



OPEN Association between toothbrushing habits and hypertension in the general population

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Periodontitis has been linked to cardiovascular disease (CVD), suggesting that oral care may play a role in CVD prevention. In contrast, hypertension has been linked to oral health; however, its association with toothbrushing habits is unclear. Therefore, this study aimed to investigate the relationship between toothbrushing habits and hypertension. A total of 941 participants (361 men, mean age: 67 ± 11 years) from a 2019 community-based study conducted in Tarumizu City were included. Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or use of antihypertensive medications. Toothbrushing habits were assessed using a questionnaire, and oral health was evaluated by dentists. The mean BP was $132 \pm 17/78 \pm 11$ mmHg, with a hypertension prevalence of 56%. Participants reported toothbrushing rates of 33% upon waking, 8% before breakfast, 69% after breakfast, 48% after lunch, 4% before dinner, 42% after dinner, and 51% before sleeping. In the univariable analysis, both the timing of toothbrushing (after breakfast, after lunch, or before sleeping) and brushing frequency (≥ 3 times/day) were significantly associated with a lower prevalence of hypertension. Multivariable analysis revealed a significant association between toothbrushing after breakfast and hypertension. In conclusion, toothbrushing after breakfast was independently associated with a reduced risk of hypertension.

Keywords Blood pressure, Hypertension, Toothbrushing habits, Oral status

Hypertension is the leading risk factor for cardiovascular disease (CVD), making adequate blood pressure (BP) control crucial for CVD prevention¹. Various strategies to decrease BP, including diet, exercise, and drug therapy, have been explored to achieve this goal. In Japan, BP control remains suboptimal, as some patients exhibit uncontrolled hypertension despite medications, while others remain untreated². Therefore, identifying modifiable lifestyle factors associated with hypertension could help improve BP control.

The oral cavity harbors over 700 microbial species. As such, poor oral hygiene can lead to gum disease and periodontitis, a complex infection involving multiple gram-negative anaerobic bacteria that is associated with various systemic diseases, including rheumatism³, diabetes⁴, and non-alcoholic fatty liver^{5,6}. Notably, oral health has been linked to CVDs, independent of other risk factors such as age, sex, and lifestyle (e.g., dyslipidemia, hypertension, diabetes, smoking)^{7–9}.

Periodontitis treatment has been shown to improve arterial function and prevent CVD. For example, patients with coronary artery disease demonstrated enhanced endothelial function, as evidenced by increased flow-dependent vasodilation 6 months following periodontal treatment¹⁰. A systemic review and meta-analysis demonstrated similar results, suggesting that periodontal disease treatment improves endothelial function and reduces atherosclerosis biomarkers¹¹. Given the connection between periodontal disease and hypertension, oral care, particularly toothbrushing habits, becomes paramount in periodontitis prevention. A large cohort study

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in Scotland investigated the self-reported frequency of toothbrushing, reporting that low frequency was a risk factor for CVD development¹². This was consistent with the findings of a study in Japan, which asserted that toothbrushing frequency and duration were associated with cardiovascular events¹³. Although few studies have explored the timing of toothbrushing and CVD, some evidence suggests that nighttime toothbrushing may reduce the CVD risk in patients ≥ 20 years admitted for surgery, testing, or medical treatment¹⁴.

While the relationship between periodontal diseases and hypertension has been established¹⁵, as reported by a randomized intervention trial showing that intensive periodontal treatment reduced systolic BP¹⁶, the influence of toothbrushing habits on BP control remains unclear. Thus, this study aimed to investigate the relationship between toothbrushing habits and hypertension.

Methods

Study population

A flowchart depicting the participant selection process is presented in Fig. 1. Since 2017, we have been conducting a regional study in Tarumizu, a city in Japan^{17,18}. Study participants include residents over the age of 40 who live in Tarumizu and responded to our request to participate in the study. Participants were recruited through announcements such as the city bulletin, community notice boards, online announcements, local health programs, and postcards sent by mail. There are no other exclusion criteria. Of the participants in the 2019 Tarumizu study, 81 participants without teeth and three with missing data were excluded. Ultimately, 940 participants were included in the final analysis.

Written informed consent was obtained from all participants prior to the study. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Graduate School of Medical and Dental Sciences at Kagoshima University (No. 170351).

