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Chronic Periodontitis and Acute Respiratory Infections: A Nationwide Cohort Study

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Abstract: Chronic periodontitis (CP) may increase the risk of exacerbation of and hospitalization for respiratory infections. The aim of the present study was to determine whether CP is associated with acute respiratory infections by analyzing a population-based longitudinal database from the National Health Insurance Service—National Sample Cohort. Univariate and multivariate logistic regression analyses were conducted to assess the association between CP and acute respiratory infections, including acute nasopharyngitis, acute pharyngitis, acute tonsillitis, acute laryngitis and tracheitis, acute bronchitis, and acute bronchiolitis, while adjusting for the confounding effects of sociodemographic variables (sex, age, household income, and smoking status) and comorbidities (diabetes mellitus). Among 545,416 recruited participants, 98,490 (18.1%) had CP. Multivariate analysis, adjusted for sociodemographic variables and comorbidities, showed that except influenza and pneumonia, total acute respiratory infections (odds ratio (OR), 1.33; 95% confidence interval (CI), 1.28–1.38; $p < 0.001$), acute upper respiratory infections (OR, 1.26; 95% CI, 1.22–1.29; $p < 0.001$), and acute lower respiratory infections (OR, 1.23; 95% CI, 1.20–1.26; $p < 0.001$) were significantly associated with CP. The findings of the current cohort study suggest an association between CP and acute respiratory infections. Particularly, CP seems to increase the risk of acute upper and lower respiratory infections.

Keywords: chronic periodontitis; cohort analysis; periodontal disease; respiratory tract infections; respiratory tract diseases

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1. Introduction

Chronic periodontitis (CP) is one of the most common chronic inflammatory diseases. Severe localized or generalized CP affects >10% of the global population and is a major public oral health problem [1,2]. CP progressively and pathologically destroys the tooth-supporting soft and hard tissues, including the cementum, periodontal ligament, and alveolar bone, and may ultimately cause tooth loss [3]. Although previous epidemiologic and cohort studies have suggested that CP is a unidirectional risk factor for lifestyle-related non-communicable diseases, such as cardiovascular disease, hypertension, diabetes mellitus, rheumatoid arthritis, osteoporosis, erectile dysfunction, and cancer, there is increasing evidence indicating that the association between CP and major systemic diseases is bidirectional [4–7].

Several epidemiologic and etiologic studies have suggested a potential association between CP and acute and chronic respiratory infections such as pneumonia, acute bronchitis, lung abscess, and chronic obstructive pulmonary disease [8,9]. Moreover, previous systematic reviews have confirmed a positive causal association between CP and respiratory infections [10,11].

Accumulation of oral pathogens, especially *Fusobacterium nucleatum*, associated with CP may increase the risk of exacerbation and hospitalization in patients with respiratory infections [8]. These infections possibly share the direct bacterial-respiratory pathway

and the same proinflammatory cytokines or products, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, and IL-8 [12]. Major immunoinflammatory cells and inflammatory mediators from the mucosal epithelial cells of the upper and lower respiratory tract make the respiratory tract more susceptible to infection and development of severe respiratory disease [12].

While research on the association between CP and chronic respiratory infections, particularly chronic obstructive pulmonary disease, has steadily progressed over recent decades, relevant studies between CP and acute respiratory infections are scarce and scattered [13,14]. Consequently, the epidemiological association between CP and acute respiratory infections remains unclear and requires further research. Therefore, the goal of the present study was to evaluate the associations between CP and acute respiratory infections by analyzing a population-based longitudinal database from the National Health Insurance Service—National Sample Cohort (NHIS-NSC) in South Korea.

2. Materials and Methods

2.1. Study Design and Data Source

This study used the longitudinal NHIS-NSC database compiled by the National Health Insurance Sharing Service. Data for 1,000,000 individuals, representing 2% of the 48.22 million Korean nationals whose data are maintained in the national health insurance service (NHIS) or medical aid program (MAP) since 2006, were extracted through a multistage stratified sampling method (2142 layers) to ensure similar characteristics in terms of sex (two groups: male and female), age (17 groups: 1–79 years in 5-year intervals and >80 years), region of residence (3 groups: metropolitan, urban, and rural areas), and household income level (21 groups: NHIS in 20 groups and MAP in 1 group). All personal and sensitive information was de-identified prior to the analysis. Among the participants included in the NHIS-NSC database, only adults over 20 years of age who had undergone a routine health examination under the NHIS between 2006 and 2015 were included in this study. A detailed flowchart of the inclusion and exclusion of the participants is shown in Figure 1.

