

# Allergic Rhinitis Is Associated With Periodontitis: A Population-Based Study

Shih-Han Hung,\* Ming-Chieh Tsai,<sup>†‡</sup> Heng-Ching Lin,<sup>§</sup> and Shiu-Dong Chung,<sup>¶||</sup>

**Background:** Little is known regarding associations of periodontitis with diseases of the nose, one of the structures adjacent to the mouth. This study aims to explore the association between periodontitis and previous allergic rhinitis (AR) using a matched patient–control study design from a population-based dataset in Taiwan.

**Methods:** Data were sourced from the Longitudinal Health Insurance Database 2000 for 71,182 patients with chronic periodontitis (CP) and 71,182 controls without periodontitis. Generalized linear mixed-model analyses were used to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for previous AR diagnosis in patients and controls.

**Results:** Significant difference was found in prevalence of prior AR for patients and controls (28.4% versus 24.2%;  $P < 0.001$ ). Generalized linear mixed model suggested that the OR of previous AR for patients was 1.24 (95% CI: 1.22 to 1.27;  $P < 0.001$ ) compared with controls. Adjustments were made for: 1) monthly income; 2) urbanization level; 3) diabetes mellitus; 4) hypertension; 5) coronary heart disease; 6) hyperlipidemia; 7) alcohol abuse; 8) tobacco use disorder; and 9) random effect of geographic region. After adjusting, OR of previous AR diagnosis among patients was 1.21 (95% CI: 1.18 to 1.23;  $P < 0.001$ ) compared with controls.

**Conclusions:** An association between periodontitis and prior AR is demonstrated. It is recommended that physicians be more alert for potential risk of subsequent development of CP in patients with AR. *J Periodontol* 2016;87:749-755.

## KEY WORDS

Epidemiology; periodontitis; rhinitis, allergic.

Chronic periodontitis (CP) is a common disease of the oral cavity consisting of chronic inflammation of periodontal tissues, and it is one of seven destructive periodontal diseases.<sup>1,2</sup> The condition is reported to be present in up to 90% of the population of the United States.<sup>3</sup> Inflammatory periodontal diseases, one of the most common chronic infections in adults, exhibit associations with multiple systemic conditions including: 1) diabetes mellitus (DM); 2) cardiovascular disease; 3) osteoporosis; 4) preterm babies or those with low birth weight; 5) respiratory diseases; and 6) rheumatoid arthritis.<sup>4</sup> It is generally believed that periodontal disease is multifactorial, and commonly known risk factors of CP include: 1) aging; 2) smoking; 3) DM; 4) specific microorganisms; 5) psychologic factors; 6) improper host immune response; 7) osteoporosis; and 8) genetic factors.<sup>5</sup> Interestingly, little is known regarding associations of CP with diseases of the nose, one of the structures adjacent to the mouth.

Allergic rhinitis (AR) is a common disease characterized by: 1) paroxysms of sneezing; 2) rhinorrhea; and 3) nasal obstruction, often accompanied by itching of eyes, nose, and palate.<sup>6</sup> Other common symptoms are: 1) postnasal drip, 2) coughing, 3) irritability, and 4) fatigue.<sup>7</sup> These conditions are especially common in South Asian countries with a climate of high humidity suitable for development of various allergens.<sup>8,9</sup>

AR has been associated with glaucoma and nasopharyngeal carcinoma.<sup>10,11</sup> Many studies have also shown that nasal allergy

\* Department of Otolaryngology, Taipei Medical University Hospital, Taipei, Taiwan.

† Department of Internal Medicine, Cathay General Hospital, Hsinchu, Taiwan.

‡ Sleep Research Center, Taipei Medical University, Taipei, Taiwan.

§ School of Oral Hygiene, Taipei Medical University.

|| Department of Surgery, Far Eastern Memorial Hospital, New Taipei City, Taiwan.

¶ Graduate Program in Biomedical Informatics, College of Informatics, Yuan-Ze University, Chung-Li, Taiwan.

processes influence adjacent structures.<sup>12,13</sup> The purpose of this study is to explore the association between periodontitis and prior AR using a matched patient-control study design from a population-based dataset in Taiwan.