Data collection

Regarding the study participants' medical history, we asked whether or not they were taking antihypertensive drugs, hypoglycemic drugs, or lipid-lowering drugs. Further, we asked them whether they were current smokers, have smoked in the past, or have never smoked. We defined both former and current smokers as smokers, and categorized participants into two groups: smokers and non-smokers. Educational history was obtained using a questionnaire, and nutritional intake was assessed using the Brief-Type Self-Administered Diet History Questionnaire (BDHQ)¹⁹. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of height (m^2).

BP measurement and definition of hypertension

Experimental health nurses measured BP using the oscillometric method during the community-based study. Measurements were taken in a seated position after a 5-min rest period. In cases where BP ≥ 180 mmHg (or higher than the usual value), a second measurement was obtained, and the average was used for analysis. Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or the use of antihypertensive medications.

Evaluation of toothbrushing habits and oral health

A questionnaire was administered to investigate toothbrushing habits. Participants reported timing and frequency of brushing at these specific times: upon waking, before and after breakfast, after lunch, before and after dinner, and before sleeping. Frequent toothbrushing was defined as brushing ≥ 3 times per day. In addition, participants indicated their brushing duration per session as follows: ≤ 30 s, 30–60 s, 1–2 min, 2–3 min, and ≥ 3 min. Long brushing duration was defined as brushing duration ≥ 2 min. Oral assessment with teeth enumeration was performed by an oral surgeon. Poor oral hygiene was evaluated based on the revised Tongue Coating Index (TCI)²⁰, which involves visually inspecting the tongue coating. The tongue was divided into three regions (anterior, central, and posterior) for assessment and each section was evaluated using a 3-point scale, resulting in a total score of 9 points²¹.

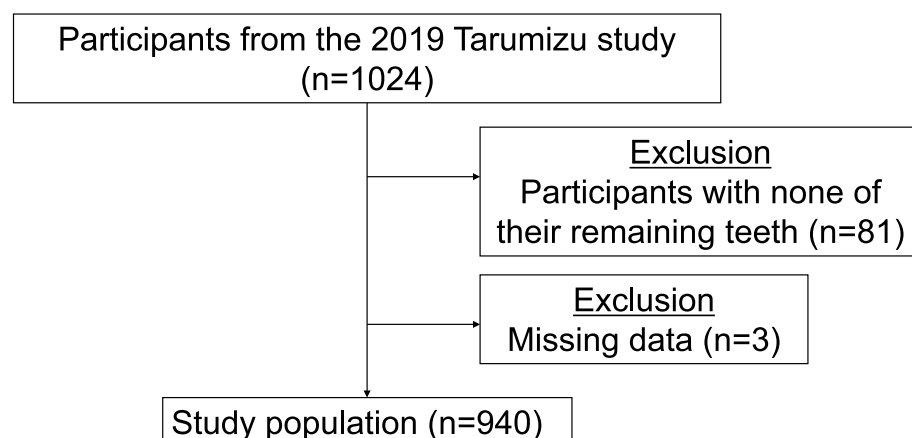


Fig. 1. Flowchart of participants' enrollment.

Statistical analysis

Continuous variables were expressed as means $\pm$ standard deviation (SD), whereas categorical variables, including the proportion of participants receiving medication, were presented as numbers and percentages. Continuous and categorical variables were compared between the two groups using Student's unpaired t-test and the chi-square test, respectively. The Wilcoxon rank-sum test was employed to compare the distribution of the number of teeth between the groups due to non-normal data distribution. Univariable logistic regression analysis was performed with hypertension as the dependent variable and timing and frequency of toothbrushing as independent variables. Multivariable logistic analyses were then adjusted for age and sex (Model 1) and further adjusted for age, sex, BMI, smoking history, and use of medications, years of education, and total energy intake per day, sugar and sodium intakes per 1000 kcal evaluated using BDHQ (Model 2). We carried out multivariable analyses with each toothbrushing timing or toothbrushing frequency ≥ 3 times per day and other factors as dependent variables for hypertension. Additionally, we also carried out multivariable analyses with all toothbrushing timings, toothbrushing frequency ≥ 3 per day, and other factors as dependent variables. Stratified analyses were conducted using separate multivariable logistic analysis models for older and non-older groups, with an age cut-off of 65 years. All statistical analyses were performed using the JMP Pro version 17 for Windows (SAS Institute Inc., Cary, NC, USA), with statistical significance set at $P < 0.05$.

Results

Participant characteristics

Table 1 summarizes the participant characteristics based on hypertension status. Among the 940 participants, 529 (56.3%) were in the hypertension group, while 411 (43.7%) were in the non-hypertension group. The overall mean BP was $132 \pm 17/78 \pm 11$ mmHg, and the mean number of remaining teeth was 21.4 ± 7.8 . The hypertension group was considerably older and comprised more men compared to the non-hypertension group. In addition, the hypertension group had a significantly higher BMI and fewer teeth (19.9 ± 8.2) than the non-hypertension group (23.2 ± 6.9).

