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*Article*

# Association of Chronic Periodontitis with Migraine in a Korean Adult Population: A Nationwide Nested Case-Control Study

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**Abstract**

**Background:** Migraine and chronic periodontitis are prevalent inflammatory disorders that may share common pathophysiological pathways. Growing evidence suggests an association between periodontal inflammation and migraine, yet large-scale population-based studies are limited. **Objective:** To investigate the association between chronic periodontitis and the occurrence of migraine using a nested case-control design in a nationally representative Korean adult cohort. **Methods:** This study utilized data from the Korean National Health Insurance Service-Health Screening cohort (2002–2019). A total of 43,359 individuals diagnosed with migraine (ICD-10: G43) were matched 1:4 by age, sex, income, and residence with 173,436 controls. Chronic periodontitis was identified using ICD-10 code K053. Conditional logistic regression was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for demographic, behavioral, and clinical covariates. **Results:** A significant association was observed between chronic periodontitis and migraine. Individuals with at least one diagnosis of periodontitis within one year prior to migraine onset had increased odds of migraine (adjusted OR = 1.10, 95% CI: 1.08–1.13). Similar associations were observed for two diagnoses within one year (OR = 1.05; 95% CI: 1.01–1.09) and one diagnosis within two years (OR = 1.10; 95% CI: 1.08–1.13). No association was found with three or more diagnoses in one year. Subgroup analyses confirmed consistent associations across migraine subtypes and demographic strata. **Conclusion:** This study demonstrated a statistically significant association between chronic periodontitis and migraine, suggesting a potential shared inflammatory or neurovascular mechanism. Recognizing periodontal disease as a modifiable factor may offer new insights into migraine prevention and management. Further longitudinal and interventional studies are warranted to establish causality.

**Keywords:** chronic periodontitis; inflammation; migraine; neurovascular mechanism; oral health

## 1. Introduction

Migraine is a prevalent and disabling neurological disorder experienced by approximately 15.1% of the world's population [1]. It is typically characterized by recurrent episodes of moderate to

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severe headache, usually unilateral and pulsatile in nature, and frequently accompanied by nausea, photophobia, and phonophobia. These symptoms are generally exacerbated by routine physical activity. The pathogenesis of migraine involves a multifactorial interplay of environmental, genetic, and hormonal factors, with a notably higher prevalence among women [2–4]. Current research into migraine pathophysiology centers on two main areas: the involvement of specific neurotransmitters and the contribution of inflammatory processes.

Chronic periodontitis, similarly, is a persistent and multifactorial inflammatory disease affecting the supporting structures of the teeth. It arises from the host's immune response to bacterial biofilm that accumulates on the nonshedding surfaces of the oral cavity. Like migraine, chronic periodontitis is a significant contributor to the global burden of chronic diseases and poses a major public health concern. The disease processes slowly and painlessly, leading to periodontal attachment loss and alveolar bone resorption, which may ultimately result in tooth mobility and loss. Although historically considered a localized oral condition, growing evidence now suggests that chronic periodontitis contributes to systemic inflammation and is associated with various systemic conditions, including ischemic stroke and Alzheimer's disease [5–7]. Chronic periodontitis has also been linked to other systemic disorders, such as diabetes mellitus, cardiovascular diseases, rheumatoid arthritis, osteoporosis, and reproductive health issues in both men and women. Importantly, associations with neurodegenerative and neurological conditions–including Alzheimer's, disease, Parkinson's disease, and migraine–have also been identified [8].

The objective of this study is to comprehensively examine the association between chronic periodontitis and the occurrence of migraine in the Korean adult population, utilizing data from a large-scale national healthcare database.

## 2. Methods

### *2.1. Data Source and Study Population*

This study was approved by the Ethics Committee of Hallym University (2019-10-023). The Institutional Review Board waived the requirement for written informed consent. All procedures complied with the ethical standards and regulations set by the Hallym University Ethics Committee.

