

Association between oral health and cardiovascular outcomes in patients with hypertension: a nationwide cohort study

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Objective: Studies on the association of oral hygiene indicators with cardiovascular disease in hypertensive patients have been lacking. Oral hygiene is directly or indirectly associated with systemic inflammation, one of the essential mechanisms of cardiovascular disease. Therefore, we hypothesized that oral hygiene would be related to the risk of cardiovascular diseases in hypertensive patients.

Methods: We included 52 677 hypertensive participants who completed oral health checkups from the Korean National Health Insurance Service-National Health Screening Cohort between 2003 and 2004. We collected data on periodontitis diagnosis and treatment history, number of teeth loss, number of dental caries, and frequency of tooth brushing from medical records of health claims and oral health examination. The primary outcome was defined as composite outcomes of stroke and myocardial infarction. Follow-up was done until the date of primary outcome, or 31 December 2015.

Results: During the 11.26 ± 2.39 years (mean \pm standard deviation) of the study follow-up, 3292 participants developed primary outcomes [stroke ($n = 2430$), myocardial infarction ($n = 862$)]. In multivariable Cox regression analyses, participants with dental caries (≥ 5) were independently associated with occurrence of a primary outcome [adjusted hazard ratio: 1.37; 95% confidence interval (CI): 1.10–1.72; $P = 0.006$]. Frequent tooth brushing (≥ 2 times/day) was significantly related to lower risk of primary outcomes (adjusted hazard ratio: 0.88; 95% CI: 0.81–0.96; $P = 0.002$).

Conclusion: Our study demonstrated that multiple dental caries were related to the risk of cardiovascular diseases in hypertensive patients. Better oral hygiene may attenuate the risk of cardiovascular events in hypertensive patients.

Keywords: cardiovascular disease, hypertension, oral hygiene, periodontitis

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD-10, *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; NHIS-HEALS, National Health Insurance Service-National Health Screening Cohort

INTRODUCTION

Hypertension is a major global health problem, with a prevalence of over 1.4 billion people in 2010 that is predicted to exceed 1.6 billion in 2025 [1]. Hypertension is one of the leading causes of cardiovascular disease-related morbidity and mortality [2,3]. For cardiovascular disease prevention, patients with hypertension need to lose weight, maintain a healthy diet, lower their salt intake, engage in regular physical activity, and take appropriate antihypertensive agents [4]. However, there is still a lack of knowledge on associative cardiovascular risk factors in hypertensive patients [4].

Periodontitis, one of the most prevalent chronic inflammatory diseases, is caused by bacterial microorganisms and can lead to the gradual destruction of periodontal soft tissue and alveolar bone [5]. Periodontitis, tooth loss, and dental caries are associated with inflammatory conditions in surrounding tissues [6]. Good oral hygiene, such as frequent tooth brushing, is essential to prevent tooth loss and dental caries [7]. Insufficient oral care can induce local infections, leading to systemic inflammation and endothelial dysfunction, which are essential pathological mechanisms contributing to cardiovascular disease [8]. Paradoxically, transient bacteremia is also caused by regular tooth brushing [9].

Hypertension and poor oral health are two highly prevalent conditions with a significant impact on cardiovascular disease [2,3,10,11]. Poor oral health is associated with increased prevalence of hypertension and may have an influence on BP control [12,13]. Risk factors, such as older age, male, smoking, obesity, diabetes, low socio-economic status have been considered the common

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denominators underpinning this relationship [14–19]. However, recent evidence indicates that the association between oral health and hypertension is independent of common risk factors, and may, in fact, be causal in nature [13,20,21]. Systemic inflammation, in particular, represents the major underlying mechanisms in this relationship [20]. Since the causal relationship between these two conditions, patients with hypertension may have an altered association of oral health and cardiovascular disease compared with those without hypertension. However, research on the association between oral hygiene and cardiovascular disease in hypertensive patients is lacking. Thus, we investigated whether oral hygiene indicators were linked to the development of major cardiovascular diseases in hypertensive patients in a longitudinal study setting.

