Prolonged Exposure to Air Pollution Increases Periodontal Disease Risk: A Nationwide, Population-Based, Cohort Study

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Abstract: (1) Background: No association between air pollution and periodontitis has yet been shown. Thus, we merged two nationwide databases to evaluate the risk of periodontitis in Taiwanese residents with long-term exposure to air pollution. (2) Methods: We conducted a nationwide retrospective cohort study using the Longitudinal Generation Tracking Database and the Taiwan Air Quality-Monitoring Database. The daily average air pollutant concentrations were categorized into quartiles (Q1, Q2, Q3, and Q4). We carried out Cox proportional hazards models to compute the hazard ratios of periodontitis, with 95% confidence intervals, in Q2–Q4 of the daily average air pollutant concentrations, compared with Q1. (3) Results: The adjusted HR (95 CI%) for periodontitis in Q2–Q4 increased with increased exposure to SO2, NO, NO2, NOX, PM2.5, and PM10 from 1.72 (1.70, 1.76) to 4.86 (4.78–4.94); from 1.89 (1.85–1.93) to 2.64 (2.59–2.70); from 1.04 (1.02–1.06) to 1.52 (1.45–1.55); from 1.61 (1.58–1.64) to 2.51 (2.47–2.56); from 1.48 (1.45–1.51) to 2.11 (2.07–2.15); from 2.02 (1.98–2.06) to 22.9 (22.4–23.4, and from 2.71 (2.66–2.77) to 17.2 (16.8–17.6), respectively, compared to Q1. (4) Conclusions: Residents in Taiwan with long-term exposure to higher levels of air pollutants had a greater risk of periodontitis.

Keywords: air pollution; periodontitis; longitudinal generation tracking database; Taiwan air quality-monitoring database

1. Introduction

In recent decades, air pollution has become an important global issue, being highly correlated with human economic activity and climate change [1]. Many countries have seen rapid industrialization and population density, and there is growing evidence that
substantial air pollutant exposure is associated with changes in the levels of inflammatory cytokines and biomarkers, including C-reactive protein (CRP); interleukins (ILs)-1β, 6, 8, 10; tumor necrosis factor (TNF)-α; vascular cell adhesion molecule-1 (VCAM-1); intercellular adhesion molecule-1 (ICAM-1); and reactive oxygen species (ROS) or reactive nitrogen species [2–9]. Inflammatory mediators such as IL-6 and TNF-α may induce destruction of soft tissues near the teeth by stimulating the production of enzymes [10,11]. In addition, inflammatory cells are recruited, and adhesion to the vascular endothelium is enhanced [12]. Endothelial barrier dysfunction follows, allowing the facile translocation of inflammatory mediators [12–14]. Eventually, systemic inflammatory reactions are promoted, accompanied by multiorgan responses, such as suppressed vasodilatation, enhanced endothelial senescence, increased smooth muscle proliferation, and bone marrow activation [15–18]. Moreover, evidence has demonstrated that long-term exposure to ambient air pollution may be linked to adverse health conditions, including asthma, cardiovascular diseases, stroke, elevated cancer risk, neurological disorders, and increased morbidity and mortality [19–27].

Periodontal diseases, namely gingivitis and periodontitis, involve a protracted inflammatory process characterized by gingival swelling, redness, and irritability, as in gingivitis, or even by loss of supportive connective tissue or bone, as in periodontitis. These processes are related to chronic inflammatory conditions of oxidative stress [28–30]. The most recognized causes of periodontal diseases include dental biofilm plaque and peri-implant diseases [31–33]. Both of these conditions stimulate antimicrobial activity and ROS, which not only eradicate intrusive pathogens but also act as a double-edged sword, causing overwhelming oxidant load [34–36]. In our perspectives, evidence from various studies could be summarized into three pathogenic mechanisms of periodontal diseases: (1) promoted systemic and local inflammatory response [37] iron and heme sequestration, resulting in dysregulation of intracellular homeostasis [38], (2) augmented inflammation in the presence of oral microbiota, especially Porphyromonas gingivalis [39]. Local inflammatory responses, with systemic extension and upregulated ROS, lead to various pathological changes, resulting in the destruction of host tissues and damage to intracellular biomolecules and the cell membrane [37,40].

