Periodontitis and the subsequent risk of glaucoma: results from the real-world practice

Kuo-Ting Sun¹,²,¹⁰, Te-Chun Shen³,⁴,¹⁰, Shih-Chueh Chen⁵, Chia-Ling Chang⁴,⁶, Ching-Hao Li⁷, Xin Li⁷, Kalaiselvi Palanisamy⁷, Ning-Yi Hsia⁸,²², Wen-Shin Chang⁸, Chia-Wen Tsai⁹, Da-Tian Bau⁷,⁹ & Chi-Yuan Li⁷

Periodontitis is a multifactorial inflammatory disease that can cause tooth loss and contribute to systemic inflammation. It is suggested that periodontitis may be associated with the development of glaucoma. Based on data from Taiwan’s National Health Insurance Research Database, a retrospective cohort study was conducted to investigate the risk of developing glaucoma in patients with periodontitis. The periodontitis cohort consisted of newly diagnosed adult patients ($n = 194,090$, minimum age = 20 years) between 2000 and 2012. The comparison group included age-, gender-, and diagnosis date-matched people without periodontitis ($n = 194,090$, minimum age = 20 years). Incident glaucoma was monitored until the end of 2013. Hazard ratios (HRs) with confidence intervals (CIs) were established based on the Cox proportional hazard models. The risk of developing glaucoma was higher in patients with periodontitis than those without periodontitis (31.2 vs. 23.3 patients per 10,000 person-years, with an adjusted HR of 1.26 [95% CI 1.21–1.32]). A high risk was evident even after stratifying by age (adjusted HRs = 1.34 [1.26–1.44] for ages 20–49, 1.24 [1.13–1.36] for ages ≥ 65, and 1.20 [1.12–1.29] for ages 50–64 years), sex (adjusted HRs = 1.33 [1.24–1.41] and 1.21 [1.14–1.28] for men and women, respectively), presence of comorbidity (adjusted HRs = 1.38 [1.29–1.47] and 1.18 [1.12–1.25] for without and with comorbidity, respectively), and corticosteroid use (adjusted HRs = 1.27 [1.21–1.33] and 1.21 [1.08–1.35] for without and with corticosteroid use, respectively). Specifically, patients with periodontitis exhibited a significantly high risk of primary open-angle glaucoma (adjusted HR = 1.31 [1.21–1.32]) but not for primary closed-angle glaucoma (adjusted HR = 1.05 [0.94–1.17]). People with periodontitis are at a greater risk of glaucoma than individuals without periodontitis. Ocular health should be emphasized for such patients, and the underlying mechanisms need further investigation.

Periodontitis is a common disease worldwide that features inflammation of the gums and supporting tooth structures¹². Periodontal health is important for maintaining an adequate quality of life, and poor periodontal conditions can lead to pain, tooth loss, and malnutrition⁴. In addition, periodontal plaque can induce local and even systemic inflammation⁴. Association was reported between periodontitis and various systemic diseases, including atherosclerosis⁵, diabetes mellitus⁶, metabolic syndrome⁷, osteoporosis⁸, rheumatoid arthritis⁹, and respiratory diseases¹⁰. In addition, periodontitis can affect the development of ocular diseases¹¹,¹². Belonging to a group of progressive optic neuropathies, glaucoma represents a disease featuring degenerative changes in both retinal ganglion cells and optic nerve, mostly due to high intraocular pressure (IOP)¹³. Primary open-angle glaucoma (POAG) is the most common glaucoma type, accounting for approximately 80% of all cases, followed by primary closed-angle glaucoma (PCAG)¹⁴. The results of population-based studies suggest that glaucoma is the leading cause of blindness globally, with an estimated 60 million people worldwide having visual