The data for this nested case-control study were retrieved from the Korean National Health Insurance Service-Health Screening Cohort data, consisting of 514,866 participants and 895,300,177 medical claim codes from 2002 to 2019. The detailed information of the Korean National Health Insurance Service-Health Screening Cohort data was described elsewhere thoroughly.

The migraine group included patients with at least two diagnoses of migraine (ICD-10 codes: G43) between 2002 and 2019 (n = 54,877). Two subtypes were defined: migraine with aura (G431) and migraine without aura (G430). Individuals diagnosed with migraine in 2002 and 2003 were excluded to ensure that only new diagnoses were considered (n = 11,510). Individuals with missing data were also excluded (n = 8).

The control group was selected from participants not included in the migraine group (n = 459,989). Individuals with only one diagnosis of migraine between 2002 and 2019 were excluded (n = 50,307). Four control participants per migraine participant were randomly selected, matched by age, sex, income, and region of residence. The index date was defined as the date of the first migraine diagnosis for the case group and assigned accordingly for each matched control. Unmatched individuals were excluded (n = 236,246). The final analysis included 43,359 migraine participants and 173,436 control participants (Figure 1).

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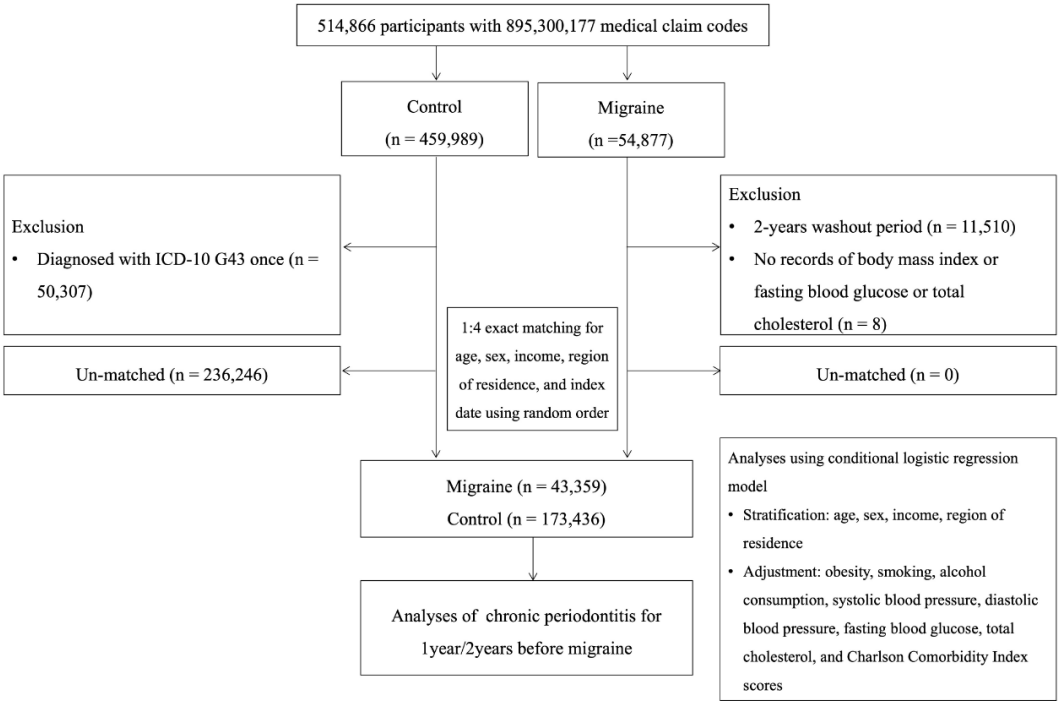


**Figure 1.** Flowchart illustrating the inclusion and exclusion criteria for this study. A total of 514,866 participants were enrolled in the study, including 43,359 subjects with migraine and 173,436 control subjects matched for age, sex, income, and region of residence.

