in the database, these recordings are lesser than the actual situation for some unknown reasons. Therefore, we could not adjust the HR according to the records of smoking and drinking habits in the database. To obtain more accurate information, we estimated the adjusted HRs of the enrolled subjects according to HPL, DM, CVD, and CAD—the concomitant diseases that are closely related to smoking and drinking.

Lastly, the intracranial aneurysm is an important cause of ICBH and SAH [6,18,20]. However, it was unclear whether a subject had a history of intracranial aneurysm and, therefore, could not be further evaluated.

6. Conclusions

Regular DS was consistently associated with lower ICH risk in subjects aged 30–59 years, which may benefit from the decreased HBP risk. DS had a potential role in the prophylaxis for ICH, a condition with a high disability or mortality.

Author contribution statement

Yi-Wei Kao; Linglong Ye: Performed the experiments; Analyzed and interpreted the data.
Lei Qin: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Hsin-Chung Cheng; Win-Ping Deng: Contributed reagents, materials, analysis tools or data.
Jin-Shui Pan: Conceived and designed the experiments; Wrote the paper.
Ben-Chang Shia; De-Zhi Kang: Conceived and designed the experiments.

Data availability statement

Data included in article/supplementary material/referenced in article.

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Author statements

All authors agreed to submit the manuscript, read and approved the final draft, and take full responsibility for its content, including the accuracy of the data and its statistical analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18431.

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