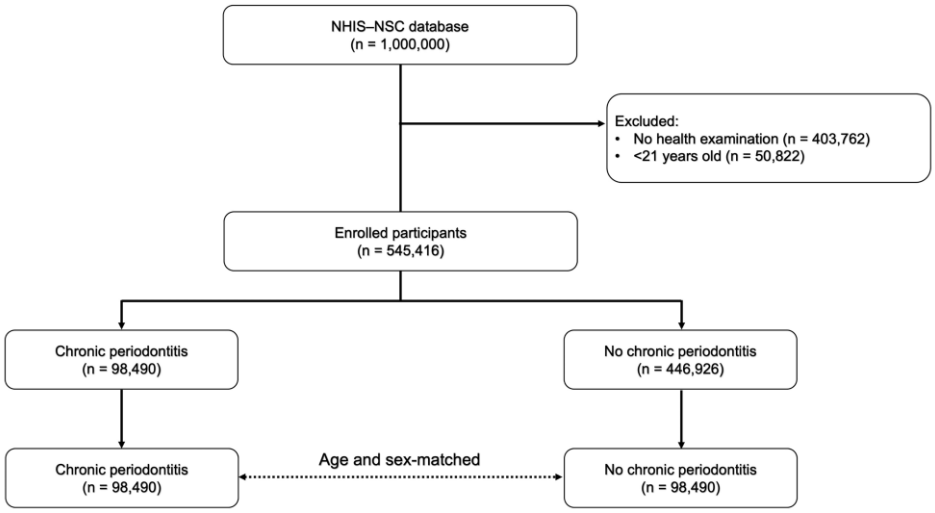

Figure 1. Flowchart of the inclusion and exclusion criteria for the study participants, NHIS-NSC, National Health Insurance Service—National Sample Cohort.

This study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines and followed the guidelines of the Declaration of Helsinki of 1975, as revised in 2013. The protocol was approved by the Institutional Review Board of Daejeon Dental Hospital, Wonkwang University (Approval No. W2107/001-001), and the requirement for written consent was waived because of the retrospective nature of this study.

2.2. Study Variables and Definitions

Similar to our previous studies, the definition of CP was limited to those who were diagnosed with CP (Korean Classification of Diseases, sixth revision [KCD-6], code K05.3, corresponding to the International Classification of Disease, 10th revision [ICD-10], code K05.3), and received one or more of the following prescription codes for periodontal surgery: U1051-1052, simple or complicated periodontal flap operation; U1071-1072, autograft, allogenic, xenogeneic, or substitute bone graft for alveolar bone defects; U1081-1083, guided tissue regeneration with or without bone graft [15,16].

Using medical records from 2006 to 2015, participants who were diagnosed with acute respiratory infections by a medical doctor at a private or general hospital using the following diagnostic codes: acute nasopharyngitis (KCD-6/ICD-10 code J01), acute pharyngitis (KCD-6/ICD-10 code J02), acute tonsillitis (KCD-6/ICD-10 code J03), acute laryngitis and tracheitis (KCD-6/ICD-10 code J04), influenza (KCD-6/ICD-10 codes J09–J12), pneumonia (KCD-6/ICD-10 codes J13–18), acute bronchitis (KCD-6/ICD-10 codes J20), and acute bronchiolitis (KCD-6/ICD-10 codes J21), were included in this cohort study.

Patients were categorized into subgroups based on sociodemographic variables and comorbidities, including sex, (2 groups: male and female), age (5 groups: 21–60 years in 5-year intervals and ≥61 years), household income level (5 groups: NHIS in 5 groups, with those in the MAP in the first quintile), smoking status, and diabetes mellitus (KCD-6/ICD-10 codes E10–E14).