Toothbrushing habits

Table 2 presents the toothbrushing habits of the participants. The overall toothbrushing rates were as follows: 33% upon waking, 8% before breakfast, 69% after breakfast, 48% after lunch, 4% before dinner, 42% after dinner, and 51% before sleeping. A total of 476 participants (51%) brushed their teeth three or more times. The hypertension group brushed less frequently after breakfast, after lunch, and before sleeping than the non-hypertension group. Similarly, the hypertension group had fewer participants who brushed their teeth frequently (≥ 3 times daily). Brushing duration was not significantly associated with hypertension. In addition, we performed a multivariable regression analysis adjusted for age and sex to assess the association between toothbrushing habits and oral environment. No significant associations were found between tongue coating scores and either toothbrushing timing or frequency of brushing (≥ 3 times per day).

Variables	All participants (N=940)	Hypertension group (N=529)	Non-Hypertension group (N=411)	P value
Age (years)	67 $\pm$ 11	70 $\pm$ 10	63 $\pm$ 11	< 0.001
Men/Women	361/579	230/299	131/280	< 0.001
Height (cm)	157 $\pm$ 9	157 $\pm$ 10	158 $\pm$ 9	0.113
Weight (kg)	58 $\pm$ 11	59 $\pm$ 11	56 $\pm$ 10	< 0.001
Body mass index (kg/m ²)	23.2 $\pm$ 3.4	24.0 $\pm$ 2.5	22.4 $\pm$ 3.1	< 0.001
Systolic BP (mmHg)	132 $\pm$ 17	141 $\pm$ 16	121 $\pm$ 11	< 0.001
Diastolic BP (mmHg)	78 $\pm$ 11	81 $\pm$ 11	73 $\pm$ 8	< 0.001
Medications				
Antihypertensive drugs, n (%)	361 (38)	361 (68)	0 (0)	< 0.001
Hypoglycemic drugs, n (%)	76 (8)	64 (12)	12 (3)	< 0.001
Lipid-lowering drugs, n (%)	193 (21)	141 (27)	52 (13)	< 0.001
Smoking history, n (%)	291 (31)	179 (34)	112 (27)	0.033
Education history (years)	12 [11, 14]	12 [10, 13]	12 [12, 14]	< 0.001
Total energy (Kcal/day)	1877 $\pm$ 586	1918 $\pm$ 578	1824 $\pm$ 592	0.014
Sugar intake (g/1000 kcal)	6.2 $\pm$ 4.1	6.2 $\pm$ 4.3	6.2 $\pm$ 3.8	0.9153
Sodium intake (g/1000 kcal)	2.3 $\pm$ 0.4	2.3 $\pm$ 0.5	2.3 $\pm$ 0.4	0.3762
Number of teeth	25 [17, 27]	23 [13, 27]	26 [21, 28]	< 0.001
Tongue coating scores	5 [4, 7]	6 [5, 8]	5 [4, 7]	0.004

Table 1. Participant characteristics. Continuous variables are expressed as means $\pm$ standard deviation; P value: Hypertension group vs. Non-Hypertension group. BP blood pressure.

Variables	All participants (N = 940)	Hypertension group (N = 529)	Non-Hypertension group (N = 411)	P value
Toothbrushing timing				
Upon waking	313 (33%)	175 (33%)	138 (34%)	0.889
Before breakfast	73 (8%)	46 (9%)	27 (7%)	0.269
After breakfast	648 (69%)	338 (64%)	310 (75%)	<0.001
After lunch	448 (48%)	220 (42%)	228 (55%)	<0.001
Before dinner	34 (4%)	16 (3%)	18 (4%)	0.294
After dinner	396 (42%)	235 (44%)	161 (39%)	0.110
Before sleeping	479 (51%)	252 (48%)	227 (55%)	0.022
Toothbrushing frequency ≥ 3 times per day	476 (51%)	234 (44%)	242 (59%)	<0.001
Long brushing duration	462 (49%)	263 (50%)	199 (48%)	0.693

Table 2. Toothbrushing habits of participants. Continuous variables are expressed as means $\pm$ standard deviation; P value: Hypertension group vs. Non-Hypertension group.