## MATERIALS AND METHODS

### Database

Data were sourced from the Longitudinal Health Insurance Database 2000 (LHID2000), derived from medical claims records of the Taiwan National Health Insurance (NHI) program, and consisted of original medical claims and registration files for 1,000,000 enrollees in the program. According to Taiwan NHI administration law, every Taiwanese citizen with official residency or foreign national living in Taiwan with an Alien Resident Certificate, regardless of age, sex, or employment status, must enroll in the program. These 1,000,000 enrollees in LHID2000 were randomly selected from all enrollees listed in the 2000 Registry of Beneficiaries (N = 23.72 million) by the Taiwan National Health Institute. Many papers using the dataset derived from the Taiwan NHI program have been published in internationally peer-reviewed journals.<sup>14</sup> In addition, prior studies have reported high validity of data from the NHI program.<sup>15,16</sup>

### Selection of Cases and Controls

To select study data, 98,611 patients were identified, aged  $\geq 18$  years and who had received a first diagnosis of periodontitis (International Classification of Diseases, ninth edition, clinical modification [ICD-9-CM] code 523.4) in an ambulatory care visit (including outpatient departments of hospitals and clinics) from January 1, 2003 to December 31, 2012. According to previous studies,<sup>17,18</sup> a diagnosis of periodontitis was defined on the basis of the following procedures: 1) subgingival curettage, 2) periodontal flap operation, and 3) gingivectomy (excluding those with restorative or esthetic indications), as prescribed by the NHI system. Claim codes for these procedures were 91006C, 91007C, 91008C, 91009B, 91010B, 91011C, and 91012 under the NHI system. Only patients who had ever had subgingival curettage, periodontal flap operation, and/or gingivectomy were included. Ultimately, 71,182 patients (35,511 males and 36,671 females, aged 18 to 105 years; mean age 45.8 years) with periodontitis were included in this study. The year in which patients received their first diagnosis of periodontitis was defined as the index year, and the date of their first ambulatory care visit for receiving this diagnosis was defined as the index date for the patient group.

Controls for this study were retrieved from remaining enrollees of LHID2000. Patients who had a history of periodontitis since the beginning of the

NHI program in 1995 were excluded, and 71,182 controls (one control per patient) were randomly selected to match patients by: 1) sex; 2) age group (18 to 29, 30 to 39, 40 to 49, 50 to 59, and  $>59$  years); and 3) index year. For controls, index year was simply a matched year in which they needed medical care. First use of medical care occurring in the index year was defined as the index date for controls. This study was exempt from full review by Institutional Review Board (IRB) of the Taipei Medical University IRB since the LHID2000 consists of de-identified secondary data released to the public for research purposes.

### Exposure Assessment

Patients with AR were identified based on ICD-9-CM codes 477 or 477.0 to 477.9. In this study, to increase validity of AR diagnoses sourced from the administrative database, only patients who had received at least one AR diagnosis from a certified otolaryngologist were considered. In addition, patients with AR were included only if their first AR diagnosis was made before the index date.

### Statistical Analyses

Statistical analysis software<sup>#</sup> was used to perform all statistical analyses in this study;  $\chi^2$  tests were used to examine differences in sociodemographic characteristics of patients and controls. Furthermore, a generalized linear mixed model<sup>\*\*</sup> was used to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for previous AR diagnosis in patients and controls. In contrast to the generalized linear model, a generalized linear mixed model characterizes ability to model with random effects. Therefore, the latter was chosen to account for the random effect of geographic region. In regression models, selected comorbidities were taken into consideration, including: 1) DM; 2) hypertension; 3) coronary heart disease; 4) hyperlipidemia; 5) alcohol abuse; and 6) tobacco use disorder. Conventional  $P \leq 0.05$  was used to assess statistical significance.