2.3. Statistical Analysis

Descriptive statistics were used for sociodemographic variables and comorbidities of participants, and categorical parameters were expressed as numbers and percentages. In this retrospective cohort study, we used the chi-square test to compare patients with CP with and without acute respiratory infections. Univariate (model 1) and multivariate (models 2–4) logistic regression analyses were performed to evaluate the crude and adjusted associations between CP and acute respiratory infections. The odds ratios (ORs) are presented with 95% confidence intervals (CIs), and statistical significance was set at $p < 0.05$. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Distribution According to CP

The prevalence of CP in the study participants is shown in Table 1. The percentages of men aged 41–50 years in the CP and non-CP groups were 54.5% and 32.3%, respectively. In the CP group, 28,588 (29.0%) individuals were in the fifth quintile of household income, 33,402 (33.9%) were current smokers, and 25,870 (26.3%) had diabetes mellitus; these values were significantly different from those in the non-CP group ($p < 0.001$). The prevalence of acute upper and lower respiratory infections in patients with CP was 89.6% and 81.1%, respectively, which was significantly higher than that in patients without CP ($p < 0.001$).

Table 1. Demographic distribution according to chronic periodontitis.

Variables	Chronic Periodontitis		Non-Chronic Periodontitis		*p*-Value
	n	%	*n*	%	
Total	98,490	100.0	98,490	100.0	
Sex					
Male	53,660	54.5	53,660	54.5	
Female	44,830	45.5	44,830	45.5	
Age group (years)					
21–30	9963	10.1	9963	10.1	
31–40	23,821	24.2	23,821	24.2	
41–50	31,777	32.3	31,777	32.3	
51–60	19,979	20.3	19,979	20.3	

Table 1. *Cont.*

Variables	Chronic Periodontitis		Non-Chronic Periodontitis		*p*-Value
	n	%	*n*	%	
≥61	12,950	13.1	12,950	13.1	
Household income [1]					
Low	13,327	13.5	13,084	13.3	<0.001
Middle-low	14,515	14.7	15,155	15.4	
Middle	18,787	19.1	19,058	19.4	
Middle-high	23,273	23.6	23,423	23.8	
High	28,588	29.0	26,770	27.2	
Smoking status					
Yes	33,402	33.9	31,432	31.9	<0.001
No	65,088	66.1	67,058	68.1	
Comorbid diseases					
Diabetes mellitus	25,870	26.3	22,633	23.0	<0.001
Acute respiratory infections					
Acute upper respiratory infections	88,262	89.6	85,900	87.2	<0.001
Acute lower respiratory infections	79,828	81.1	76,434	77.6	<0.001
Influenza and pneumonia	14,382	14.6	14,311	14.5	0.650

[1] Quintiles based on each household's insurance status (with a medical aid program in the first quintile)

3.2. Distribution According to Acute Respiratory Infections

The percentages of participants who were male, aged 41–50 years, and in the fifth quintile of household income among all patients with acute respiratory infections were 53.0%, 31.9%, and 28.2%, respectively. Among patients with acute respiratory infections, 58,448 (31.8%) were current smokers, and 46,219 (25.1%) had diabetes mellitus; these values were significantly different from those among patients without acute respiratory infection ($p < 0.001$). Lastly, among all patients with acute respiratory infection, 92,867 (50.5%) had CP, which was significantly higher than that in patients without acute respiratory infections ($p < 0.001$). The prevalence of acute respiratory infections among the study participants is shown in Table 2.

Table 2. Demographic distribution according to acute respiratory infections.

Variables	Total Acute Respiratory Infections		Acute Upper Respiratory Infections		Acute Lower Respiratory Infections		Influenza and Pneumonia	
	n (%)	*p*-Value	*n* (%)	*p*-Value	*n* (%)	*p*-Value	*n* (%)	*p*-Value
Total	183,972 (100.0%)		174,162 (100.0%)		156,262 (100.0%)		28,693 (100.0%)	
Sex								
Male	97,477 (53.0%)	<0.001	90,993 (52.2%)	<0.001	79,657 (51.0%)	<0.001	13,533 (47.2%)	<0.001
Female	86,495 (47.0%)		83,169 (47.8%)		76,605 (49.0%)		15,160 (52.8%)	
Age group (years)								
21–30	18,607 (10.1%)	<0.001	17,810 (10.2%)	<0.001	15,747 (10.1%)	<0.001	2779 (9.7%)	0.099
31–40	44,244 (24.0%)		42,174 (24.2%)		37,076 (23.7%)		5970 (20.8%)	
41–50	58,737 (31.9%)		55,324 (31.8%)		49,366 (31.6%)		7806 (27.2%)	
51–60	37,589 (20.4%)		35,424 (20.3%)		32,601 (20.9%)		6304 (22.0%)	
≥61	24,795 (13.5%)		23,430 (13.5%)		21,472 (13.7%)		5834 (20.3%)	
Household income [a]								