¹School of Dentistry, China Medical University, Taichung, Taiwan. ²Department of Pediatric Dentistry, China Medical University Hospital, Taichung, Taiwan. ³Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan. ⁴School of Medicine, China Medical University, Taichung, Taiwan. ⁵Department of Endocrinology, Cheng Ching Hospital, Taichung, Taiwan. ⁶Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan. ⁷Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan. ⁸Department of Ophthalmology, China Medical University Hospital, No. 2 Yude Road, Taichung 404, Taiwan. ⁹Terry Fox Cancer Research Laboratory, Department of Medical Research, China Medical University Hospital, Taichung, Taiwan. ¹⁰These authors contributed equally: Kuo-Ting Sun and Te-Chun Shen. ¹¹email: deepwhite1111@hotmail.com
impairment due to glaucoma. Although its etiology is still not sufficiently understood, there are numerous risk factors, from genetic to environmental factors, such as family history, race, age, high IOP, lifestyle, sleep quality, diet, exercise, corticosteroid use, and inflammation.

There has been limited interest in the relationship between periodontitis and glaucoma. In fact, periodontitis increased the systemic inflammatory reaction, and glaucoma, as a neurodegenerative disease, could be exacerbated by the result of the chronic systemic inflammation. In a case–control study including 119 POAG cases and 78 controls, Polla et al. reported that patients with POAG have fewer natural teeth and higher number of oral bacteria (Streptococci) than those without POAG. Pasquale et al. conducted a prospective study (40,536 men) showing a lack of association between POAG and tooth number, periodontal disease, or root canal treatment. However, they reported that within the past 2 years, both losing teeth and having a prevalent periodontal disease diagnosis were associated with a 1.85-fold increased risk of POAG. The results of previous studies were inconsistent and showed some limitations, such as relatively low sample size and inclusion of only men. Therefore, we conducted a retrospective population-based cohort study based on Taiwan’s National Health Insurance Research Database (NHIRD) to clarify the potential association of periodontitis and development of glaucoma and its subtypes, POAG and PCAG.

Materials and methods

Data source. The National Health Insurance (NHI) program was established in 1995 in Taiwan and contains information on more than 99.9% of residents to date. The NHIRD is managed and updated by the National Health Research Institutes. For this study, we selected a subset of NHIRD marked as the Longitudinal Health Insurance Database 2000 (LHID2000). This database includes medical claim information of 1,000,000 people randomly selected in 2000 and data on demographic status, diagnostic codes, and medication and procedure claims between 1995 and 2013. This study was conducted with permission from the ethics committee (Research Ethics Committee of the China Medical University and Hospital [CMUH-104-REC2-115]). All methods were performed following the Strengthening the Reporting of Observational Studies in Epidemiology guideline. Informed consent was unnecessary for the de-identified data and waived by the Research Ethics Committee of the China Medical University and Hospital.

Study population. Adult patients in whom periodontitis (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes 523.3 and 523.4) was first diagnosed (index date) between 2000 and 2012 were chosen for the periodontitis cohort (n = 194,090, minimum age = 20 years). We excluded those with age < 20 years, incomplete age and sex information, as well as those diagnosed with glaucoma before the index date. The comparison group included people without periodontitis, and these individuals were age-, gender-, and index year-matched with the periodontitis cohort (n = 194,090, minimum age = 20 years). This group also included only individuals with complete information, similar to the periodontitis cohort. All participants (n = 388,180) were monitored until the first record of any of the following: development of glaucoma, withdrawal from the NHI program, death, or the end of 2013 (Fig. 1).

Study outcome and comorbidities. The occurrence of glaucoma (ICD-9-CM code 365) was the primary outcome. We further identified two documented subtypes of glaucoma: POAG (with ICD-9-CM code 365.1) and PCAG (with ICD-9-CM code 365.2). In addition, we collected several comorbidities related to glaucoma and the most related medication, corticosteroid, as potential confounders. Detailed comorbidities assessed included the presence of cardiometabolic diseases, such as hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250) and hyperlipidemia (ICD-9-CM code 272), migraine (ICD-9-CM code 346), asthma/chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 493 and 496), chronic liver disease and cirrhosis (CLD; ICD-9-CM code 571), chronic kidney disease (CKD; ICD-9-CM code 585), and rheumatic diseases (ICD-9-CM codes 446.5, 710.0–710.4, 714.0–714.2, 714.8, and 725).