## RESULTS

Mean ages with standard deviations (SDs) were  $45.8 \pm 15.9$  and  $45.8 \pm 16.6$  years for sampled patients and controls, respectively ( $P = 0.918$  between both groups). After matching for sex, age group, and index date, as Table 1 shows, there were significant differences for patients and controls (all  $P < 0.001$ ) with regard to: 1) geographic region; 2) monthly income; and 3) urbanization level. Compared with controls, patients had a higher prevalence of all selected comorbidities, including: 1) DM; 2) hypertension; 3)

<sup>#</sup> SAS system for Windows, SAS Institute, Cary, NC.

<sup>\*\*</sup> SAS PROC GLIMMIX model, SAS Institute.

**Table 1.****Demographic Characteristics of Patients With Periodontitis and Controls in Taiwan (N = 394,444)**

| Variable                   | No. Patients With Periodontitis<br>(n = 71,182) (%) | No. Controls<br>(n = 71,182) (%) | P Value |
|----------------------------|-----------------------------------------------------|----------------------------------|---------|
| Males                      | 34,511 (48.5)                                       | 34,511 (48.5)                    | >0.999  |
| Age, years (mean $\pm$ SD) | 45.8 $\pm$ 16.6                                     | 45.8 $\pm$ 15.9                  | 0.918   |
| DM                         | 9,289 (13.1)                                        | 7,304 (10.3)                     | <0.001  |
| Hypertension               | 18,634 (26.2)                                       | 17,335 (24.4)                    | <0.001  |
| Coronary heart disease     | 8,373 (11.8)                                        | 6,554 (9.2)                      | <0.001  |
| Hyperlipidemia             | 16,390 (23.0)                                       | 12,567 (17.7)                    | <0.001  |
| Alcohol abuse              | 64 (0.13)                                           | 92 (0.09)                        | 0.025   |
| Tobacco use disorder       | 1,585 (2.2)                                         | 1,178 (1.7)                      | <0.001  |
| Urbanization level         |                                                     |                                  | <0.001  |
| 1 (most urbanized)         | 21,311 (29.9)                                       | 26,206 (36.8)                    |         |
| 2                          | 19,864 (27.9)                                       | 20,531 (28.8)                    |         |
| 3                          | 11,555 (16.2)                                       | 10,666 (15.0)                    |         |
| 4                          | 9,827 (13.8)                                        | 8,000 (11.2)                     |         |
| 5 (least urbanized)        | 8,625 (12.1)                                        | 5,779 (8.1)                      |         |
| Monthly income             |                                                     |                                  | <0.001  |
| $\leq$ NT\$15,840          | 27,947 (39.3)                                       | 27,145 (38.1)                    |         |
| NT\$15,841 to \$25,000     | 25,060 (35.2)                                       | 22,199 (31.2)                    |         |
| $\geq$ NT\$25,001          | 18,175 (25.5)                                       | 21,838 (30.7)                    |         |
| Geographic region          |                                                     |                                  | <0.001  |
| Northern                   | 33,043 (46.4)                                       | 38,240 (53.7)                    |         |
| Central                    | 16,669 (23.4)                                       | 15,469 (21.7)                    |         |
| Southern                   | 19,921 (28.0)                                       | 16,237 (22.8)                    |         |
| Eastern                    | 1,549 (2.2)                                         | 1,236 (1.7)                      |         |

NT = New Taiwan. The average exchange rate in 2015 was US\$1.00 $\approx$ NT\$32. The average monthly income in 2015 was NT\$35,986.

**Table 2.****Prevalence and OR for Prior AR Among Sampled Patients**

| Variables                         | No. Sampled (n = 142,364) | No. Patients With Periodontitis<br>(n = 71,182) | No. Controls (n = 71,182) |
|-----------------------------------|---------------------------|-------------------------------------------------|---------------------------|
| Presence of prior AR, n (%)       | 37,400 (26.3)             | 20,201 (28.4)                                   | 17,199 (24.2)             |
| Crude OR (95% CI)*                | NA                        | 1.24 (1.22 to 1.27)                             | 1.00                      |
| Adjusted OR (95% CI) <sup>†</sup> | NA                        | 1.21 (1.18 to 1.23)                             | 1.00                      |

OR was calculated using a generalized linear mixed model. NA = not applicable.

\*  $P < 0.001$ .