Table 2. *Cont.*

Variables	Total Acute Respiratory Infections		Acute Upper Respiratory Infections		Acute Lower Respiratory Infections		Influenza and Pneumonia	
	n (%)	*p*-Value	*n* (%)	*p*-Value	*n* (%)	*p*-Value	*n* (%)	*p*-Value
Low	25,413 (13.8%)	<0.001	23,843 (13.7%)	<0.001	21,591 (13.8%)	<0.001	3993 (13.9%)	<0.001
Middle-low	27,594 (15.0%)		26,121 (15.0%)		23,463 (15.0%)		4325 (15.1%)	
Middle	35,186 (19.1%)		33,298 (19.1%)		29,942 (19.2%)		5360 (18.7%)	
Middle-high	43,819 (23.8%)		41,554 (23.9%)		37,342 (23.9%)		6812 (23.7%)	
High	51,960 (28.2%)		49,346 (28.3%)		43,924 (28.1%)		8203 (28.6%)	
Smoking status								
Yes	58,448 (31.8%)	<0.001	54,350 (31.2%)	<0.001	47,610 (30.5%)	<0.001	7904 (27.5%)	<0.001
No	125,524 (68.2%)		119,812 (68.8%)		108,652 (69.5%)		20,789 (72.5%)	
Comorbid diseases								
Diabetes mellitus	46,219 (25.1%)	<0.001	43,885 (25.2%)	<0.001	40,312 (25.8%)	<0.001	8629 (30.1%)	<0.001
Chronic periodontitis	92,867 (50.5%)	<0.001	88,262 (50.7%)	<0.001	79,828 (51.1%)	<0.001	14,382 (50.1%)	0.652

[a] Quintiles based on each household's insurance status (with a medical aid program in the first quintile).

3.3. CP and Acute Respiratory Infections

The outcomes of the univariate and multivariate logistic regression analyses performed to investigate the association between the prevalence of CP and acute respiratory infections are shown in Table 3. Univariate analysis showed that total acute respiratory infections (OR, 1.33; 95% CI, 1.29–1.38; $p < 0.001$), acute upper respiratory infections (OR, 1.26; 95% CI, 1.23–1.30; $p < 0.001$), and acute lower respiratory infections (OR, 1.23; 95% CI, 1.20–1.26; $p < 0.001$) were significantly associated with CP. In models 2–4, in which adjustments for sociodemographic variables and comorbidities were performed, participants with CP had a higher chance of having acute respiratory infections, except influenza and pneumonia, compared with participants without CP ($p < 0.001$). More specifically, in model 4, in which all confounders were adjusted, CP was positively and significantly related to the risk of total acute respiratory infections (OR, 1.33; 95% CI, 1.28–1.38; $p < 0.001$), acute upper respiratory infections (OR, 1.26; 95% CI, 1.22–1.29; $p < 0.001$), and acute lower respiratory infections (OR, 1.23; 95% CI, 1.20–1.26; $p < 0.001$). Figure 2 shows the associations of detailed acute respiratory infectious diseases with chronic periodontitis in the univariate and multivariate analyses.

Table 3. ORs and 95% CIs for chronic periodontitis in participants with acute respiratory infections in univariate and multivariate logistic regression models.

Variables	Model 1		Model 2		Model 3		Model 4	
	Crude OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
Total acute respiratory infections	1.33 (1.29–1.38)	<0.001	1.34 (1.29–1.39)	<0.001	1.35 (1.30–1.40)	<0.001	1.33 (1.28–1.38)	<0.001
Acute upper respiratory infections	1.26 (1.23–1.30)	<0.001	1.27 (1.23–1.30)	<0.001	1.27 (1.23–1.31)	<0.001	1.26 (1.22–1.29)	<0.001
Acute lower respiratory infections	1.23 (1.20–1.26)	<0.001	1.24 (1.21–1.26)	<0.001	1.24 (1.21–1.27)	<0.001	1.23 (1.20–1.26)	<0.001
Influenza and pneumonia	1.00 (0.98–1.03)	0.650	1.00 (0.98–1.03)	0.648	1.00 (0.98–1.03)	0.643	0.99 (0.97–1.02)	0.902

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: model 2 plus adjustment for smoking and household income status. Model 4: model 3 plus adjustment for diabetes mellitus. OR, odds ratio; CI, confidence interval.