### *2.2. Identification of Chronic Periodontitis and Confounders*

Chronic periodontitis was defined using ICD-10 codes K053 [9]. Participants were divided into ten age groups in 5-year intervals starting from age 40. Income was categorized into five levels (class 1: lowest income to class 5: highest income). Region of residence was classified as urban (including Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) or rural (comprising Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju). Smoking status was categorized as nonsmoker, past smoker, or current smoker. Alcohol consumption was categorized as less than once per week or once or more per week. Obesity was assessed using body mass index (BMI, kg/m2) and classified per the Asia-Pacific Western Pacific Regional Office (WPRO) 2000 standards: underweight (< 18.5), normal (18.5–23), overweight (23–24.9), obese I (25–29.9), and obese II (≥ 30). Clinical measurements included systolic and diastolic blood pressure (mmHg), fasting blood glucose (mg/dL), and total cholesterol (mg/dL). The Charlson Comorbidity Index (CCI) was used to assess comorbid disease burden.

### *2.3. Statistical Analysis*

Demographics between the migraine and control groups were compared using standardized differences. The number of chronic periodontitis cases one or two years prior to the index date was described. Conditional logistic regression was applied to estimate odds ratios (OR) and 95% confidence interval (CI) for the association between chronic periodontitis and migraine. Model 1 adjusting for smoking status, alcohol use, obesity, and CCI score. Model 2 further adjusted for systolic and diastolic blood pressure (SBP and DBP), total cholesterol, and fasting blood glucose. Chronic periodontitis was assessed as: at least once, at least twice, and at least three times within one year, and at least once within two years. Subgroup analyses were performed based on migraine subtype and baseline characteristics. All analyses used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), with two-tailed significance level of 0.05.

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## 3. Results

Among 43,359 individuals with migraine and 173,436 controls, both groups were matched for sex, age, income, and region of residence (standardized difference = 0). The migraine group had slightly lower smoking and alcohol consumption rates, lower DBP, but higher total cholesterol and CCI scores. SBP and fasting glucose levels were similar between groups. The number of periodontitis cases was higher in the migraine group both within one year (1.34%) and two years (2.08%) prior to the index date compared to the control group (1.28% and 1.99%, respectively, Table 1).

**Table 1.** General Characteristics of Participants.

| Characteristics | Total participants | | |
|---|---|---|---|
| | Migraine | Control | Standardized Difference |
| Age (years old) (n, %) | | | |
| 40-44 | 934 (2.15) | 3736 (2.15) | |
| 45-49 | 4641 (10.70) | 18,564 (10.70) | |
| 50-54 | 6815 (15.72) | 27,260 (15.72) | |
| 55-59 | 7283 (16.80) | 29,132 (16.80) | |
| 60-64 | 6608 (15.24) | 26,432 (15.24) | 0 |
| 65-69 | 6589 (15.20) | 26,356 (15.20) | |
| 70-74 | 5349 (12.34) | 21,396 (12.34) | |
| 75-79 | 3290 (7.59) | 13,160 (7.59) | |
| 80-84 | 1423 (3.28) | 5692 (3.28) | |
| 85+ | 427 (0.98) | 1708 (0.98) | |
| Sex (n, %) | | | |
| Male | 14,717 (33.94) | 58,868 (33.94) | 0 |
| Female | 28,642 (66.06) | 114,568 (66.06) | |
| Income (n, %) | | | |
| 1 (lowest) | 8026 (18.51) | 32,104 (18.51) | |
| 2 | 6113 (14.10) | 24,452 (14.10) | 0 |
| 3 | 7035 (16.23) | 28,140 (16.23) | |
| 4 | 9060 (20.90) | 36,240 (20.90) | |
| 5 (highest) | 13,125 (30.27) | 52,500 (30.27) | |
| Region of residence (n, %) | | | |
| Urban | 16,999 (39.21) | 67,996 (39.21) | 0 |
| Rural | 26,360 (60.79) | 105,440 (60.79) | |
| Obesity† (n, %) | | | |
| Underweight | 1046 (2.41) | 4411 (2.54) | |
| Normal | 15,442 (35.61) | 62,425 (35.99) | 0.07 |
| Overweight | 11,743 (27.08) | 46,280 (26.68) | |
| Obese I | 13,760 (31.74) | 54,495 (31.42) | |
| Obese II | 1368 (3.16) | 5825 (3.36) | |
| Smoking status (n, %) | | | |
| Nonsmoker | 34,538 (79.66) | 136,296 (78.59) | 0.03 |
| Past smoker | 2541 (5.86) | 10,243 (5.91) | |
| Current smoker | 6280 (14.48) | 26,897 (15.51) | |
| Alcohol consumption (n, %) | | | |
| <1 time a week | 35,332 (81.49) | 138,775 (80.02) | 0.04 |
| ≥1 time a week | 8027 (18.51) | 34,661 (19.98) | |
| Systolic blood pressure (n, %) | | | 0.06 |
| <120 mmHg | 13,930 (32.13) | 53,541 (30.87) | |