However, no association between air pollution and periodontitis has yet been shown. Thus, we merged two national nationwide databases to evaluate the risk of periodontitis in Taiwanese residents with long-term exposure to air pollution.

2. Materials and Methods
2.1. Data Source

To explore the risk of periodontitis associated with air pollution in Taiwan, we conducted a nationwide retrospective cohort study using the Longitudinal Generation Tracking Database (LGTD 2000) and the Taiwan Air Quality-Monitoring Database (TAQMD). The LGTD contains the data of two million individuals randomly selected from the National Health Insurance Research Database (NHIRD), which was established in 1995 and contains the comprehensive healthcare data of approximately 99% of Taiwanese residents, with information on outpatient visits, ambulatory care, and inpatient hospitalization, as well as diagnostic codes formatted according to the 9th and 10th revisions of the International Classification of Diseases, Clinical Modification (ICD-9-CM, ICD-10-CM). In 2016, Taiwan’s Ministry of Health and Welfare established the Health and Welfare Data Center (HWDC) to standardize the management of available healthcare data. The TAQMD has been maintained by the Taiwan Environmental Protection Agency (EPA) since 1998 and includes the daily concentrations of air pollutants from 74 ambient air quality-monitoring stations across Taiwan. We connected the residential areas of the insured population from the LGTD with the air pollutant information from the nearest TAQMD station. The study was approved by the Central Regional Research Ethics Committee of China Medical University, Taichung, Taiwan (CMUH109-109-REC2-031).
2.2. Study Participants

People residing in the vicinity of an air quality-monitoring station and covered by the NHI were selected as the study population. Their healthcare data from January 2005 to 31 December 2016 were then extracted. Each subject was monitored from the index date (2005/01/01) until a new diagnosis of periodontitis was made or until the subject was censored due to loss to follow-up, death, withdrawal from insurance, or the end of follow-up on 31 December 2017. The index date was defined as the date on which the subjects entered the LGTD. Individuals aged under 18 years were excluded, as were those with missing data on pollutant levels. Those who had ever been diagnosed with periodontitis before the baseline were also excluded.

2.3. Exposure Collection and Outcome Measurement

A total of 74 air pollution monitoring stations are located on Taiwan’s main island. The location of each monitoring station is determined by the population density. Participants’ residential addresses were not available from the TNHI program in compliance with the Personal Data Protection Act. Thus, the residential area of the study subjects was defined by the location of their most common clinic or hospital for cold diagnosis (ICD-9-CM 460). Each resident was assigned a pollutant-exposure level in accordance with the information received from the monitoring station located in the residential area. The air pollutants of interest were $\text{SO}_2$, $\text{CO}$, $\text{NO}$, $\text{NO}_x$, $\text{NO}_2$, $\text{PM}_{2.5}$, and $\text{PM}_{10}$. The daily concentrations of air pollution data were measured automatically by the monitoring stations. The outcome event was the diagnosis of periodontitis (ICD-9-CM codes 5233, 5234; ICD-10-CM codes K0520, K0521, K0522, K0530, K0531, and K0532). The endpoint of follow-up was the date of withdrawal from the NHI program, development of periodontitis, or 31 December 2017, whichever occurred first. The daily average air pollutant concentrations were categorized into quartiles, with three cut-off points (25th, 50th, and 75th percentiles) as follows: $\text{SO}_2$ concentration (Q1: $<2.71$ ppb, Q2: $2.71–3.26$ ppb, Q3: $3.26–3.79$ ppb, and Q4: $>3.79$ ppb); $\text{CO}$ concentration (Q1: $<0.38$ ppm, Q2: $0.38–0.46$ ppm, Q3: $0.46–0.56$ ppm, and Q4: $>0.56$ ppm); $\text{NO}$ concentration (Q1: $<2.74$ ppm, Q2: $2.74–4.24$ ppm, Q3: $4.24–6.65$ ppm, and Q4: $>6.65$ ppm); $\text{NO}_x$ concentration (Q1: $<13.6$ ppm, Q2: $13.6–17.2$ ppm, Q3: $17.2–20.8$ ppm, and Q4: $>20.8$ ppm); $\text{NO}_2$ concentration (Q1: $<16.3$ ppm, Q2: $16.3–21.6$ ppm, Q3: $21.6–27.3$ ppm, and Q4: $>27.3$ ppm); $\text{PM}_{2.5}$ concentrations (Q1: $<17.5 \mu g/m^3$, Q2: $17.5–206 \mu g/m^3$, Q3: $20.6–27.2 \mu g/m^3$, and Q4: $>27.2 \mu g/m^3$); and $\text{PM}_{10}$ concentrations (Q1: $<3.65 \mu g/m^3$, Q2: $3.65–42.9 \mu g/m^3$, Q3: $42.9–52.6 \mu g/m^3$, and Q4: $>52.6 \mu g/m^3$). The two-year average concentrations of air pollutants were calculated within two years before the PD diagnosis date or index date.