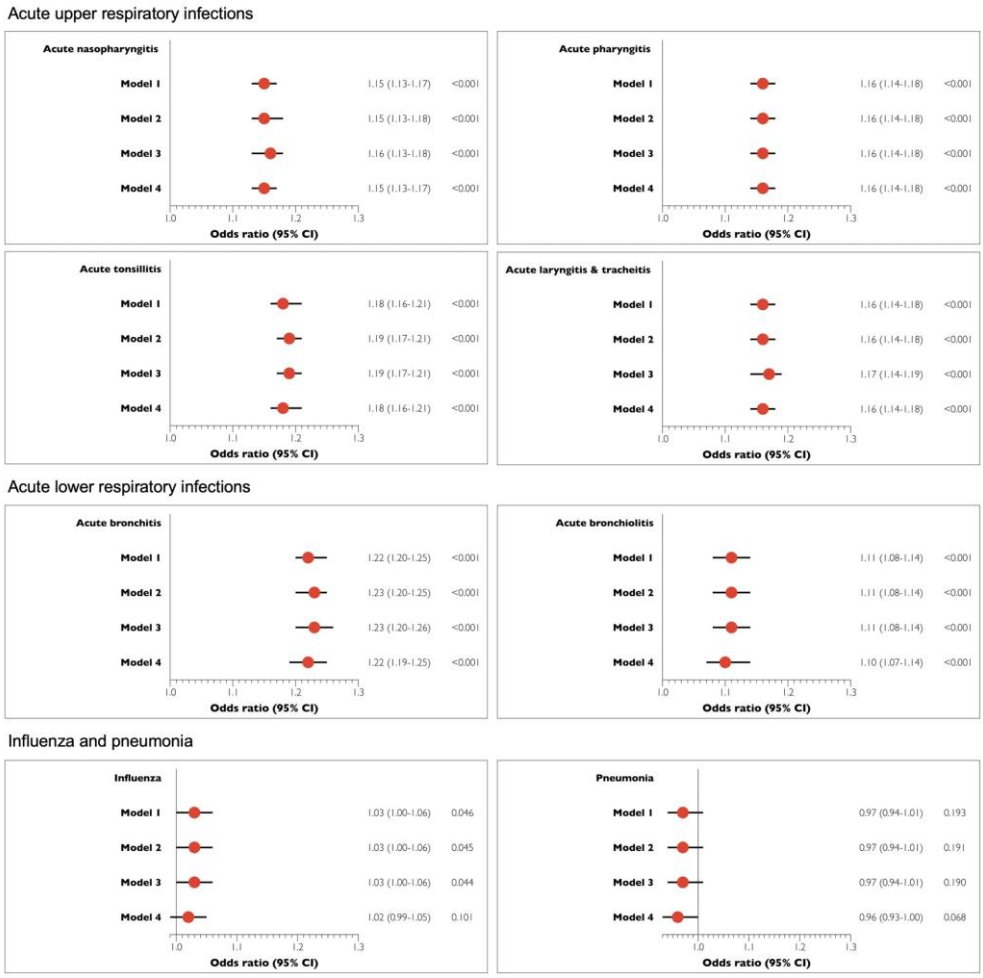

Figure 2. Associations of acute respiratory infections with chronic periodontitis in the univariate and multivariate logistic regression analysis. Model 1: unadjusted, Model 2: adjusted for age and sex, Model 3: model 2 plus adjustment for smoking and household income status, and Model 4: model 3 plus adjustment for diabetes mellitus.

4. Discussion

Poor oral hygiene associated with local oral infections, especially CP, is known to be a risk factor for acute and chronic respiratory infections. In this study, a significant positive association was found between CP and acute respiratory infections, excluding influenza and acute pneumonia, even after adjusting for sociodemographic variables and comorbidities.