Statistical analysis. Chi-square test and t-test were used to compare the distribution of baseline characteristics between the groups (periodontitis vs. nonperiodontitis) for categorical and continuous variables, respectively. To evaluate the cumulative incidence of glaucoma in both groups, we created the Kaplan–Meier curves followed by testing inter-group differences with a log-rank test. Cox proportional hazard models were used to estimate the hazard ratios (HRs) along with 95% confidence intervals (CIs). The multivariate Cox model was applied to estimate the adjusted HRs (aHRs) after controlling for age, sex, comorbidities, and corticosteroid use, which were significant in the univariate model. For further data analysis, we assessed the effects of periodontitis on the risk of POAG and PCAG. Similar analyses were performed using univariate and multivariate Cox proportional hazard models. All the analyses were performed using STATA statistical software (StataCorp. 2015, R 14, StataCorp LP). Statistical significance was determined using a two-tailed test, and p-values were considered significant if lower than 0.05.

Results

We recruited the periodontitis and comparison cohorts consisting of 194,090 adult persons each (Table 1). The distributions of age and gender were similar between the periodontitis and comparison groups. The periodontitis cohort had an average age of 42.5 ± 15.1 years. In both cohorts, 51.0% of the individuals were women. Compared with individuals without periodontitis, patients with periodontitis had a significantly higher prevalence of hypertension, CLD, hyperlipidemia, diabetes mellitus, asthma/COPD, migraine, rheumatic diseases, and corticosteroid use (p < 0.05).
A retrospective cohort study sampled from the Longitudinal Health Insurance Database 2000 (N=1,000,000)

Newly diagnosed periodontitis during 2000–2012 (N=244,606)

Exclusion:
- Age <20 (N=42,567)
- Loss of demographic data (N=0)
- Previous glaucoma (N=4,002)

Non-periodontitis throughout the database (N=755,394)

Exclusion:
- Age <20
- Loss of demographic data
- Previous glaucoma

Periodontitis patients (N=198,037)

1:1 matched for age, sex, and diagnosed year (cannot match N = 3,947)

Comparison persons (N=194,090)

Periodontitis cohort (N=194,090) Follow-up to the end of 2013
Mean follow-up 8.05 years
Follow-up 1,562,893 person-years
4,875 glaucoma events identified

Comparison cohort (N=194,090) Follow-up to the end of 2013
Mean follow-up 7.78 years
Follow-up 1,510,223 person-years
3,516 glaucoma events identified

Figure 1. Flow chart showing subject selection, follow-up time, and identified events.

| Periodontitis | No | Yes | p-value* |
|---------------|----|-----|----------|
| N = 194,090  |    |     |          |
| n % | n % |        |
| Age (years) |    |     |          |
| 20–49 | 135,730  | 69.9 | 135,730  | 69.9 |
| 50–64 | 40,420   | 20.8 | 40,420   | 20.8 |
| ≥65   | 17,940   | 9.24 | 17,940   | 9.24 |
| Mean ± SD | 42.5 ± 15.1 | 42.5 ± 15.1 |
| Gender |    |     |          |
| Women | 98,942   | 51.0 | 98,942   | 51.0 |
| Men   | 95,148   | 49.0 | 95,148   | 49.0 |
| Comorbidity |    |     |          |
| Hypertension | 30,742  | 15.8 | 33,608   | 17.3 | <0.0001 |
| Diabetes mellitus | 14,512  | 7.48 | 16,817   | 8.66 | <0.0001 |
| Hyperlipidemia | 20,977  | 10.8 | 27,229   | 14.0 | <0.0001 |
| Migraine | 5048   | 2.60 | 6262     | 3.23 | <0.0001 |
| Asthma/COPD | 13,027  | 6.71 | 14,979   | 7.72 | <0.0001 |
| CLD   | 23,616   | 12.2 | 30,246   | 15.6 | <0.0001 |
| CKD   | 1798    | 0.93 | 1798     | 0.93 | 0.39 |
| Rheumatic diseases | 3487   | 1.80 | 4749     | 2.45 | <0.0001 |
| Medication |    |     |          |
| Corticosteroid use | 16,661  | 8.58 | 20,761   | 10.7 | <0.0001 |