2.4. Confounding Factors

To control for covariates, the confounding factors we considered were age, sex, population density level, and comorbidities of alcohol abuse/dependence (ICD-9-CM code 303, 3050, 30301, 30302, 30303, 30390, 30391, 30392, 30393, 30500, 30501, 30502, 30503; ICD-10-CM code F10120, F10129, F10220, F10229, F1020, F1021, F1010), tobacco abuse/dependence (ICD-9-CM code 3051; ICD-10-CM code F17200, F17201, F17210, F17211, F17220, F17221, F17290, F17291), chronic obstructive pulmonary disease (ICD-9-CM code 490–492, 494, and 496; ICD-10-CM code J40, J41, J43, J44, J47), diabetes mellitus (DM, ICD-9-CM code250; ICD-10-CM codeE08, E09, E10, E11, E13), rheumatoid arthritis(RA, ICD-9-CM code 714; ICD-10-CM codeJ40), obesity (ICD-9-CM code 278; ICD-10-CM code E65, E66, E67, E68) and asthma (ICD-9-CM code 493; ICD-10-CM code J45). Population density was categorized into four levels from the highest to the lowest density.

2.5. Statistical Analysis

In descriptive statistics, the distributions of gender, age, comorbidity, and periodontitis were presented as percentages (%), whereas air pollutants were presented as mean (standard deviation). The chi-squared test was used to test the differences among the
quartiles of the daily average concentrations of SO$_2$, CO, NO, NO$_2$, NO$_X$, PM$_{2.5}$, and PM$_{10}$ at each population density level. The incidence of periodontitis per 1000 person-years was then calculated. We carried out Cox proportional hazards models to compute the hazard ratios (HRs) of periodontitis, with 95% confidence intervals (CIs), in Q2–Q4 of the two-year average air pollutant concentrations, compared with Q1. Multivariable models were adjusted for age, sex, population density level, monthly income, comorbidities of alcohol abuse/dependence, tobacco abuse/dependence, chronic obstructive pulmonary disease, asthma, diabetes, obesity, and rheumatoid arthritis.

Furthermore, we considered each pollutant level as a continuous measure in multivariate analyses and computed the HRs of periodontitis, with 95% CIs in Appendix A.

In Appendix B, we have re-defined the PD patient via diagnosis of periodontitis (ICD-9-CM codes 5233, 5234; ICD-10-CM codes K0520, K0521, K0522, K0530, K0531, and K0532) and with two dental examinations within a year before PD diagnosis.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided $p$-value < 0.05 was considered significant.

3. Results

3.1. Demographic Characteristics and Air Pollutants of Study Population

A total of 292,263 participants were enrolled in the study. The proportion of females was slightly higher than that of males (55.1% vs. 44.9%), and the mean age at enrollment was 41.1 ± 16.2 years. The proportion of participants who lived in areas with the highest population density was 59.9%. There were 4512 (1.54%) participants who showed alcohol abuse, 47,458 (16.2%) who showed tobacco abuse, and 43,818 (15.0%) with chronic obstructive pulmonary disease. The two-year average concentrations of SO$_2$, CO, NO, NO$_2$, NO$_X$, PM$_{2.5}$, and PM$_{10}$ were 4.42 ± 1.68 ppb, 0.60 ± 0.23 ppm, 8.69 ± 8.77 ppm, 28.6 ± 14.0 ppm, 30.2 ± 7.88 µg/m$^3$ and 54.3 ± 12.8 µg/m$^3$, respectively. At the end of the study, 126,167 participants had experienced periodontitis during the study period. The mean follow-up time was 11.4 ± 2.80 years (Table 1).
Table 1. Cont.