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| | | | |
|---|---|---|---|
| 120-139 mmHg | 20,775 (47.91) | 81,965 (47.26) | |
| ≥140 mmHg | 8654 (19.96) | 37,930 (21.87) | |
| Diastolic blood pressure (n, %) | | | |
| <80 mmHg | 21,324 (49.18) | 83,804 (48.32) | 0.04 |
| 80-89 mmHg | 15,278 (35.24) | 59,928 (34.55) | |
| ≥90 mmHg | 6757 (15.58) | 29,704 (17.13) | |
| Fasting blood glucose (n, %) | | | |
| <100 mg/dL | 28,602 (65.97) | 109,716 (63.26) | 0.07 |
| 100-125 mg/dL | 11,581 (26.71) | 47,996 (27.67) | |
| ≥126 mg/dL | 3176 (7.32) | 15,724 (9.07) | |
| Total cholesterol (n, %) | | | |
| <200 mg/dL | 22,632 (52.20) | 90,891 (52.41) | 0 |
| 200-239 mg/dL | 14,471 (33.37) | 57,592 (33.21) | |
| ≥240 mg/dL | 6256 (14.43) | 24,953 (14.39) | |
| CCI score (n, %) | | | |
| 0 | 23,948 (55.23) | 105,933 (61.08) | 0.04 |
| 1 | 8581 (19.79) | 27,566 (15.89) | |
| ≥2 | 10,830 (24.98) | 39,937 (23.03) | |
| The number of chronic periodontitis (Mean, Standard deviation) | | | |
| within 1 year | 0.50 (1.34) | 0.47 (1.28) | 0.02 |
| within 2 years | 0.95 (2.08) | 0.90 (1.99) | 0.02 |

CCI, Charlson comorbidity index., †Obesity (BMI, body mass index, kg/m²) was categorized as <18.5 (underweight), ≥18.5 to <23 (normal), ≥23 to <25 (overweight), ≥25 to <30 (obese I), and ≥30 (obese II).

An increased probability of migraine was associated with at least one diagnosis of periodontitis within one year (OR in model 2 = 1.10, 95% CI = 1.08–1.13), two diagnoses within one year (OR in model 2 = 1.05, 95% CI = 1.01–1.09), and one diagnosis within two years (OR in model 2 = 1.10, 95% CI = 1.08–1.13). No association was found for three or more diagnoses within one year (OR in model 2 = 1.02, 95% CI = 0.97–1.06). These associations remained consistent across migraine subtypes, except that two diagnoses within one year were not significantly associated with migraine with aura (Table 2).