Table 1. Baseline characteristics of the periodontitis cohort and control group of patients. COPD chronic obstructive pulmonary disease, CLD chronic liver disease and cirrhosis, CKD chronic kidney disease, SD standard deviation. *Chi-squared test and t-test.
As shown in Table 2, the overall incidence rates of glaucoma in the periodontitis and comparison groups were 31.2 and 23.3 (per 10,000 person-years), respectively. Compared with that in the comparison group, the aHR for glaucoma in the periodontitis cohort was 1.26 (95% CI 1.21–1.32) after controlling for the effects of age, sex, comorbidities, and corticosteroid use. Higher age was associated with a higher risk of glaucoma, with aHRs of 2.65 (95% CI 2.51–2.80) and 3.43 (95% CI 3.21–3.67) for patients aged 50–64 and over 65 years, respectively, compared with those aged between 20 and 49 years. The patients with diabetes showed a higher risk of glaucoma (aHR = 1.60, 95% CI 1.50–1.70) than those without diabetes. The risk of glaucoma was also increased in patients with hyperlipidemia (aHR = 1.27, 95% CI 1.20–1.35), hypertension (aHR = 1.26, 95% CI 1.19–1.33), corticosteroid use (aHR = 1.26, 95% CI 1.18–1.35), CKD (aHR = 1.19, 95% CI 1.02–1.39), rheumatic diseases (aHR = 1.17, 95% CI 1.04–1.31), and CLD (aHR = 1.12, 95% CI 1.06–1.19) than in individuals without these comorbidities or medication.

Table 2. Analysis of risk factors for development of glaucoma. CI confidence interval, CKD chronic kidney disease, CLD chronic liver disease and cirrhosis, COPD chronic obstructive pulmonary disease, HR hazard ratio, PY person-years. # Incidence rate per 10,000 person-years; † Multivariable analysis including age, gender, comorbidities, and corticosteroid use; * p < 0.05, **p < 0.001.
in women and men, respectively, in the periodontitis cohort compared with that in the comparison group. The aHRs for glaucoma were 1.38 (95% CI 1.29–1.47) and 1.18 (95% CI 1.12–1.25) in individuals without and with any comorbidity in the periodontitis cohort compared with that in the comparison group, respectively. Lastly, the aHRs for glaucoma were 1.27 (95% CI 1.16–1.40) and 1.21 (95% CI 1.13–1.36) in individuals without and with corticosteroid use in the periodontitis cohort compared with that in the comparison group, respectively.

We further identified the documented POAG (ICD-9-CM 365.1, n = 1219) and PCAG (ICD-9 CM 365.2, n = 1264) cases in overall glaucoma cases (n = 8391; Table 4). Compared with individuals without periodontitis, patients with periodontitis had a significant relationship with POAG (aHR = 1.31, 95% CI 1.17–1.47) but not with PCAG (aHR = 1.05, 95% CI 0.94–1.17). Cumulative incidences of glaucoma in individuals with and without periodontitis are illustrated in Fig. 2. The log-rank test showed that the patients with periodontitis demonstrated a significantly increased cumulative incidence of glaucoma compared with the comparison group (p < 0.0001).