	Odds ratio	95% confidence interval	P value
Toothbrushing timing			
Upon waking	0.978	0.774–1.285	0.873
Before breakfast	1.354	0.827–2.219	0.229
After breakfast	0.577	0.433–0.768	<0.001
After lunch	0.571	0.441–0.741	<0.001
Before dinner	0.681	0.343–1.352	0.272
After dinner	1.241	0.955–1.613	0.106
Before sleeping	0.737	0.569–0.955	0.021
Toothbrushing frequency ≥ 3 times per day	0.554	0.427–0.719	<0.001

Table 3. Univariable logistic regression analysis of hypertension.

Logistic analyses of hypertension

Univariable logistic regression analysis revealed that toothbrushing after breakfast (Odds ratio [OR] 0.577, 95% confidence interval [CI] 0.433–0.768, $P < 0.001$), after lunch (OR 0.571, 95% CI 0.441–0.741, $P < 0.001$), and before sleeping (OR 0.737, 95% CI 0.569–0.955, $P = 0.021$), as well as frequency of brushing ≥ 3 times per day (OR 0.554, 95% CI 0.427–0.719, $P < 0.001$) were all significantly associated with a lower risk of hypertension (Table 3). Multivariable logistic regression analyses are shown in Table 4. In Model 1 (adjusted for age and sex), toothbrushing after breakfast (OR 0.604, 95% CI 0.444–0.823, $P = 0.001$) and brushing ≥ 3 times per day (OR 0.735, 95% CI 0.554–0.973, $P = 0.032$) were significantly associated with a lower risk of hypertension (Table 5). After adjusting for age, sex, BMI, smoking history, and use of medications, years of education, and total energy intake per day, and sugar and sodium intakes per 1000 kcal as covariates (Model 2), only toothbrushing after breakfast was independently associated with reduced hypertension risk (OR 0.688, 95% CI 0.496–0.954, $P = 0.025$). Furthermore, in multivariable analyses using all toothbrushing timings, toothbrushing frequency, and other variables, toothbrushing after breakfast was independently associated with hypertension (Supplementary Table 1).

Stratified analyses divided by age

Stratified analysis was conducted by categorizing the participants by age with a cut-off of 65 years. Supplementary Table 2 shows the characteristics of study participants divided into older (age > 65 years) and non-older (age < 65 years) groups. The older group had a significantly higher rate of participants with hypertension than the non-older group (67% vs. 37%). Participants in the older group also had fewer remaining teeth. Additionally, the older group had fewer participants who brushed their teeth after lunch and before sleeping compared to non-older participants, but more participants who brushed their teeth after dinner (Supplementary Table 3). The number of participants who brushed their teeth ≥ 3 times per day in the non-older group was significantly higher than that in the older group. In older participants, multivariable analysis, adjusted for age and sex (Model 1), identified toothbrushing after breakfast and high toothbrushing frequency as independent factors associated with lower hypertension risk. Further adjustment for age, sex, BMI, smoking history, and the use of medications, years of education, and total energy intake per day, and sugar and sodium intakes per 1000 kcal (Model 2) revealed that only toothbrushing after breakfast was independently associated with a reduced risk of hypertension. In contrast, no specific variables or characteristics were associated with hypertension in non-older participants.

	Odds ratio	95% confidence interval	P value
Model 1			
Upon waking	1.102	0.821–1.478	0.519
Before breakfast	1.040	0.619–1.749	0.882
After breakfast	0.604	0.444–0.823	0.001
After lunch	0.769	0.580–1.018	0.066
Before dinner	0.566	0.266–1.206	0.141
After dinner	1.069	0.806–1.417	0.645
Before sleeping	0.983	0.742–1.302	0.905
Toothbrushing frequency ≥ 3 times per day	0.735	0.554–0.973	0.032
Model 2			
Upon waking	1.065	0.781–1.453	0.691
Before breakfast	1.026	0.598–1.760	0.925
After breakfast	0.688	0.496–0.954	0.025
After lunch	0.907	0.669–1.231	0.532
Before dinner	0.670	0.309–1.569	0.382
After dinner	1.111	0.824–1.498	0.492
Before sleeping	0.990	0.736–1.332	0.947
Toothbrushing frequency ≥ 3 times per day	0.869	0.640–1.179	0.367

Table 4. Multivariable logistic regression analysis for hypertension with each toothbrushing timing or toothbrushing frequency ≥ 3 times per day and other factors as dependent variables. *Model 1:* Adjusted for age and sex. *Model 2:* Adjusted for age, sex, body mass index, smoking history, use of hypoglycemic and lipid-lowering medications, years of education, and total energy intake per day, and sugar and sodium intakes per 1000 kcal.