METHODS

Data sources

This study was performed using the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) dataset in South Korea [22]. NHIS-HEALS is a cohort of participants who participated in health screening programs provided by the NHIS in South Korea. South Korea has a universal health insurance system. NHIS is a non-profit, single-payer organization in South Korea. Every 2 years, the NHIS provides complimentary nationwide health checkups to all South Korean citizens aged at least 40 years. NHIS-HEALS included 514 866 participants who underwent health screening examination between 2002 and 2003 [22]. NHIS-HEALS dataset consisted of the consecutive health checkup data including BMI, blood and urine laboratory findings, an oral health checkup questionnaire and dental results, blood pressure measurements, and a lifestyle survey. As NHIS is a single payer, NHIS-HEALS dataset contained all health claim resources regarding hospital visit, diagnosis (based on *International Statistical Classification of Diseases and Related Health Problems 10th, Revision*, ICD-10), medication, and procedures between 2002 and 2015.

Study participants

We included participants who had hypertension and completed oral health checkups at the baseline health examination in 2003–2004. Hypertensive patients were defined as participants who satisfied at least one of following conditions: received prescription blood pressure lowering agents (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, calcium-channel blocker, diuretics, and beta-blockers) with hypertension diagnostic codes (ICD-10: I10–I15) before the health examination, had a SBP at least 140 mmHg or DBP at least 90 mmHg at the blood pressure measurement; checked ‘yes’ on the self-report questionnaire for hypertension at the baseline health examination. Exclusion criteria were: no hypertension at baseline; unavailable oral health examination data; prior history of cardiovascular diseases (stroke and myocardial infarction), and missing data for at least one collected covariate. Figure 1 is a flow chart for inclusion and exclusion criteria.

Oral hygiene indicators and covariates

During the oral checkup at baseline health examination, dentists investigated the number of teeth lost and dental caries, regardless of the cause, which were classified accordingly (i.e. into groups of 0, 1–4, and ≥ 5 teeth lost or dental caries). Although dental results provided by NHIS-HEALS data set was examined and recorded by a professional dentist, information on interrater reliability among dentist and accuracy for teeth loss and dental caries was not included. Periodontitis was defined as the provision of the periodontitis diagnostic code (ICD-10 code: K052–K054) more than twice by a professional dentist or treatment for periodontal disease (health claim codes: U1010, U1020, U1051–1052, U1071–1072, and U1081–1083) by a dentist with the ICD-10 codes within 1 year of the health examination [23,24]. On the basis of the oral health self-questionnaire in health examination, the frequency of tooth brushing was subclassified as 1 or less and at least two times/day.

From NHIS-HEALS dataset, we collected information for sex, age, household income, smoking habits, alcohol consumption, exercise frequency, BMI, total cholesterol, and SBP at the baseline health examination [24–26]. Diabetes mellitus was defined as a fasting serum glucose level of at least 7.0 mmol/l at the health examination or the presence of diabetes mellitus diagnostic codes (ICD-10 code of E11–E14) with a prescription of antidiabetic drugs (sulfonylurea, biguanide, alpha-glucosidase inhibitor, thiazolidinedione, meglitinide, dipeptidyl peptidase-4 inhibitor, and insulin) before the health examination [27]. According to the health claims before the baseline health examination, the presence of atrial fibrillation, renal disease, and malignancy were also evaluated. Atrial fibrillation was defined by the diagnosis ICD-10 code I48, and renal disease was identified by the relevant ICD-10 codes (N17–N19, E082, E102, E112, E132, or I12–I13). Malignancy was defined as at least one claim per year based on the ICD-10 code C00–C97. The diagnostic accuracy of these comorbidities was previously validated [24,28,29].