| Exposure of air pollutants                  | N = 292,263 | n  | %  |
|---------------------------------------------|-------------|----|----|
| SO\textsubscript{2} level (two-year average, ppb) | 4.42        | 0.60 | 1.68 |
| CO level (two-year average, ppm)            | mean, SD    | 8.69 | 8.77 |
| NO level (two-year average, ppm)            | mean, SD    | 17.3 | 5.74 |
| NO\textsubscript{2} level (two-year average, ppm) | mean, SD   | 28.6 | 14.0 |
| NO\textsubscript{X} level (two-year average, ppm) | mean, SD   | 30.2 | 7.88 |
| PM\textsubscript{2.5} (two-year average, µg/m\textsuperscript{3}) | mean, SD | 54.3 | 12.8 |
| PM\textsubscript{10} (two-year average, µg/m\textsuperscript{3}) | mean, SD | 126,167 | 56.8 |

Outcome

| Periodontitis | Follow-up time, years |
|--------------|-----------------------|
| Yes          | mean, SD              |
| Follow-up time, years Median, IQR | 13.0 (10.9–13.0) |

† The population density was categorized into 4 levels, with level 1 as the highest level and level 4 as the lowest level; CO, carbon monoxide; NO, nitric oxide; NO\textsubscript{X}, nitrogen oxides; SD, standard deviation.

3.2. Population Density among the Daily Average Concentration of Air Pollutants

As shown in Table 2, the quartiles of the two-year average concentrations of SO\textsubscript{2}, CO, NO, NO\textsubscript{2}, NO\textsubscript{X}, PM\textsubscript{2.5}, and PM\textsubscript{10} showed significant differences among the four levels of population density (p < 0.001). Participants residing in the highest population density were exposed to the highest concentrations of CO (29.2%), NO (30.0%), and NO\textsubscript{X} (28.9%).

Table 2. Baseline population density level among quartiles of daily average concentration of air pollutants in Taiwan children, 2005–2016.

| Air Pollutant Concentration | Q1 (Lowest) | Q2 | Q3 | Q4 (Highest) | p-Value * |
|-----------------------------|-------------|----|----|--------------|-----------|
| N = 292,263                 | n (%)       | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |

SO\textsubscript{2} Population density level

1  39,998  22.9  43,645  24.9  49,253  28.2  42,081  24.1
2  29,281  30.6  19,745  20.6  20,922  21.9  25,782  26.9
3  2554  13.6  5611  30.0  6808  36.4  3748  20.0
4  1244  43.9  496  17.5  574  20.3  521  18.4

CO (missing = 288) Population density level

1  38,272  21.9  39,671  22.7  45,926  26.3  51,048  29.2
2  32,180  33.7  28,937  30.3  17,163  18.0  17,227  18.0
3  4742  25.3  3171  16.9  6618  35.4  4186  22.4
4  1082  38.2  528  18.6  651  23.0  573  20.2

NO Population density level

1  41,331  23.6  38,245  21.9  42,926  24.5  52,475  30.0
2  28,985  30.3  28,564  29.8  20,592  21.5  17,589  18.4
3  4671  25.0  3298  17.6  6623  35.4  4129  22.1
4  1032  36.4  568  20.0  647  22.9  588  20.7

NO\textsubscript{2} Population density level

1  39,621  22.6  41,999  24.0  47,193  27.0  46,164  26.4
2  30,102  33.7  28,937  30.3  17,163  18.0  17,227  18.0
3  4742  25.3  3171  16.9  6618  35.4  4186  22.4
4  1108  39.1  583  20.6  624  22.9  520  18.3

*p-Value < 0.001.
### Table 2. Cont.