<sup>†</sup> Adjustments were made for each patient's urbanization level, monthly income, and DM, hypertension, coronary heart disease, hyperlipidemia, alcohol abuse, and tobacco use disorder, accounting for random effect of geographic region.

Table 3.  
Sensitivity Analyses in Patients With Periodontitis

| Variables                   | Excluding Patients<br>With AR Diagnosis<br>Within 1 Year<br>(n = 69,754) | Controls<br>(n = 69,836) | Excluding Patients<br>With AR Diagnosis<br>Within 2 Years<br>(n = 68,568) | Controls<br>(n = 68,593) | Excluding Patients<br>With AR Diagnosis<br>Within 3 Years<br>(n = 67,626) | Controls<br>(n = 67,333) |
|-----------------------------|--------------------------------------------------------------------------|--------------------------|---------------------------------------------------------------------------|--------------------------|---------------------------------------------------------------------------|--------------------------|
| Presence of prior AR, n (%) | 18,773 (26.9)                                                            | 15,853 (22.7)            | 17,587 (25.7)                                                             | 14,610 (21.3)            | 16,645 (24.6)                                                             | 13,350 (19.8)            |
| OR (95% CI)*                | 1.25 (1.22 to 1.29)                                                      | 1.00                     | 1.28 (1.24 to 1.31)                                                       | 1.00                     | 1.32 (1.29 to 1.36)                                                       | 1.00                     |
| Adjusted OR (95% CI)†       | 1.22 (1.19 to 1.25)                                                      | 1.00                     | 1.24 (1.20 to 1.27)                                                       | 1.00                     | 1.28 (1.24 to 1.30)                                                       | 1.00                     |

OR was calculated using a generalized linear mixed model.

\*  $P < 0.001$ .

† Adjustments were made for each patient's urbanization level, monthly income, and DM, hypertension, coronary heart disease, hyperlipidemia, alcohol abuse, and tobacco use disorder, accounting for the random effect of geographic region.

coronary heart disease; 4) hyperlipidemia; 5) alcohol abuse; and 6) tobacco use disorder.

Table 2 presents prevalence of prior AR in patients and controls. Of 142,364 sampled patients, 37,400 (26.3%) received AR diagnosis before the index date. There was a significant difference in prevalence of previous AR in patients and controls (28.4% versus 24.2%;  $P < 0.001$ ). Table 2 also presents ORs and corresponding 95% CIs for previous AR diagnosis in patients and controls. The generalized linear mixed model suggested that OR of prior AR for patients was 1.24 (95% CI: 1.22 to 1.27;  $P < 0.001$ ) compared with controls. Adjustments were made for: 1) monthly income; 2) urbanization level; 3) DM; 4) hypertension; 5) coronary heart disease; 6) hyperlipidemia; 7) alcohol abuse; 8) tobacco use disorder; and 9) random effect of geographic region. After adjusting, OR of previous AR diagnosis among patients was 1.21 (95% CI: 1.18 to 1.23;  $P < 0.001$ ) compared with controls.

Sensitivity analysis of the relationship between periodontitis and prior AR is presented in Table 3. It consistently showed that periodontitis was significantly associated with previous AR diagnosis. After excluding patients diagnosed with AR within 1, 2, or 3 years before index date, respective adjusted ORs for previous AR diagnosis were 1.22, 1.24, and 1.28 for patients compared with controls.

Additionally, Table 4 shows that CP is consistently and significantly associated with prior AR, including patients who received only one, two, or three or more AR diagnoses before index date. Adjusted ORs were 1.22, 1.21, and 1.20 for patients with one, two, or three or more AR diagnoses before index date, respectively.

DISCUSSION

In this study, patients with previous AR diagnosis were associated with periodontitis. Risk factors for periodontitis have long been studied and are generally grouped into modifiable and non-modifiable factors. Non-modifiable risk factors include: 1) genetic factors; 2) improperly regulated immune responses to bacterial infections; 3) deficiencies of neutrophil functions; and 4) aging.<sup>5</sup> Because these factors appear to be difficult to manipulate, dentists more commonly focus on modifiable risk factors, such as: 1) smoking; 2) DM; 3) poor oral hygiene; and 4) psychologic stress. Little is known about possible relationships between nasal problems and periodontitis. Only one study by Keller et al.<sup>19</sup> reported that chronic rhinosinusitis increased risk of CP.