Outcomes

The primary outcome was defined as the occurrence of major cardiovascular events (composite outcomes of stroke and myocardial infarction). Stroke was defined as admission with a primary diagnosis of ICD-10 code ‘I60–I63’ (ischemic stroke: ‘I63’, hemorrhagic stroke: ‘I60–I62’) and with a brain computed tomography or magnetic resonance imaging at hospitalization, or a death certificate declaring ‘I60–I63’ as the main cause of death. Myocardial infarction was defined as admission with a primary diagnosis of ICD-10 code ‘I21’, or a death certificate stating I21 as the main cause of death. The diagnostic accuracy of stroke and myocardial infarction based on the health claims data was validated in prior studies [30,31]. After the date of baseline health examination (index date), participants were followed up until the occurrence of a study outcome or loss of NHIS eligibility because of emigration, mortality, or the end of data collection (31 December 2015).

Statistical analysis

The categorical and continuous variables were expressed as a number (%) and mean \pm standard deviation. We illustrated cumulative incidence curves according to the oral

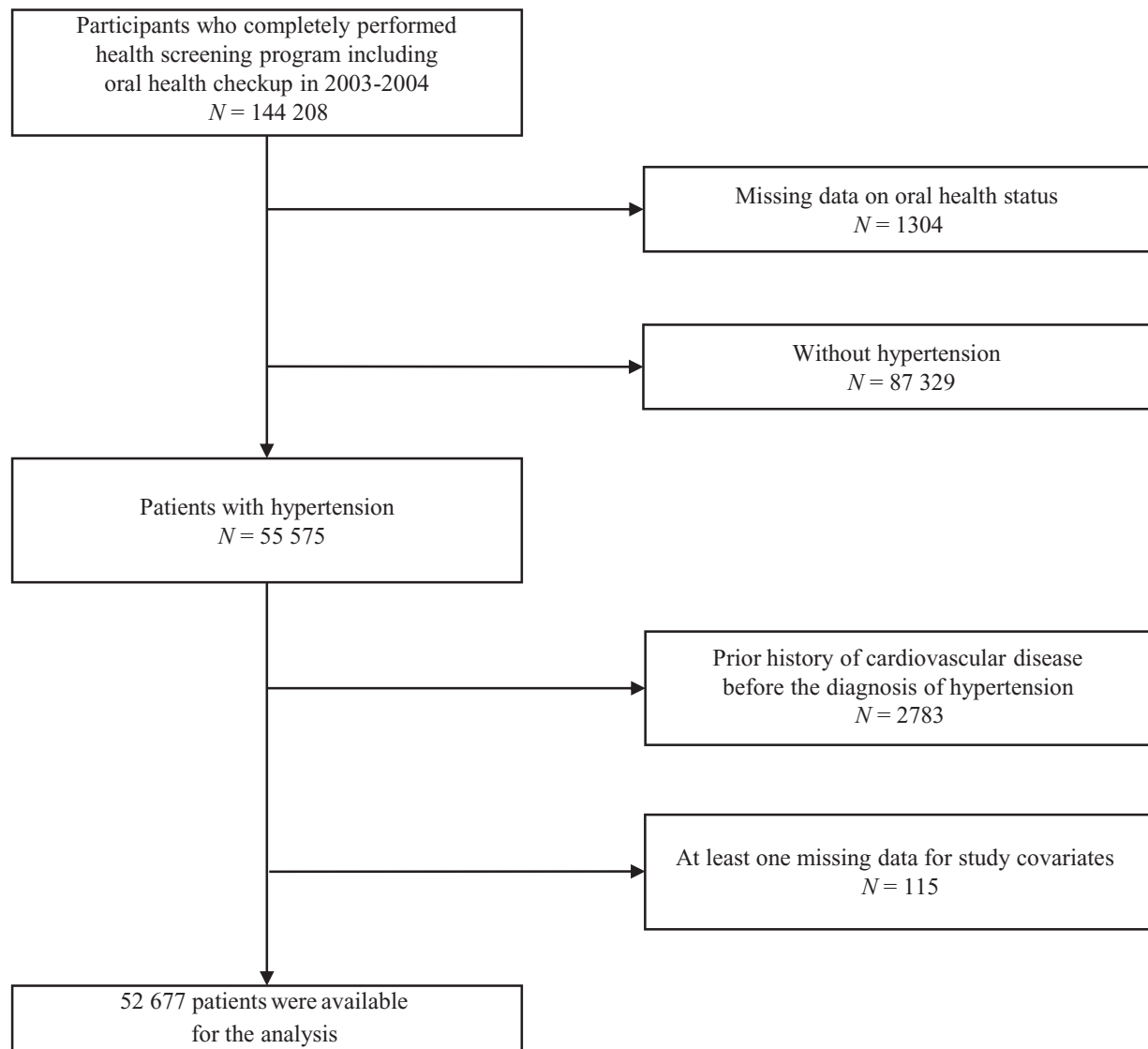


FIGURE 1 Flow chart of inclusion and exclusion criteria. NHIS-HEALS, National Health Insurance Service-National Health Screening Cohort in Korea.

hygiene indicators. The hazard ratio (HR) and 95% confidence interval (CI) regarding the oral hygiene indicators were calculated by Cox proportional hazard regression models. In the multivariate Cox regression model, sex, age, smoking habits, alcohol consumption, exercise frequency, BMI, total cholesterol, SBP, and comorbidities were adjusted. The proportional hazard assumption in the Cox model was tested based on Schoenfeld residuals, which were satisfied. For the secondary analysis, we constructed individual Cox regression models for each outcome (stroke, ischemic stroke, hemorrhage stroke, and myocardial infarction). All data manipulation and statistical analyses were performed using the SAS 9.4 version (SAS Inc., Cary, North Carolina, USA), with a statistical significance defined as a two-sided P -value less than 0.05.

RESULTS

On the basis of the inclusion and exclusion criteria, 52 677 hypertensive patients were included in this study. The