| Air Pollutant Concentration | Q1 (Lowest) | Q2 | Q3 | Q4 (Highest) | p-Value * |
|-----------------------------|-------------|----|----|--------------|-----------|
| N = 292,263                | n (%)       | n (%) | n (%) | n (%) | n (%) |
| NOX Population density level |             |     |     |    |     |
| 1 40,795                        | 23.3        | 37,624 | 21.5 | 45,971 | 26.3 | 50,587 | 28.9 |
| 2 28,008                        | 29.3        | 29,461 | 30.8 | 20,342 | 21.3 | 17,919 | 18.7 |
| 3 4685                         | 25.0        | 3298  | 17.6 | 6827  | 36.5 | 3911   | 20.9 |
| 4 1049                         | 37.0        | 549   | 19.4 | 665   | 23.5 | 572    | 20.2 |
| PM2.5 Population density level |             |     |     |    |     |
| 1 43,382                        | 24.8        | 49,195 | 28.2 | 42,824 | 24.5 | 39,211 | 22.5 |
| 2 21,414                        | 22.4        | 21,115 | 22.1 | 24,360 | 25.5 | 28,618 | 30.0 |
| 3 4963                         | 26.6        | 4597  | 24.6 | 4476  | 24.0 | 4646   | 24.9 |
| 4 1095                         | 38.7        | 708   | 25.0 | 536   | 18.9 | 492    | 17.4 |
| PM10 Population density level  |             |     |     |    |     |
| 1 40,974                        | 23.4        | 50,695 | 29.0 | 42,270 | 24.2 | 41,038 | 23.5 |
| 2 24,707                        | 25.8        | 19,129 | 20.0 | 18,542 | 19.4 | 33,352 | 34.8 |
| 3 4712                         | 25.2        | 5539  | 29.6 | 4100  | 21.9 | 4370   | 23.3 |
| 4 809                          | 28.5        | 921   | 32.5 | 602   | 21.2 | 503    | 17.7 |

* Chi-square test; The population density level was categorized into 4 levels, with level 1 as the highest level and level 4 as the lowest level; The two-year average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant.

### 3.3. Risk of Periodontitis Based on the Quartiles of Daily Average Air Pollutant Concentrations

The incidence rates and hazard ratios (95% CI) of periodontitis for SO\(_2\), CO, NO, NO\(_2\), NO\(_X\), PM\(_2.5\), and PM\(_{10}\) are presented in Table 3 and stratified into quartiles. From Q1 to Q4, the incidence rates of periodontitis for SO\(_2\), CO, NO, NO\(_2\), NO\(_X\), PM\(_2.5\), and PM\(_{10}\) increased from 27.9% to 67.2%, from 24.6% to 55.1%, from 27.8% to 53.0%, from 25.1% to 58.6%, from 25.9% to 56.4%, from 20.9% to 62.6% and from 22.1% to 54.5% person-years, respectively. After controlling for age, sex, population density, and comorbidities, the adjusted HR (95 CI%) for periodontitis in Q2–Q4 increased with increased exposure to SO\(_2\), CO, NO, NO\(_2\), NO\(_X\), PM\(_2.5\), and PM\(_{10}\) from 1.28 (1.26, 1.30) to 3.39 (3.34–3.44); from 1.58 (1.55–1.61) to 2.77 (2.73–2.82); from 1.34 (1.32–1.36) to 2.30 (2.26–2.33); from 1.63 (1.60–1.65) to 3.02 (2.97–3.07); from 1.31 (1.28–1.33) to 4.25 (4.18–4.32), and from 1.69 (1.66–1.72) to 3.17 (3.12–3.22), respectively, compared to Q1.

### Table 3. Comparisons of different periodontal disease incidences and associated hazard ratios among 4 levels of air pollutants.

| Pollutant | Levels | Event | IR | cHR (95% CI) | aHR † (95% CI) |
|-----------|--------|-------|----|-------------|----------------|
| SO\(_2\)  | Q1     | 24,645| 27.9| Reference group | Reference group |
|           | Q2     | 28,002| 33.7| 1.27         | 1.28 (1.26, 1.30) |
|           | Q3     | 28,342| 30.2| 1.09         | 1.11 (1.09, 1.13) |
|           | Q4     | 45,178| 67.2| 3.37         | 3.39 (3.34–3.44) |
| CO        | Q1     | 22,740| 24.6| Reference group | Reference group |
|           | Q2     | 30,904| 36.3| 1.58         | 1.58 (1.55, 1.61) |
|           | Q3     | 31,484| 39.4| 1.75         | 1.78 (1.75, 1.81) |
|           | Q4     | 40,976| 55.1| 2.75         | 2.77 (2.73, 2.82) |
| NO        | Q1     | 25,583| 27.8| Reference group | Reference group |
|           | Q2     | 29,243| 35.3| 1.34         | 1.34 (1.32, 1.36) |
|           | Q3     | 30,915| 38.1| 1.46         | 1.48 (1.46, 1.51) |
|           | Q4     | 40,426| 53.0| 2.27         | 2.30 (2.26, 2.33) |
Table 3. Cont.