Table 3. Incidences and hazard ratios of glaucoma for individuals with and without periodontitis stratified by age, gender, comorbidity, and corticosteroid use. PY person-years, HR hazard ratio, CI confidence interval.

| Periodontitis | Crude HR (95% CI) | Adjusted HR† (95% CI) |
|---------------|-------------------|-----------------------|
| No | Yes |
| Age | Event PY Rate # | Event PY Rate # | |
| 20–49 | 1400 | 1,100,619 | 12.7 | 2026 | 1,129,321 | 17.9 | 1.41 (1.31–1.51)*** | 1.34 (1.26–1.44)*** |
| 50–64 | 1336 | 295,198 | 45.3 | 1746 | 305,648 | 57.1 | 1.26 (1.17–1.35)*** | 1.20 (1.12–1.29)*** |
| ≥ 65 | 780 | 114,406 | 68.2 | 1103 | 127,925 | 86.2 | 1.27 (1.16–1.40)*** | 1.24 (1.13–1.36)*** |
| Gender | | | |
| Women | 1920 | 776,981 | 24.7 | 2483 | 797,717 | 31.1 | 1.26 (1.19–1.34)*** | 1.21 (1.14–1.28)*** |
| Men | 1596 | 733,242 | 21.8 | 2392 | 765,177 | 31.3 | 1.43 (1.35–1.53)*** | 1.33 (1.24–1.41)*** |
| Comorbidity‡ | | | |
| No | 1584 | 1,082,235 | 14.6 | 2021 | 1,026,924 | 19.7 | 1.34 (1.25–1.43)*** | 1.38 (1.29–1.47)*** |
| Yes | 1932 | 427,988 | 45.1 | 2854 | 535,970 | 53.3 | 1.32 (1.26–1.39)*** | 1.27 (1.21–1.33)*** |
| Corticosteroid | | | |
| No | 3033 | 1,414,281 | 21.5 | 4073 | 1,432,931 | 28.4 | 1.32 (1.26–1.39)*** | 1.22 (1.09–1.37)*** |
| Yes | 483 | 95,942 | 50.3 | 802 | 129,963 | 61.7 | 1.22 (1.09–1.37)*** | 1.21 (1.08–1.35)*** |

Table 4. Incidences and hazard ratios of documented POAG and PCAG for individuals with and without periodontitis. HR hazard ratio, CI confidence interval, ICD-9-CM international classification of diseases, 9th revision, clinical modification, PCAG primary closed-angle glaucoma, POAG primary open-angle glaucoma.

| Periodontitis | Event Rate # | Crude HR (95% CI) | Adjusted HR† (95% CI) |
|---------------|--------------|-------------------|-----------------------|
| Overall glaucoma | n = 8391 | | |
| Event | 3516 | 4875 | 23.3 | 31.2 |
| Crude HR (95% CI) | Reference | 1.34 (1.28–1.40)*** |
| Adjusted HR (95% CI)† | Reference | 1.26 (1.21–1.32)*** |
| Confirmed POAG (ICD-9-CM 365.1) | n = 1219 | | |
| Event | 499 | 720 | 3.30 | 4.61 |
| Crude HR (95% CI) | Reference | 1.39 (1.24–1.56)*** |
| Adjusted HR (95% CI)† | Reference | 1.31 (1.17–1.47)*** |
| Confirmed PCAG (ICD-9-CM 365.2) | n = 1264 | | |
| Event | 587 | 677 | 3.89 | 4.33 |
| Crude HR (95% CI) | Reference | 1.11 (1.00–1.24) |
| Adjusted HR (95% CI)† | Reference | 1.05 (0.94–1.17) |

† Multivariable analysis including age, gender, comorbidities, and corticosteroid use. ** p < 0.01, ***p < 0.001.
Discussion
This retrospective population-based cohort study analyzed the occurrence of glaucoma in individuals with periodontitis and in a comparison group of individuals without periodontitis. Results showed that compared with people without periodontitis, the presence of periodontitis is associated with a significant risk of glaucoma, although the reduction is in the magnitude of the risk after adjustment. As expected, the risk of glaucoma increased in older people, those with comorbidity, and those with corticosteroid use. Furthermore, glaucoma was more likely in the periodontitis group than in the comparison group even after stratification by age, sex, presence of comorbidity, or corticosteroid use. Moreover, patients with periodontitis had more association with POAG than PCAG.