median age of all participants was 54.99 ± 9.51 years, and 33 317 (63.25%) of the participants were male. Periodontal disease was identified in 3672 (6.97%) participants. There were 3295 (6.26%) participants who lost more than five teeth, 848 (1.61%) participants had more than five dental caries, and 43 604 (82.78%) participants brushed their teeth at least twice a day (Table 1).

Regarding the risk for primary outcomes (major cardiovascular events) according to oral health status, in the 11.26 ± 2.39 (mean \pm standard deviation) year study follow-up period, 3292 participants developed primary outcomes [stroke ($n = 2,430$, with 1,752 ischemic strokes and 678 hemorrhagic strokes), myocardial infarction ($n = 862$)]. A cumulative incidence curve (Fig. 2) demonstrated that primary outcome occurrence depended on the number of teeth lost ($P < 0.001$), number of dental caries ($P < 0.001$), and frequency of tooth brushing per day ($P < 0.001$). In a multivariable Cox regression analyses (Table 2), multiple dental caries (≥ 5) were independently associated with primary outcome occurrence (adjusted hazard ratio: 1.37;

TABLE 1. Baseline characteristics of the study population

Characteristics	Total
N	52 677
Age (years)	54.99 ± 9.51
Sex (male)	33 317 (63.25)
Household income	
Q1, lowest	14 850 (28.19)
Q2	12 250 (23.25)
Q3	14 779 (28.06)
Q4, highest	10 798 (20.50)
Alcohol consumption, frequency per week	
<1 time	25 542 (48.49)
1–2 times	20 242 (38.43)
3–4 times	4 444 (8.44)
≥5 times	2 449 (4.65)
Smoking habits	
None	32 161 (61.05)
Former smoker	8 077 (15.33)
Current smoker	12 439 (23.61)
Exercise frequency, days per week	
<1 day	25 741 (48.87)
1–4 days	21 319 (40.47)
≥ 5 days	5 617 (10.66)
Anthropometric measurements	
BMI (kg/m ²)	24.68 ± 2.97
SBP (mmHg)	140.88 ± 15.44
DBP (mmHg)	88.24 ± 10.02
Comorbidities	
Diabetes mellitus	3 796 (7.21)
Atrial fibrillation	472 (0.90)
Renal disease	1 515 (2.88)
Malignancy	1 457 (2.77)
Laboratory findings	
Total cholesterol (mmol/l)	5.24 ± 0.96
Oral health status	
Presence of periodontal disease	3 672 (6.97)
Number of teeth lost	
0	38 192 (72.50)
1–4	11 190 (21.24)
≥5	3 295 (6.26)
Number of dental caries	
0	42 300 (80.30)
1–4	9 529 (18.09)
≥5	848 (1.61)
Number of times teeth brushed per day	
0–1 time	9 073 (17.22)
≥2 times	43 604 (82.78)