Although AR seems to be irrelevant to development of CP, there is some evidence that AR does affect adjacent structures through various mechanisms.<sup>12,13,20</sup> AR is believed to be a disease with complicated pathophysiology.<sup>21</sup> Patients with AR are

Table 4.

Associations Between Periodontitis and Prior AR, Including Patients With Periodontitis Who Received  $\geq 1$ ,  $\geq 2$ , or  $\geq 3$  AR Diagnoses

| Variables                   | Patients With $\geq 1$ AR Diagnosis | Controls      | Patients With $\geq 2$ AR Diagnoses | Controls      | Patients With $\geq 3$ AR Diagnoses | Controls     |
|-----------------------------|-------------------------------------|---------------|-------------------------------------|---------------|-------------------------------------|--------------|
| Presence of prior AR, n (%) | 20,201 (28.4)                       | 17,199 (24.2) | 13,508 (19.0)                       | 11,312 (15.9) | 10,092 (14.3)                       | 8,419 (11.8) |
| Crude OR (95% CI)*          | 1.24 (1.22 to 1.27)                 | 1.00          | 1.24 (1.21 to 1.27)                 | 1.00          | 1.23 (1.19 to 1.27)                 | 1.00         |
| Adjusted OR (95% CI)†       | 1.22 (1.19 to 1.25)                 | 1.00          | 1.21 (1.18 to 1.25)                 | 1.00          | 1.20 (1.17 to 1.24)                 | 1.00         |

OR was calculated by a generalized linear mixed model.

\*  $P < 0.001$ .

† Adjustments were made for each patient's urbanization level, monthly income, and DM, hypertension, coronary heart disease, hyperlipidemia, alcohol abuse, and tobacco use disorder, accounting for the random effect of geographic region.

at greater risk of suffering asthma, rhinosinusitis, and other related upper airway conditions.<sup>22</sup> A previous study demonstrated that patients with AR were more likely to develop nasopharyngeal carcinoma.<sup>23</sup> This evidence suggests that AR should no longer be regarded as a localized disease, but one that interacts with many other systems in the human body.<sup>24,25</sup>

One probable mechanism linking these two diseases is through the immune system. It was proposed that interleukin (IL)-12 plays a key role in AR.<sup>26</sup> Chen et al.<sup>27</sup> reported that imbalances of IL-12, IL-13, and IL-16 play crucial roles in regulating the onset and development of AR. Many studies showed abnormally increased levels of cytokines in patients with AR.<sup>28-34</sup> These elevated levels possibly contribute to development of periodontal diseases. Tsai et al.<sup>35</sup> reported that IL-12 and IL-16 may be related to pathogenesis of periodontal disease.

Much research has proved that concentration of nitric oxide (NO) appears to be high in the nasal airway and paranasal sinuses and increases in airway inflammatory conditions, such as asthma and AR.<sup>36-39</sup> Expression of inducible NO synthase in nasal epithelial cells in patients with AR was also reported,<sup>40</sup> although whole-blood nitrite concentration in patients with periodontal disease was found to be higher than that of healthy individuals.<sup>29</sup> Using an experimental model, researchers showed that applying NO synthase inhibitors was effective in inhibiting inflammatory bone resorption in rats with periodontitis.<sup>30</sup> Strong evidence in these findings of high levels of NO in patients with allergies indirectly suggests a relationship between AR and development of CP.<sup>41,42</sup>

Another possible mechanism is related to breathing through the mouth. Its influence on periodontal tissues was proposed decades ago.<sup>43</sup> More recently, it was shown that obstructive sleep apnea is associated with development of periodontitis.<sup>44,45</sup> Although patients with AR might not necessarily present with symptoms of nasal obstruction, these common symptoms possibly play a role.