It is important to note that the incidence of glaucoma increased with age in both the periodontitis and comparison cohorts. However, the crude and adjusted periodontitis to nonperiodontitis HRs were higher in the youngest age group. Similarly, the incidence of glaucoma increased with the presence of comorbidity and with corticosteroid use in both the periodontitis and comparison cohorts. However, the crude and adjusted periodontitis to nonperiodontitis HRs were higher in the noncomorbidity and noncorticosteroid use groups (Table 3). This phenomenon reflects that periodontitis alone is associated with glaucoma risk. However, age, comorbidity, and corticosteroid use could further modify the relationship (having more impact on the nonperiodontitis group than the periodontitis group).

The mechanisms between periodontitis and glaucoma remain uncertain, but several hypotheses have been suggested. First, oral microbiome from periodontitis can cause immune responses and exacerbate glaucomatous neurodegeneration. Astafurov et al.24 reported that patients with glaucoma had higher bacterial loads in the oral cavity compared with people without glaucoma. In an animal model, they also found that the administration of lipopolysaccharide in mice could enhance the development of glaucoma via the upregulation of the complement system and toll-like receptor 4-signaling activity along with microglial activation in the optic nerve24. Second, endothelial cell dysfunction can be involved in the pathophysiology of glaucoma25. Periodontitis could induce chronic subclinical systemic inflammation leading to endothelial cell dysfunction. Endothelial dysfunction can lead to impaired flow-mediated vasodilation that causes poor perfusion of the optic nerve, which contributes to glaucoma development26. In addition, bacterial products can directly be linked to neurodegeneration. Neurotoxicity from some pathogenic species could be mediated by nitric oxide production through effects on microglia and astrocytes27. The localization of bacteria in these structures may not be necessary, and the bacterial products can initiate a local inflammatory response that leads to glaucomatous neurodegeneration27.

POAG is less common than PAOG; however, it is more prevalent in Asian countries28. PCAG is more common in older people and women, as well as in individuals with shallow anterior chamber or short axial length (hypermetropic eye) that is based on the pupillary block together with the anterior movement of the lens29. In addition, Chen and Lin23 reported that patients with PCAG are associated with comorbid cataracts and certain systemic or distant diseases (headaches, peptic ulcer, hyperlipidemia, and liver diseases). However, compared with POAG, PCAG is less associated with systemic diseases29. Our findings are in accordance with the above concept, that is, we found that patients with periodontitis had more association with POAG than PCAG. Incident PCAG was higher in the periodontitis group than in the comparison group, but the statistical significance was not reached in our analysis. Because the confirmed subtype (PAOG and PCOG) was only 30% of the total glaucoma events in the study, the real number of PAOG and PCOG was much underestimated. Therefore, the precise association between periodontitis and glaucoma subtype needs further investigation.

The present study's strength primarily stems from population-based data to enroll sufficient periodontitis (n = 194,040) and nonperiodontitis (n = 194,040) cases to evaluate glaucoma development. Taiwan's NHIRD is a large database with nationwide coverage, and no difference was found in the demographic distribution between LHID2000 and the original NHIRD. In addition, the universal coverage (> 99.9%) in the insurance program ensures that all citizens can have no access barriers to health care, irrespective of socioeconomic factors30. The
NHIRD allowed us to reflect a “real-world” scenario in which periodontitis, glaucoma, and other comorbidities were diagnosed directly during medical consultation\(^1\)\(^\text{(2015)}\). However, our study had some limitations. First, diagnoses were based on ICD format (for periodontitis, glaucoma, and comorbidities), which is strongly dependent on the performance of physicians. The definition of cases and events may be inconsistent. Audits were regularly performed to ensure that negligence and misdiagnoses were kept to a minimum. Another limitation is that the NHRI research center did not collect all comprehensive data that may be confounding factors (e.g., smoking and alcohol consumption habits, physical activity and diet style, occupation, body mass index, family history, and environmental exposure). Moreover, the database did not contain some important clinical variables (e.g., dental and ocular findings, laboratory data such as inflammatory markers, culture results, and pathologic reports). Therefore, the severity of the disease or the disease subtypes for periodontitis and glaucoma could not be precisely evaluated. Finally, one must bear in mind that the study could be biased because of possible unmeasured or unknown confounding variables.