Data are represented as the number, number of participants (%) or mean ± standard deviation. Q, quartile.

95% CI: 1.10–1.72; *P* = 0.006). Frequency of tooth brushing per day (at least two times) was significantly related to a lower risk of major cardiovascular events (adjusted hazard ratio: 0.88; 95% CI: 0.81–0.96; *P* = 0.002). In contrast, presence of periodontitis was not significantly associated with major cardiovascular events.

In the secondary analysis for individual cardiovascular outcomes, an increased number of teeth lost (at least five) was associated with an increased risk of hemorrhagic stroke (adjusted hazard ratio: 1.33; 95% CI: 1.04–1.71; *P* = 0.004). A higher number of dental caries (at least five) was related to an increased risk of all stroke (adjusted hazard ratio: 1.33; 95% CI: 1.03–1.73; *P* = 0.003) and ischemic stroke (adjusted hazard ratio: 1.43; 95% CI: 1.06–1.93; *P* = 0.002). Brushing teeth frequently (at least two times per day) was associated with a lower risk of all stroke (adjusted hazard ratio: 0.87; 95% CI: 0.79–0.96; *P* = 0.004) and hemorrhagic stroke

(adjusted hazard ratio: 0.77; 95% CI: 0.64–0.92; *P* = 0.003) compared with brushing teeth 0–1 times per day (Table 3).

DISCUSSION

Our key study findings are that patients with hypertension who have poor oral hygiene indicators, such as dental caries, had a higher risk of major cardiovascular events. In contrast, better oral hygiene behavior (such as tooth brushing) was negatively related to the risk of major cardiovascular events.

Previous research suggests that tooth loss, a marker of poor oral hygiene, was significantly associated with an increased risk of ischemic stroke in the general population [11], coronary artery occlusive disease in elderly United States veterans [32], and peripheral artery occlusive disease in male health professionals [33]. Advanced/severe dental caries were related to an increased occurrence of coronary heart disease with a dose–response relationship in middle-aged individuals [12]. The number of decayed teeth significantly increased the mortality hazard ratio in patients receiving hemodialysis [34]. Brushing teeth is an established, effective intervention that removes dental plaque and prevents periodontitis and dental caries [35]. Studies suggest a potential cardiovascular preventive role of tooth brushing [36]. More tooth brushing per day decreases the risk of new stroke, atrial fibrillation, and heart failure [24,37]. In a health survey among Scottish volunteers, participants who reported never/rarely brushing their teeth had an increased risk of cardiovascular diseases [38]. Infrequent teeth brushing (≤1 time/day) was related to the development of obesity and hyperglycemia [39]. Although tooth loss showed an insignificant relationship for the occurrence of cardiovascular events, our study’s findings are consistent with previous studies suggesting a relationship between oral hygiene and cardiovascular outcomes, especially in hypertensive patients who are at a greater risk compared with healthy individuals. We provided evidence of the association between poor oral hygiene and cardiovascular risk in a longitudinal study setting using a nationwide, population-based cohort. To reduce the risk of cardiovascular events, future studies must establish the underlying mechanism and potential roles of interventions aimed at improving oral hygiene.