There are limitations to the present study. First, like much research using health insurance database analyses, there is the possibility of surveillance bias. Patients with AR were more likely to have visited outpatient clinics, which may have led to early detection of periodontitis because of increased exposure to medical services. Considering this, patients with periodontitis who received an AR diagnosis within 1 or 2 years before index date were excluded, and results remained statistically significant. The number of patients resulting from surveillance bias was likely to have been greatly reduced by this method.

Second, treatment information for patients with AR was unknown in this study, making it difficult to

evaluate how these patients were managed. Therefore, some patients who were adequately treated for AR may still have been included in the AR group. This could have affected accuracy of data interpretation, although this potential bias would have had little effect on conclusions drawn. If many patients treated well for AR were included in the AR group, theoretically the result would be affected toward the null hypothesis. As results of this study reached statistical significance, this limitation is assumed to be fairly acceptable.

Finally, it is difficult to determine how long a patient was affected by AR and then subsequently developed periodontitis. The present study may have universally included all patients with relatively long and short intervals between diagnoses of AR and periodontitis. Therefore, it is difficult to determine cause-effect relationships due to variable exposure periods.

This study also reveals some evidence supporting the association between AR and periodontitis. There is already evidence supporting periodontitis as a possible focal source of extra-oral infections of structures adjacent to the mouth.<sup>46,47</sup> Periodontal infections are reported to be associated with cardiovascular disease, adverse pregnancy outcomes, and head and neck cancer.<sup>48</sup> It seems that inflammation or infections in different subsites of the head and neck region tend to affect adjacent structures. However, much remains to be studied.

## CONCLUSIONS

Despite study limitations, AR is associated with periodontitis. Because this is only an observational study, readers are made aware of results of a study by Friedrich et al.<sup>49</sup> that is especially noteworthy because of the conclusion that there was an inverse association between periodontitis and respiratory allergies. It is clear that more studies are needed to reveal the true relationship between these two diseases.

## ACKNOWLEDGMENTS

No funding was received. Authors S-H Hung, M-C Tsai, and H-C Lin contributed equally to this study. The authors report no conflicts of interest related to this study.

## REFERENCES

1. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol* 1999;4:1-6.
2. Loesche WJ, Grossman NS. Periodontal disease as a specific, albeit chronic, infection: Diagnosis and treatment. *Clin Microbiol Rev* 2001;14:727-752.
3. Burt B, Research, Science and Therapy Committee of the American Academy of Periodontology. Position paper: Epidemiology of periodontal diseases. *J Periodontol* 2005;76:1406-1419.
4. Otomo-Corgel J, Pucher JJ, Rethman MP, Reynolds MA. State of the science: Chronic periodontitis and systemic health. *J Evid Based Dent Pract* 2012;12 (Suppl. 3):20-28.
5. Van Dyke TE, Sheilesh D. Risk factors for periodontitis. *J Int Acad Periodontol* 2005;7:3-7.
6. Skoner DP. Allergic rhinitis: Definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001;108(Suppl. 1):S2-S8.
7. Wallace DV, Dykewicz MS, Bernstein DI, et al; Joint Task Force on Practice; American Academy of Allergy; Asthma & Immunology; American College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol* 2008;122(Suppl. 2):S1-S84.
8. Wu WF, Wan KS, Wang SJ, Yang W, Liu WL. Prevalence, severity, and time trends of allergic conditions in 6-to-7-year-old schoolchildren in Taipei. *J Investig Allergol Clin Immunol* 2011;21:556-562.
9. Hwang C-Y, Chen Y-J, Lin M-W, et al. Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: A national study 2000 to 2007. *Acta Derm Venereol* 2010;90:589-594.
10. Chung SD, Lin HC, Hung SH. Allergic rhinitis is associated with open-angle glaucoma: A population-based case-control study. *Am J Rhinol Allergy* 2014;28:e148-e151.
11. Chung SD, Wu CS, Lin HC, Hung SH. Association between allergic rhinitis and nasopharyngeal carcinoma: A population-based study. *Laryngoscope* 2014;124:1744-1749.
12. Balyeat RM, Bowen R. Facial and dental deformities due to perennial nasal allergy in childhood. *Int J Orthodont Dent Child* 1934;20:445-460.
13. Tomonaga K, Kurono Y, Mogi G. The role of nasal allergy in otitis media with effusion. A clinical study. *Acta Otolaryngol Suppl* 1988;458:41-47.
14. Chen Y-C, Yeh H-Y, Wu J-C, Haschler I, Chen T-J, Wetter T. Taiwan's National Health Insurance Research Database: Administrative health care database as study object in bibliometrics. *Scientometrics* 2011;86:365-380.
15. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf* 2011;20:236-242.
16. Kang JH, Chen YH, Lin HC. Comorbidity profiles among patients with ankylosing spondylitis: A nationwide population-based study. *Ann Rheum Dis* 2010;69:1165-1168.
17. Chou S-H, Tung Y-C, Lin Y-S, et al. Major adverse cardiovascular events in treated periodontitis: A population-based follow-up study from Taiwan. *PLoS One* 2015;10:e0130807.
18. Lin T-H, Lung C-C, Su H-P, et al. Association between periodontal disease and osteoporosis by gender: A nationwide population-based cohort study. *Medicine (Baltimore)* 2015;94:e553.
19. Keller JJ, Wu CS, Lin HC. Chronic rhinosinusitis increased the risk of chronic periodontitis: A population-based matched-cohort study. *Laryngoscope* 2013;123:1323-1327.
20. Trask GM, Shapiro GG, Shapiro PA. The effects of perennial allergic rhinitis on dental and skeletal development: A comparison of sibling pairs. *Am J Orthod Dentofacial Orthop* 1987;92:286-293.