**Conclusion**

Patients with periodontitis may increase the risk of glaucoma development compared with individuals without periodontitis. The association between periodontitis and glaucoma remained statistically significant regardless of age, gender, presence of comorbidity, and corticosteroid use. Particularly, patients with periodontitis exhibited a higher risk of POAG. Ocular health should be emphasized for such patients, and the underlying mechanisms need further investigation.

**Data availability**

The datasets analyzed in the current study can be accessed from the Taiwan National Health Insurance Research Database repository (https://nhird.nhri.org.tw/en).

Received: 21 April 2020; Accepted: 9 July 2020

Published online: 10 October 2020

**References**

1. Slots, J. Periodontitis: facts, fallacies and the future. *Periodontology* **2000** (75), 7–23 (2017).
2. Papapanou, P. N. & Susic, C. Periodontitis epidemiology: is periodontitis under-recognized, over-diagnosed, or both? *Periodontology* **2000** (75), 45–51 (2017).
3. Pihlstrom, B. L., Michalowicz, B. S. & Johnson, N. W. Periodontal diseases. *Lancet* **366**, 1809–1820 (2005).
4. Cardoso, E. M., Reis, C. & Manzanares-Céspedes, M. C. Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases. *Postgrad. Med.* **130**, 98–104 (2018).
5. Suh, J. S. et al. Rosuvastatin prevents the exacerbation of atherosclerosis in ligature-induced periodontal disease mouse model. *Sci. Rep.* **10**, 6383 (2020).
6. Polak, D. & Shapira, L. An update on the evidence for pathogenic mechanisms that may link periodontitis and diabetes. *J. Clin. Periodontol.* **43**, 150–166 (2018).
7. Daudt, L. D. et al. Association between metabolic syndrome and periodontitis: a systematic review and meta-analysis. *Braz. Oral Res.* **32**, e35 (2018).
8. Pennoni, D. C., Vettore, M. V., Torres, S. R., Farias, M. & Leão, A. An investigation of the bidirectional link between osteoporosis and periodontitis. *Arch. Osteoporos.* **14**, 94 (2019).
9. Corrêa, J. D. et al. Oral microbial dysbiosis linked to worsened periodontal condition in rheumatoid arthritis patients. *Sci. Rep.* **9**, 43739 (2019).
10. Moghadam, S. A., Shirzaiy, M. & Risbaf, S. The associations between periodontitis and respiratory disease. *J. Nepal. Health Res. Councl.* **15**, 1–6 (2017).
11. Banthia, R. et al. Evaluation of the association between periodontal disease and diabetic retinopathy. *Gen. Dent.* **62**, e28–e32 (2014).
12. Sun, K. T. et al. Risk of age-related macular degeneration in patients with periodontitis: a nationwide population-based cohort study. *Retina* Dec 30 (2019) [Epub ahead of print].
13. Weinreb, R. N., Aung, T. & Medeiros, F. A. The pathophysiology and treatment of glaucoma: a review. *JAMA* **311**, 1901–1911 (2014).
14. Mantravadi, A. V. & Vadhar, N. Glaucoma. *Prim. Care* **42**, 437–449 (2015).
15. Infeld, D. A. & O’Shea, J. G. Glaucoma: diagnosis and management. *Postgrad. Med. J.* **74**, 709–715 (1998).
16. Quigley, H. A. Glaucoma. *Lancet* **377**, 1367–1377 (2011).
17. Hecht, I., Achiorn, A., Man, V. & Burgansky-Eliash, Z. Modifiable factors in the management of glaucoma: a systematic review of current evidence. *Graefes Arch. Clin. Exp. Ophthalmol.* **255**, 789–796 (2017).