Various possible underlying physiological mechanisms for the role of oral bacteria in the pathogenesis of acute and chronic respiratory infections have been suggested [17,18]. First, dental plaque and calculus can serve as a reservoir for pulmonary pathogens that cause respiratory infection in high-risk elderly people in medical or surgical units. Second, salivary enzymes associated with CP can promote the adhesion of respiratory pathogens to the mucosal tissues of the oral cavity and respiratory tract. In particular, *Porphyromonas gingivalis*-induced hydrolytic enzymes may destroy the salivary pellicles that resist pathogenic bacteria. Finally, a large variety of cytokines and other biologically active inflammatory mediators induce alteration of respiratory epithelial tissues, which is another potential biological mechanism in the pathogenesis of respiratory infections.

The incidence and severity of chronic respiratory infections are likely to be affected by the severity of CP [19–22]. A cross-sectional study of the National Health and Nutrition Examination Survey (NHANES) III database reported an increased risk of respiratory infection in patients with clinical attachment loss $\geq$3 mm compared to those with clinical

attachment loss <3 mm (OR, 1.45; 95% CI, 1.02–2.05). Another long-term study found that increased alveolar bone loss is associated with an increased risk of respiratory infection (OR, 1.8; 95% CI, 1.3–2.5). [19,20] Bgyi et al. suggested that the comparative risk of developing postoperative respiratory infection in patients with severe CP was 3.5-fold higher than that in patients with incipient CP ($p < 0.0001$) [21]. Moreover, a longitudinal retrospective investigation demonstrated that elderly patients (aged > 80 years) with CP may have a higher and increased risk of mortality associated with respiratory infection (Hazard ratio, 3.9; 95% CI, 1.1–3.9; $p < 0.05$) [22].

However, there are very few studies on the association between CP and acute respiratory infections. This cohort study found that both acute upper and lower respiratory tract infections (including acute nasopharyngitis, acute pharyngitis, acute tonsillitis, acute laryngitis and tracheitis, acute bronchitis, and acute bronchiolitis) were significantly associated with CP; these findings are similar to the corresponding findings with regard to chronic respiratory infections. The results of this study did not show a statistically significant association between CP and influenza and acute pneumonia ($p > 0.05$). In particular, there was a negative correlation between CP and acute pneumonia, although this was not statistically significant (OR, 0.96; 95% CI, 0.93–1.00; $p = 0.068$). The relationship between CP and respiratory infections remains unclear because influenza and acute pneumonia are fast-developing respiratory illnesses. Underestimation of the prevalence of influenza and acute pneumonia may weaken the causal relationship and association of CP with influenza and acute pneumonia.

Various clinical and epidemiological studies have demonstrated that self- or professional-driven good oral hygiene practices, such as tooth brushing and professional periodontal treatment, can significantly reduce the incidence or severity of respiratory infections [23,24]. In particular, conventional management of CP, including supragingival and subgingival plaque control using ultrasonic or hand instruments is a very effective routine protocol for the prevention and treatment of respiratory diseases.

In this study, CP was defined based on a combination of diagnostic and prescription codes, but the severity of CP could not be identified because clinical and radiographic periodontal parameters (including plaque index, bleeding on probing, pocket probing depth, clinical attachment loss, marginal bone loss, and number of missing teeth) were not included. This is considered a major fundamental limitation of the NHIS-NSC database. In addition, there are limited clinical data available regarding the potential association between CP and COVID-19. Significant and substantial evidence of an association between CP and COVID-19 is expected to be established in the near future.

5. Conclusions

Within the limitations of this study, the findings of the present cohort study suggest a potential association between CP and acute respiratory infections. Particularly, CP seems to increase the risk of acute upper and lower respiratory infections. Therefore, appropriate management of CP can play a significant role in preventing or reducing the risk of acute respiratory infections. Further prospective and comparative studies are necessary to confirm our findings.

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Institutional Review Board Statement: The study design and protocol were reviewed and authorized by the Institutional Review Board of the Daejeon Dental Hospital, Wonkwang University (approval No. W2107/001-001), and the need for informed or written consent was waived as part of the study approval.

Informed Consent Statement: Patient consent was waived due to retrospective design of the study.

Data Availability Statement: Restrictions apply to the availability of these data. Data was obtained from NHIS and are available https://nhiss.nhis.or.kr (accessed on 10 October 2021) with the permission of NHIS.

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Conflicts of Interest: The authors declare no conflict of interest.

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