21. Osguthorpe JD. Pathophysiology of and potential new therapies for allergic rhinitis. *Int Forum Allergy Rhinol* 2013;3:384-392.
22. Hadley JA, Derebery MJ, Marple BF. Comorbidities and allergic rhinitis: Not just a runny nose. *J Fam Pract* 2012;61(Suppl.)S11-S15.
23. Chung S-D, Wu C-S, Lin H-C, Hung S-H. Association between allergic rhinitis and nasopharyngeal carcinoma: A population-based study. *Laryngoscope* 2013;124:1744-1749.
24. Spector SL. Overview of comorbid associations of allergic rhinitis. *J Allergy Clin Immunol* 1997;99:S773-S780.
25. Lack G. Pediatric allergic rhinitis and comorbid disorders. *J Allergy Clin Immunol* 2001;108(Suppl.)S9-S15.
26. Wei P, Kou W, Sun R, et al. Association study between interleukin-12 receptor beta1/beta2 genes and allergic rhinitis in the Chinese Han population. *Eur Arch Otorhinolaryngol* 2015;272:889-893.
27. Chen J, Kong W, Zhou Y, et al. The expression of serum IL-10,12,13,16 in patients with allergic rhinitis and vasomotor rhinitis (in Chinese). *J Clin Otorhinolaryngol Head Neck Surg* 2007;21:913-915.
28. Afifi SS, ElArab AE, Mostafa SY. Interleukin 16 (IL-16) in asthma and allergic rhinitis. A comparison between upper and lower airways. *Egypt J Immunol* 2004;11:31-36.
29. Karaki M, Dobashi H, Kobayashi R, Tokuda M, Ishida T, Mori N. Expression of interleukin-16 in allergic rhinitis. *Int Arch Allergy Immunol* 2005;138:67-72.
30. Pullerits T, Lindén A, Malmhäll C, Lötvall J. Effect of seasonal allergen exposure on mucosal IL-16 and CD4+ cells in patients with allergic rhinitis. *Allergy* 2001;56:871-877.
31. Wright ED, Christodoulouopoulos P, Frenkiel S, Hamid Q. Expression of interleukin (IL)-12 (p40) and IL-12 (beta 2) receptors in allergic rhinitis and chronic sinusitis. *Clin Exp Allergy* 1999;29:1320-1325.
32. Pawankar R, Okuda M, Yssel H, Okumura K, Ra C. Nasal mast cells in perennial allergic rhinitis exhibit increased expression of the Fc epsilonRI, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest* 1997;99:1492-1499.
33. Verhaeghe B, Gevaert P, Holtappels G, et al. Up-regulation of IL-18 in allergic rhinitis. *Allergy* 2002;57:825-830.
34. Laberge S, Durham SR, Ghaffar O, et al. Expression of IL-16 in allergen-induced late-phase nasal responses and relation to topical glucocorticosteroid treatment. *J Allergy Clin Immunol* 1997;100:569-574.
35. Tsai IS, Tsai CC, Ho YP, Ho KY, Wu YM, Hung CC. Interleukin-12 and interleukin-16 in periodontal disease. *Cytokine* 2005;31:34-40.
36. Djupesland PG, Chatkin JM, Qian W, Haight JS. Nitric oxide in the nose and paranasal sinuses – respiratory tract physiology in a new perspective (in Norwegian). *Tidsskr Nor Laegeforen* 1999;119:4070-4072.