Discussion

This study investigated the association between toothbrushing habits and hypertension in the general population. Notably, only toothbrushing after breakfast was independently associated with lower hypertension risk. While brushing ≥ 3 times per day was initially associated with reduced hypertension after adjusting for age and sex, this association became non-significant after further adjusting for BMI, smoking, and use of antihypertensive, hypoglycemic, and lipid-lowering medications. This trend was also observed in those aged ≥ 65 years; however, no significant associations were identified in those aged < 65 years. While an association has been established between toothbrushing frequency and hypertension or cardiovascular diseases, the association between the timing of toothbrushing and hypertension has not yet been clarified. To our knowledge, this is the first study to demonstrate an association between toothbrushing after breakfast and hypertension.

Previous studies have linked inflammation to hypertension. Inflammatory biomarkers, such as C-reactive protein (CRP)²² and cytokines²³, as well as white blood cell and platelet counts²⁴, are often elevated in patients with hypertension. This established link strengthens the possibility of an association between oral inflammation and hypertension, as supported by several studies^{13,25,26}. In a study involving Japanese university students, periodontal disease was reported to be significantly associated with hypertension²⁷. Similarly, tooth loss, often associated with inadequate oral care, is linked with hypertension^{28–32}. However, there is a lack of consensus on the specific number of missing teeth that defines an increased risk for hypertension. For example, a Korean study reported that tooth loss was strongly associated with hypertension, especially in women aged > 60 years²⁸. In contrast, a French study identified poor masticatory function, poor oral hygiene, and oropharyngeal inflammation as risk factors for hypertension in participants aged < 65 years³³. Regardless of age, these studies underscore the importance of maintaining a healthy oral environment and adopting appropriate toothbrushing habits.

Several reports have explored the association between toothbrushing habits and hypertension. A large Korean cohort study found that hypertension prevalence decreased with increasing toothbrushing frequency after adjusting for confounders, including periodontitis³⁴. A previous meta-analysis also showed an association between toothbrushing frequency and hypertension³⁵. In Kuwabara et al.'s large-scale epidemiological study on the association between toothbrushing and lifestyle-related diseases in the Japanese population³⁶, less frequent toothbrushing was found to be associated with a higher hypertension prevalence. However, binary logistic regression analysis showed that toothbrushing frequency was independently associated with diabetes and dyslipidemia but not hypertension. In our study, the proportion of those brushing their teeth ≥ 3 times per day was significantly higher in the non-hypertension group than that in the hypertension group; however, this association became non-significant when other risk factors were added as additional covariates. The reason for the lack of association between toothbrushing frequency and hypertension in the multivariable analysis remains unclear, but there are several speculations. One possible explanation is that toothbrushing frequency is a general indicator of oral hygiene behavior but does not necessarily reflect the actual effect of plaque removal. Brushing technique including the use of interdental brushes, electric toothbrushes, water toothpaste, or other oral care items, and consistency are also important factors, and these were not captured in our study. Therefore,

	Odds ratio	95% confidence interval	P value
Non-older participants (age < 65 years)			
Model 1			
Upon waking	0.746	0.454–1.223	0.245
Before breakfast	2.588	0.966–6.935	0.059
After breakfast	0.768	0.462–1.277	0.309
After lunch	0.854	0.533–1.368	0.511
Before dinner	0.416	0.085–2.033	0.279
After dinner	1.029	0.631–1.677	0.909
Before sleeping	1.300	0.804–2.103	0.285
Toothbrushing frequency ≥ 3 times per day	0.878	0.546–1.412	0.591
Model 2			
Upon waking	0.636	0.370–1.094	0.102
Before breakfast	2.606	0.926–7.334	0.070
After breakfast	0.893	0.513–1.555	0.690
After lunch	1.118	0.649–1.926	0.686
Before dinner	0.543	0.107–2.754	0.461
After dinner	1.021	0.604–1.726	0.938
Before sleeping	1.330	0.796–2.221	0.276
Toothbrushing frequency ≥ 3 times per day	1.090	0.636–1.869	0.753
Older participants (age ≥ 65 years)			
Model 1			
Upon waking	1.347	0.925–1.962	0.121
Before breakfast	0.741	0.742–2.452	0.326
After breakfast	0.533	0.358–0.794	0.002
After lunch	0.724	0.509–1.029	0.072
Before dinner	0.614	0.252–1.495	0.283
After dinner	1.065	0.751–1.508	0.725
Before sleeping	0.853	0.601–1.210	0.373
Toothbrushing frequency ≥ 3 times per day	0.666	0.468–0.947	0.024
Model 2			
Upon waking	1.391	0.934–2.072	0.105
Before breakfast	0.738	0.395–1.377	0.339
After breakfast	0.602	0.395–0.917	0.018
After lunch	0.802	0.549–1.172	0.255
Before dinner	0.744	0.283–1.960	0.550
After dinner	1.157	0.797–1.679	0.444
Before sleeping	0.844	0.581–1.227	0.375
Toothbrushing frequency ≥ 3 times per day	0.768	0.525–1.123	0.173