**Table 2.** Crude and adjusted odds ratios for the association between chronic periodontitis and migraine.

| Characteristics | No. of case (exposure/total, %) | No. of control (exposure/total, %) | Odds ratios for migraine (95% confidence interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Crude† | P-value | Model 1†‡ | P-value | Model 2†§ | P-value |
| Migraine (n = 216,795) | | | | | | | | |
| CP ≥1 (1 year) | 9786/43,359 (22.6%) | 36,379/173,436 (21.0%) | 1.10 (1.07-1.13) | <0.001* | 1.11 (1.08-1.13) | <0.001* | 1.10 (1.08-1.13) | <0.001* |
| CP ≥2 (1 year) | 4716/43,359 (10.9%) | 18,149/173,436 (10.5%) | 1.04 (1.01-1.08) | 0.012* | 1.05 (1.02-1.09) | 0.005* | 1.05 (1.01-1.09) | 0.005* |
| CP ≥3 (1 year) | 2584/43,359 (6.0%) | 10,242/173,436 (5.9%) | 1.01 (0.97-1.06) | 0.667 | 1.02 (0.97-1.06) | 0.473 | 1.02 (0.97-1.06) | 0.476 |
| CP ≥1 (2 years) | 15,077/43,359 (34.8%) | 56,850/173,436 (32.8%) | 1.10 (1.07-1.12) | <0.001* | 1.10 (1.08-1.13) | <0.001* | 1.10 (1.08-1.13) | <0.001* |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Migraine with aura (n = 15,760) | | | | | | | | |
| CP ≥1 (1 year) | 688/3152 (21.8%) | 2461/12,608 (19.5%) | 1.15 (1.05-1.27) | 0.004* | 1.17 (1.06-1.28) | 0.002* | 1.16 (1.06-1.28) | 0.002* |
| CP ≥2 (1 year) | 314/3152 (10.0%) | 1216/12,608 (9.6%) | 1.04 (0.91-1.18) | 0.588 | 1.05 (0.92-1.20) | 0.481 | 1.05 (0.92-1.19) | 0.501 |
| CP ≥3 (1 year) | 151/3152 (4.8%) | 659/12,608 (5.2%) | 0.91 (0.76-1.09) | 0.319 | 0.92 (0.77-1.10) | 0.366 | 0.91 (0.76-1.10) | 0.324 |
| CP ≥1 (2 years) | 1067/3152 (33.9%) | 3836/12,608 (30.4%) | 1.18 (1.08-1.28) | <0.001* | 1.19 (1.09-1.29) | <0.001* | 1.18 (1.09-1.29) | <0.001* |
| Migraine without aura (n = 201,035) (n = 15,760) | | | | | | | | |
| CP ≥1 (1 year) | 9098/40,207 (22.6%) | 33,918/160,828 (21.1%) | 1.10 (1.07-1.13) | <0.001* | 1.10 (1.07-1.13) | <0.001* | 1.10 (1.07-1.13) | <0.001* |
| CP ≥2 (1 year) | 4402/40,207 (11.0%) | 16,933/160,828 (10.5%) | 1.05 (1.01-1.08) | 0.014* | 1.05 (1.01-1.09) | 0.006* | 1.05 (1.01-1.09) | 0.006* |
| CP ≥3 (1 year) | 2433/40,207 (6.1%) | 9583/160,828 (6.0%) | 1.02 (0.97-1.06) | 0.482 | 1.02 (0.98-1.07) | 0.335 | 1.02 (0.98-1.07) | 0.33 |
| CP ≥1 (2 years) | 14,010/40,207 (34.8%) | 53,014/160,828 (33.0%) | 1.09 (1.06-1.12) | <0.001* | 1.10 (1.07-1.12) | <0.001* | 1.09 (1.07-1.12) | <0.001* |

CCI, Charlson Comorbidity Index; CP, chronic periodontitis; DBP, Diastolic blood pressure; SBP, Systolic blood pressure. *Conditional or unconditional logistic regression analysis, significance at P <0.05. †Stratified model for age, sex, income, and geographic region. ‡Model 1 was adjusted for smoking status, alcohol use, obesity, and CCI scores. §Model 2 was adjusted for model 1 plus total cholesterol, SBP, DBP, and fasting blood glucose.