37. Kharitonov SA, Rajakulasingam K, O'Connor B, Durham SR, Barnes PJ. Nasal nitric oxide is increased in patients with asthma and allergic rhinitis and may be modulated by nasal glucocorticoids. *J Allergy Clin Immunol* 1997;99:58-64.
38. Arnal JF, Didier A, Rami J, et al. Nasal nitric oxide is increased in allergic rhinitis. *Clin Exp Allergy* 1997;27:358-362.
39. Unal M. Nitric oxide in allergic rhinitis. *Antiinflamm Antiallergy Agents Med Chem* 2008;7:1-3.
40. Kawamoto H, Takeno S, Yajin K. Increased expression of inducible nitric oxide synthase in nasal epithelial cells in patients with allergic rhinitis. *Laryngoscope* 1999;109:2015-2020.
41. Hiramoto K, Kobayashi H, Orita K, Sato EF, Ishii M. Inducible nitric oxide synthase plays important roles in allergic reactions of pollinosis in mice sensitized with pollen allergy. *J Clin Biochem Nutr* 2013;52:17-21.
42. Garrelds IM, van Amsterdam JG, de Graaf-in't Veld C, Gerth van Wijk R, Zijlstra FJ. Nitric oxide metabolites in nasal lavage fluid of patients with house dust mite allergy. *Thorax* 1995;50:275-279.
43. Fukuda T, Yokomichi K, Kato H, Ishikawa J. Studies on the influence of mouth breathing to the periodontal tissue. The effect of oral screen and lip-seal tape on the gingiva in mouth breathers (in Japanese). *Nippon Shishubyo Gakkai Kaishi* 1975;17:280-288.
44. Ahmad NE, Sanders AE, Sheats R, Brame JL, Essick GK. Obstructive sleep apnea in association with periodontitis: A case-control study. *J Dent Hyg* 2013;87:188-199.
45. Sanders AE, Essick GK, Beck JD, et al. Periodontitis and sleep disordered breathing in the Hispanic community health study/study of Latinos. *Sleep* 2015;38:1195-1203.
46. Han YW, Wang X. Mobile microbiome: Oral bacteria in extra-oral infections and inflammation. *J Dent Res* 2013;92:485-491.
47. Gendron R, Grenier D, Maheu-Robert L. The oral cavity as a reservoir of bacterial pathogens for focal infections. *Microbes Infect* 2000;2:897-906.
48. Han YW, Houcken W, Loos BG, Schenkein HA, Tezal M. Periodontal disease, atherosclerosis, adverse pregnancy outcomes, and head-and-neck cancer. *Adv Dent Res* 2014;26:47-55.
49. Friedrich N, Volzke H, Schwahn C, et al. Inverse association between periodontitis and respiratory allergies. *Clin Exp Allergy* 2006;36:495-502.

Correspondence: Dr. Shiu-Dong Chung, Department of Surgery, Far Eastern Memorial Hospital, No. 21, Sec. 2, Nanya S. Rd., Banciao Dist., New Taipei City 220, Taiwan. E-mail: chungshiodong@gmail.com.

Submitted September 6, 2015; accepted for publication January 27, 2016.