In this study, we did not find a difference in cardiovascular risk between hypertensive patients with and without periodontitis. There is a significant body of evidence to support the association between periodontitis, a chronic inflammatory disease affecting the tissue surrounding the teeth, and cardiovascular risk [40,41]. Patients with periodontal disease are at an increased risk for cardiovascular disease [36,42,43]. These patients are susceptible to atherosclerosis or thrombosis [44,45]. However, some research indicates no such relationship between periodontitis and cardiovascular events [46,47]. Results of previous studies have been inconsistent regarding the association between periodontitis and cardiovascular risk. This discrepancy may be because of study design, sample size, or the study population (our study included only participants with hypertension in South Korea). For example, in a study

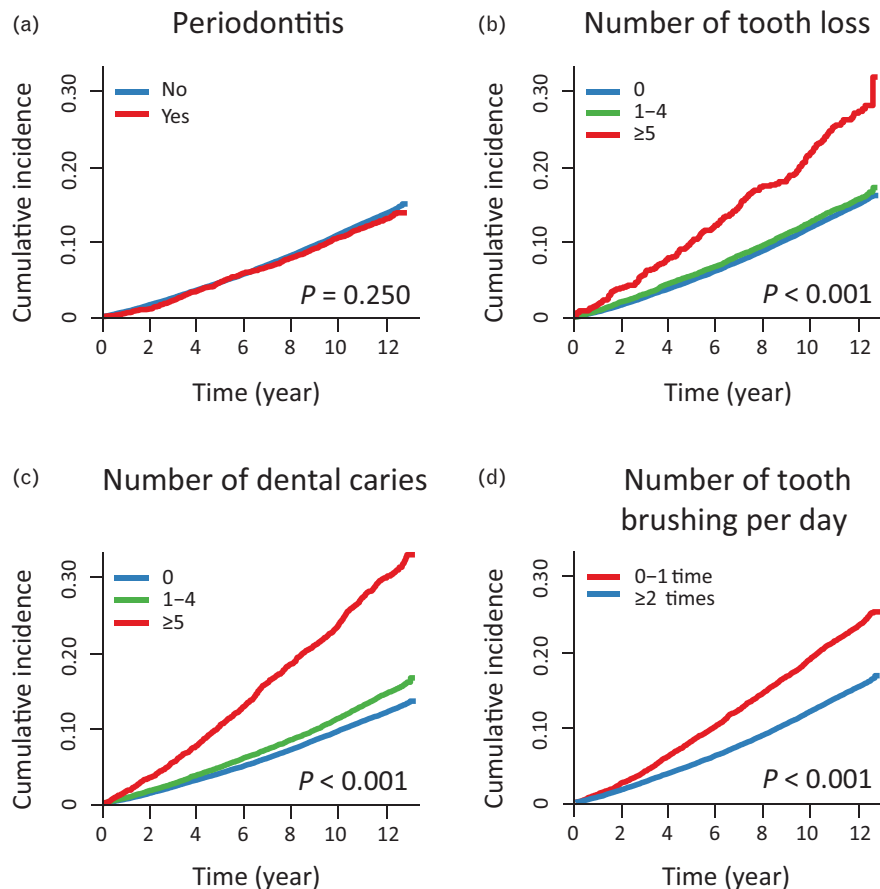


FIGURE 2 The cumulative incidence curves for major cardiovascular outcomes according to oral hygiene indicators in patients with hypertension.

involving patients receiving hemodialysis, periodontal disease was not independently related to mortality [48].