Table 5. Multivariable logistic regression analysis for hypertension with each toothbrushing timing or toothbrushing frequency ≥ 3 times per day and other factors as dependent variables. *Model 1:* Adjusted for age and sex. *Model 2:* Adjusted for age, sex, body mass index, smoking history, use of hypoglycemic and lipid-lowering medications, years of education, and total energy intake per day, and sugar and sodium intakes per 1000 kcal.

individuals who brush frequently may not necessarily achieve better oral hygiene or reduced inflammation. Another possibility is reverse causation. Participants who are more health-conscious or already diagnosed with hypertension may have adopted frequent toothbrushing as part of broader health behavior changes. Our detailed survey on toothbrushing frequency, which included the timing of toothbrushing, may have captured nuances that masked the association observed in other studies. Brushing the teeth at least thrice daily, especially after breakfast, may reduce the risk of developing hypertension.

This study identified toothbrushing after breakfast as an associated factor in lowering hypertension, which has not been identified in previous studies. Breakfast deposits food and drink in the oral cavity, which then affects the oral environment¹⁴. Therefore, not brushing after breakfast is likely to increase the risk of periodontal disease. The condition of the marginal tissue around the teeth has been shown to be associated with blood pressure³⁷. Further, a significant correlation has been shown between high blood pressure and oral hygiene, while reducing plaque accumulation can prevent periodontal disease symptoms^{38,39}. Plaque accumulation is significantly reduced among individuals who brush their teeth after breakfast⁴⁰. It is believed that brushing teeth after breakfast

to prevent plaque accumulation can help to maintain good oral hygiene, prevent periodontal disease, and even prevent hypertension. Furthermore, people who brush their teeth after breakfast may be more health conscious, and brushing their teeth after breakfast may be a contributing factor associated with hypertension. However, the specific association between toothbrushing, periodontitis prevention, and, ultimately, hypertension and CVDs remains unclear. Indeed, this study found that toothbrushing after breakfast was independently associated with hypertension, but oral hygiene status, as assessed by tongue coating score, was not associated with toothbrushing habits. While previous studies have demonstrated that tongue cleaning has an effect on tongue coating⁴¹, no reports were found regarding the influence of toothbrushing habits on tongue coating. It is possible that the results may have varied if a plaque score had been used to evaluate oral hygiene. The inclusion of detailed toothbrushing habits alongside comprehensive oral assessments for periodontal diseases in future large cohort studies could further clarify the association between toothbrushing timing and hypertension.

Despite the valuable insights shared in this study, it had some limitations. First, the cross-sectional design precludes establishing a causal relationship between toothbrushing habits and hypertension. Prospective longitudinal studies are needed to evaluate the effects of modifying toothbrushing habits on BP. Second, this study was conducted on health-examination participants; therefore, BP measurements were mostly taken once, which may not accurately reflect the true BP levels of the participants. Third, data on the use of interdental brushes, electric toothbrushes, water toothpaste, or other oral care items were not collected. Further research is necessary to clarify the relationships between these factors. Lastly, although the study targeted the general population of Tarumizu City, participation was voluntary, which may have introduced selection bias. Further studies, involving better recruitment processes, are warranted to validate our findings.

In conclusion, our study showed that toothbrushing after breakfast was independently associated with a lower risk of hypertension among individuals aged ≥ 65 years.

Data availability

Owing to privacy or ethical restrictions, the data are not publicly available. However, the datasets analyzed in this study will be made available by the corresponding author upon reasonable request, following ethical approval.

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Author contributions

Research idea and study design: A.T., T.K.; data acquisition: A.T., S.O., S.Y., Y.A., K.H., K.N., M.N., T.O.; data analysis/interpretation: A.T., T.K., S.K.; statistical analysis: A.T., S.K.; supervision or mentorship: S.K., T.T., M.O. All authors reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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