Stratification by age, sex, income, region of residence, smoking status, alcohol consumption, BP, fasting blood glucose level, total cholesterol level, and CCI scores did not alter the estimates of migraine probability (Tables S1–S3). This also apparent when classifying individuals into migraine with aura or migraine without aura (Table S4 to Table S9).

## 4. Discussion

This large-scale, nested case-control study utilizing data from the Korean national health insurance service demonstrated a statistically significant association between chronic periodontitis and the occurrence of migraine. Even after controlling for a wide array of potential confounding variables, including demographic and lifestyle factors, comorbidities, and metabolic profiles, individuals with a recent diagnosis of chronic periodontitis were more likely to experience migraine episodes. These results support and extend findings from previous observational and case-control studies that suggest a bidirectional association between periodontal inflammation and neurological disorders such as migraine [10]. Recent meta-analyses further corroborate this link, showing that individuals with chronic migraine have more than double the odds of also having periodontitis compared to controls [11,12].

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The biologic mechanisms underlying this association are likely multifactorial, involving chronic low-grade systemic inflammation, neurovascular dysregulation, and shared molecular mediators. Periodontitis is characterized by a persistent immune-inflammatory response to bacterial biofilms, leading to systemic dissemination of cytokines such as tumor necrosis factor (TNF)-$\alpha$, IL-1$\beta$, IL-6, and prostaglandins. These inflammatory mediators are capable of crossing the blood-brain barrier, where they may activate microglia and modulate the trigeminovascular system, an established pathway in migraine pathophysiology [13,14]. Elevated systemic inflammation from periodontitis could thus lower the threshold for migraine attacks or exacerbate migraine chronification. In addition to, recent investigations have identified elevated serum levels of CGRP and procalcitonin in patients with both chronic periodontitis and chronic migraine, suggesting a shared inflammatory axis [15]. Leira et al. demonstrated that individuals with both conditions exhibited significantly higher serum procalcitonin levels that those with either condition alone or healthy controls, suggesting an overlapping inflammatory axis [15]. CGRP, a potent neuropeptide involved in vasodilation and nociception, has been well-established as a central mediator in migraine, and its upregulation in periodontal disease may provide a plausible biological pathway linking the two diseases. Moreover, recent research has highlighted leptin, an adipocytokine involved in immune modulation and metabolic regulation, as another potential biomarker linking these disorders. Elevated leptin levels, which have been observed in both migraine and periodontitis patients, may contribute to enhanced systemic inflammation and vascular dysregulation, providing a plausible mechanistic pathway. A novel layer of evidence comes from a two-sample Mendelian randomization study, which demonstrated a significant genetic predisposition linking periodontitis and migraine [16]. This suggests that shared genetic pathways, potentially involving immune-regulatory genes and inflammatory cascades, may contribute to the co-occurrence of these disorders.

Interestingly, our study found that the association between periodontitis and migraine was most prominent among individuals with one or two diagnoses of chronic periodontitis within the prior one to two years. In contrast, no significant association was found for those with three or more diagnoses of chronic periodontitis within a single year. This paradoxical observation may be explained by several hypotheses. More frequent dental visits for chronic periodontitis might lead to more timely and effective treatment and improved periodontal health, thereby potentially attenuating systemic inflammation and mitigating the risk of migraine onset. Alternatively, it may reflect behavioral differences-those with severe periodontitis might also differ in health-seeking behavior or medication use, potentially influencing diagnosis coding or treatment intensity.

Our subgroup analyses further revealed that the association persisted across various demographic and clinical strata, including both migraine with and without aura. These findings align with multicenter studies such as the Spanish cross-sectional survey, which found a higher prevalence of self-reported periodontitis in chronic versus episodic migraineurs, even after adjusting for lifestyle and psychosocial variables [17]. Furthermore, recent investigations highlight that oral-systemic interactions may not be limited to periodontitis alone. Disorders such as temporomandibular dysfunction and facial myofascial pain have also been implicated in migraine development, reinforcing the notion that orofacial inflammatory or nociceptive inputs can influence central pain modulation [18].