As this is an epidemiological study, it is challenging to present the underlying mechanism for the association between poor oral hygiene and cardiovascular diseases. However, there are several potential mechanisms. Oral health is closely related to several systemic diseases [49]. Oral health conditions and cardiovascular disease share many risk factors, such as old age, diabetes mellitus, smoking, obesity, stress, and health behaviors [50]. Tooth loss and dental caries could lead to dietary pattern alterations, such as low citrus fruit, beta carotene, folate, vitamin C, and fiber intake, which are nutrients protective against cardiovascular disease. Poor oral health coupled with increased tooth loss and dental caries may be inadequate to assure sufficient masticatory function. These undesirable eating habits are closely related to cardiovascular disease development [51]. Moreover, ulceration in periodontal tissues, tooth loss, and dental caries can disseminate pathogens from the oral cavity into the systemic circulation [52], causing direct microorganism intrusion into the arterial wall. This destructive cascade can lead to atherosclerosis and inflammation, which may elicit the development of and worsen cardiovascular diseases [53]. Tooth loss can cause high virulence with dysbiosis of oral biofilm, indirectly propagating pro-inflammatory cytokines [54]. These cytokines can raise the local and systemic inflammatory burden

and are closely associated with hypertension and related cardiovascular outcomes [55]. In addition, this systemic inflammatory burden can enhance atherogenesis and increase arterial stiffness as an early sign of cardiovascular disease [56]. A previous meta-analysis showed that periodontitis was associated with an increased pulse wave velocity, an indicator of the degree of arterial stiffness [57]. Another study reported a significantly reduced arterial stiffness after periodontal treatment in periodontitis patients with refractory hypertension [58].

Our study's strengths include its large number of hypertensive patients and long-term longitudinal follow-up using a nationwide population-based cohort database. Our study also has several limitations. First, in our oral health examination dataset, the frequency of tooth brushing is based on a self-reported questionnaire, which may result in recall bias. Second, as our dataset did not evaluate severity of periodontitis, we could not prove the dose–response relationship between periodontitis and risk of cardiovascular events. Third, marital status, education level, and inflammatory biomarker data were not available in NHIS-HEALS. Finally, although this study has a longitudinal design, a causal relationship between variables cannot be determined by a retrospective study design without interventions. Therefore, prospective trials must establish whether oral health interventions effectively reduce the risk of future cardiovascular events.

TABLE 2. Risk factors for primary outcomes in hypertensive patients

	Univariate		Multivariate	
	Crude HR [95% CI]	P value	Adjusted HR [95% CI]	P value
Sex (male)	1.07 [0.99–1.14]	0.085	1.34 [1.22–1.46]	<0.001
Age (years)	1.07 [1.06–1.07]	<0.001	1.07 [1.06–1.08]	<0.001
Household income				
Q1, lowest	1 (Ref)	–	1 (Ref)	–
Q2	0.86 [0.79–0.94]	0.001	0.99 [0.90–1.09]	0.842
Q3	0.76 [0.69–0.83]	<0.001	0.94 [0.85–1.02]	0.147
Q4, highest	0.64 [0.58–0.71]	<0.001	0.78 [0.70–0.86]	<0.001
Smoking habits				
Never smoker	1 (Ref)	–	1 (Ref)	–
Former smoker	0.88 [0.79–0.97]	0.015	1.08 [0.96–1.21]	0.182
Current smoker	1.28 [1.19–1.39]	<0.001	1.71 [1.55–1.87]	<0.001
Alcohol consumption, frequency per week				
<1 time	1 (Ref)	–	1 (Ref)	–
1–2 times	0.75 [0.69–0.81]	<0.001	0.88 [0.80–0.96]	0.003
3–4 times	0.89 [0.78–1.01]	0.066	0.87 [0.76–1.00]	0.054
≥5 times	1.33 [1.15–1.53]	<0.001	0.90 [0.77–1.05]	0.175
Exercise frequency, days per week				
<1 day	1 (Ref)	–	1 (Ref)	–
1–4 days	0.70 [0.65–0.76]	<0.001	0.89 [0.82–0.96]	0.004
≥5 days	0.96 [0.86–1.07]	0.430	0.89 [0.80–0.99]	0.047
BMI (kg/m ²)	0.97 [0.96–0.98]	<0.001	0.99 [0.98–1.01]	0.320
SBP (10 mmHg)	1.12 [1.10–1.14]	<0.001	1.07 [1.05–1.09]	<0.001
Total cholesterol (mmol/l)	1.04 [1.01–1.08]	0.020	1.09 [1.05–1.12]	<0.001
Diabetes mellitus	2.18 [1.97–2.41]	<0.001	1.79 [1.62–1.99]	<0.001
Atrial fibrillation	2.87 [2.28–3.62]	<0.001	2.08 [1.65–2.62]	<0.001
Renal disease	1.27 [1.05–1.53]	0.013	1.02 [0.84–1.23]	0.849
Malignancy	1.11 [0.91–1.37]	0.313	0.91 [0.74–1.12]	0.353
Oral hygiene markers				
Periodontitis, yes	1.07 [0.94–1.22]	0.319	1.05 [0.92–1.20]	0.481
Number of teeth lost				
0	1 (Ref)	–	1 (Ref)	–
1–4	1.17 [1.08–1.27]	<0.001	1.04 [0.95–1.13]	0.416
≥ 5	2.01 [1.79–2.25]	<0.001	1.11 [0.99–1.25]	0.078
Number of dental caries				
0	1 (Ref)	–	1 (Ref)	–
1–4	1.02 [0.93–1.11]	0.114	1.06 [0.97–1.16]	0.195
≥5	1.65 [1.32–2.05]	<0.001	1.37 [1.10–1.72]	0.006
Number of times teeth are brushed per day				
0–1 time	1 (Ref)	–	1 (Ref)	–
≥2 times	0.70 [0.64–0.76]	<0.001	0.88 [0.81–0.96]	0.002