18. Kersey, J. P. & Broadway, D. C. Corticosteroid-induced glaucoma: a review of the literature. *Eye* **20**, 407–416 (2006).
19. Vohra, R., Tsai, J. C. & Kolko, M. The role of inflammation in the pathogenesis of glaucoma. *Surv. Ophthalmol.* **58**, 311–320 (2013).
20. Williams, P. A., Marsh-Armstrong, N., Howell, G. R., & Lasker/IRRF Initiative on Astrocytes and Glaucomatous Neurodegeneration Participants. Neuroinflammation in glaucoma: a new opportunity. *Exp. Eye Res.* **157**, 20–7 (2017).
21. Polla, D. et al. A pilot study to evaluate the oral microbiome and dental health in primary open-angle glaucoma. *J. Glaucoma* **26**, 320–327 (2017).
22. Pasquale, L. R. et al. Prospective study of oral health and risk of primary open-angle glaucoma in men: from the Health Professionals Follow-up Study. *Ophthalmology* **123**, 2318–2327 (2016).
23. Chen, H. Y. & Lin, C. L. Comparison of medical comorbidity between patients with primary angle-closure glaucoma and a control cohort: a population-based study from Taiwan. *BMJ Open* **9**, e024209 (2019).
24. Astafurov, K. et al. Oral microbiome link to neurodegeneration in glaucoma. *PLoS ONE* **9**, e104416 (2014).
25. Tonetti, M. S. et al. Treatment of periodontitis and endothelial function. *N. Engl. J. Med.* **356**, 911–920 (2007).
26. Su, W. W. et al. Glaucoma is associated with peripheral vascular endothelial dysfunction. *Ophthalmology* **115**, 1173–8.e1 (2008).
27. Kim, Y. S. & Tauber, M. G. Neurotoxicity of glia activated by gram-positive bacterial products depends on nitric oxide production. *Infect. Immun.* **64**, 3148–3153 (1996).
28. Chan, E. W. et al. Glaucoma in Asia: regional prevalence variations and future projections. *Br. J. Ophthalmol.* **100**, 78–85 (2016).
29. Wright, C., Tawfik, M. A., Waisbourd, M. & Katz, L. J. Primary angle-closure glaucoma: an update. *Acta Ophthalmol.* **94**, 217–225 (2016).
30. Hsing, A. W. & Ioannidis, J. P. Nationwide population science: lessons from the Taiwan national health insurance research database. *JAMA Intern. Med.* 175, 1527–1529 (2015).

31. Chang, G. H. et al. Deep neck infection in systemic lupus erythematosus patients: real-world evidence. *Sci. Rep.* 10, 4133 (2020).

32. Chang, Y. S. et al. Risk of corneal ulcer in patients with diabetes mellitus: a retrospective large-scale cohort study. *Sci. Rep.* 10, 7388 (2020).

**Acknowledgements**

The research was supported by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004) and China Medical University Hospital (DMR-109-031).

**Author contributions**

K.T.S., T.C.S., and N.Y.H., designed the study. S.C.C., C.L.C., C.H.L., X.L., K.P., W.S.C., C.W.T. analyzed and interpreted data. D.T.B. and C.Y.L. supervised the study. K.T.S., T.C.S., C.L.C., and N.Y.H. wrote the main manuscript. All authors reviewed and proved the manuscript.

**Competing interests**

The authors declare no competing interests.

**Additional information**

Correspondence and requests for materials should be addressed to N.-Y.H.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

[Open Access] This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2020