However, several limitations should be acknowledged. First, the diagnosis of migraine and chronic periodontitis relied on administrative claim codes, which may introduce misclassification bias. Nonetheless, the use of repeated diagnostic codes and large-scale population-based sampling enhance the reliability of our definitions. Second, due to the observational nature of the study, causality cannot be inferred. While our analysis adjusted for numerous confounders, residual confounding from variables not captured in the dataset, such as psychological stress, sleep quality, diet, or oral hygiene practices, cannot be ruled out. Third, the temporal proximity between chronic periodontitis and migraine onset suggests association but not a definitive sequence of disease development. Prospective studies are warranted to further investigate the temporal and causal relationship.

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Despite these limitations, our study has notable strengths. It includes a large, nationally representative cohort; thorough adjustment for confounders; and consistency of results across migraine subtypes and demographic strata. To our knowledge, this is among the largest investigations to data examining the link between periodontitis and migraine using real-world healthcare data.

From a clinical perspective, our findings suggest that oral health may play a significant but underrecognized role in migraine pathogenesis. Give the chronic, recurrent, and disabling nature of migraine, addressing modifiable contributors, such as periodontal inflammation, could represent a complementary avenue migraine management. Further interventional studies are urgently needed to determine whether treatment of periodontitis can reduce the frequency, severity, or duration of migraine episodes.

## 5. Conclusions

In summary, this study identifies a statistically significant association between chronic periodontitis and the occurrence of migraine in a Korean adult population. The findings are supported by converging lines of evidence from epidemiology, biomarker research, and genetic studies, all pointing to shared inflammatory and neurovascular pathways. Recognizing periodontitis as a potential modifiable risk factor for migraine opens the door for integrative, cross-disciplinary approaches to prevention and treatment. Future longitudinal and interventional studies will be crucial to clarify causality and determine the therapeutic potential of periodontal care in reducing migraine burden.

**Supplementary Materials:** The following supporting information can be downloaded at: Preprints.org, Table S1: Subgroup analyses of crude and adjusted odds ratios according to age, sex, income, and region of residence; Table S2: Subgroup analyses of crude and adjusted odds ratios according to obesity, smoking status, and alcohol consumption; Table S3: Subgroup analyses of crude and adjusted odds ratios according to blood pressure, fasting blood glucose, total cholesterol, and CCI scores; Table S4: Subgroup analyses of crude and adjusted odds ratios according to age, sex, income and region of residence; Table S5: Subgroup analyses of crude and adjusted odds ratios according to obesity, smoking status, and alcohol consumption; Table S6: Subgroup analyses of crude and adjusted odds ratios according to blood pressure, fasting blood glucose, total cholesterol, and CCI scores; Table S7: Subgroup analyses of crude and adjusted odds ratios according to age, sex, income, and region of residence; Table S8: Subgroup analyses of crude and adjusted odds ratios according to obesity, smoking status, and alcohol consumption; Table S9: Subgroup analyses of crude and adjusted odds ratios according to according to blood pressure, fasting blood glucose, total cholesterol, and CCI scores.

**Author Contributions:** HG Choi and JH Song: study concept and design, data acquisition and interpretation, critical revision of the manuscript. HT Lim, IB Chang, JH Wee, MJ Kwon, and HS Kang: drafting of the figures, critical revision of the manuscript. JH Kim: data interpretation, drafting of the manuscript and figures. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Hallym University (2019-10-023 on 22 December 2022).

**Informed Consent Statement:** Patient consent was waived due to the study retrieved data from the Korean National Health Insurance Sharing Service (https://nhis.or.kr).

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author (kimjihee.ns@gmail.com).

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