Data are derived from Cox proportional hazard regression analysis for the development of stroke and myocardial infarction. CI, confidence interval; HR, hazard ratio.

TABLE 3. Secondary analysis for individual cardiovascular outcome

	All stroke (ICD-10 codes I60–I63) (n = 2430)	Ischemic stroke (ICD-10 code I63) (n = 1752)	Hemorrhagic stroke (ICD-10 codes I60–I62) (n = 678)	Myocardial infarction (ICD-10 code I21) (n = 862)
Oral hygiene markers				
Periodontitis, yes	0.99 [0.85–1.16]	1.04 [0.87–1.25]	0.86 [0.62–1.18]	1.21 [0.96–1.53]
Number of teeth lost				
0	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
1–4	1.04 [0.94–1.15]	1.00 [0.89–1.13]	1.15 [0.95–1.38]	1.02 [0.87–1.21]
≥ 5	1.14 [0.99–1.30]	1.07 [0.92–1.26]	1.33 [1.04–1.71]	1.02 [0.80–1.31]
Number of dental caries				
0	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
1–4	1.05 [0.95–1.17]	1.07 [0.95–1.21]	1.00 [0.82–1.22]	1.09 [0.91–1.30]
≥ 5	1.33 [1.03–1.73]	1.43 [1.06–1.93]	1.10 [0.66–1.85]	1.48 [0.96–2.30]
Number of times teeth brushed per day				
0–1 time	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
≥ 2 times	0.87 [0.79–0.96]	0.91 [0.82–1.03]	0.77 [0.64–0.92]	0.91 [0.77–1.07]

Data derived from multivariate Cox proportional hazard regression model. Data are presented as hazard ratio [95% confidence interval]. Adjustments were performed for the covariates listed in Table 2.
ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision.

In conclusion, our study demonstrated that multiple dental caries were related to the risk of cardiovascular diseases in hypertensive patients. Better oral hygiene may attenuate the risk of cardiovascular events in hypertensive patients.

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Ethical approval: all authors were involved in conceiving the study; K.H.J. study concept and design, drafting/revising the manuscript for content. J.J. statistical analysis and interpretation of data. T.-J.S. and J.K. study concept and design, acquisition of data. All authors read and approved the final manuscript.

Data availability statement: we used the sample research data extracted and provided by the National Health Insurance Sharing System (further details available at: <https://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do>).

Conflicts of interest

The authors report no disclosures relevant to the manuscript.

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