| Pollutant | Levels | Event | IR   | cHR  | (95% CI) | aHR † | (95% CI) |
|-----------|--------|-------|------|------|----------|-------|----------|
| NO₂       | Q1     | 22,852| 25.1 | Reference group | Reference group |
|           | Q2     | 33,267| 37.2 | 1.60 | (1.57, 1.63) | 1.63  | (1.60, 1.65) |
|           | Q3     | 30,972| 36.3 | 1.54 | (1.51, 1.56) | 1.40  | (1.37, 1.42) |
|           | Q4     | 39,076| 58.6 | 2.98 | (2.93, 3.03) | 2.73  | (2.69, 2.78) |
| NOₓ       | Q1     | 23,392| 25.9 | Reference group | Reference group |
|           | Q2     | 31,500| 38.5 | 1.62 | (1.59, 1.64) | 1.61  | (1.59, 1.64) |
|           | Q3     | 29,754| 34.3 | 1.37 | (1.35, 1.40) | 1.56  | (1.53, 1.59) |
|           | Q4     | 41,521| 56.4 | 2.70 | (2.66, 2.75) | 3.02  | (2.97, 3.07) |
| PM₂.₅    | Q1     | 18,741| 20.9 | Reference group | Reference group |
|           | Q2     | 25,088| 26.3 | 1.30 | (1.28, 1.33) | 1.31  | (1.28, 1.33) |
|           | Q3     | 40,025| 49.7 | 3.05 | (3.00, 3.11) | 3.04  | (2.99, 3.09) |
|           | Q4     | 41,955| 62.6 | 4.28 | (4.21, 4.35) | 4.25  | (4.18, 4.32) |
| PM₁₀     | Q1     | 19,758| 22.1 | Reference group | Reference group |
|           | Q2     | 31,155| 33.8 | 1.68 | (1.65, 1.71) | 1.69  | (1.66, 1.72) |
|           | Q3     | 32,243| 44.7 | 2.42 | (2.38, 2.46) | 2.42  | (2.38, 2.47) |
|           | Q4     | 43,011| 54.5 | 3.20 | (3.14, 3.25) | 3.17  | (3.12, 3.22) |

IR, incidence rate (person-years); cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; Adjusted HR †, adjusted for age, sex, population density level, monthly income and comorbidities of alcohol abuse/dependence, tobacco abuse/dependence, chronic obstructive pulmonary disease, asthma, diabetes, obesity, and rheumatoid arthritis.

4. Discussion

The present retrospective cohort study was the first to assess the association between long-term air pollutant exposure and periodontitis using a large panel database. The results showed that urban resident exposed to higher level of the investigated air pollutants (Table 2). These findings corroborate those from previous studies showing that air pollutant levels are significantly associated with population density, as higher levels of air pollution are observed in metropolitan areas than in rural areas [41,42]. The possible mechanisms connecting periodontitis and air pollution remain unclear. The air pollutants studied in the present work have been widely investigated and associated with various systemic effects, such as elevated systemic oxidative stress, enhanced blood coagulation, decreased plasma antioxidant capacity, autonomic imbalance, activation of the hypothalamic-pituitary-adrenal axis, and endothelial dysfunction [17,43–50].

One cross-sectional study on two panels of adult subjects, those with chronic periodontal infections and with healthy periodontal conditions, was conducted to evaluate the connections between particulate matter and high-sensitivity C-reactive protein (hs-CRP); the results suggested that adult patients with chronic periodontitis were more susceptible to PM-associated hs-CRP elevation [51]. Furthermore, the toxicology of air pollution exposure has been found to be closely related to cigarette smoking and environmental tobacco smoke (ETS). Humic-like substances (HULIS), a complex of polyacidic organic compounds formed by organic acids and aerosol particles, have been identified as a chemical component common to cigarette smoke and air pollution particles [52]. Several studies have reported that approximately 3% of ambient air particulate matter (PM), 7–10% of tobacco smoke condensate, and 5% of diesel exhaust is composed of HULIS [52,53]. In animal studies, introduction of HULIS into the lungs from cigarette smoke resulted in phagocytosis and accumulation of intracellular iron, leading to iron sequestration and subsequent deficiency of cellular metals [52]. Consequently, the response to functional metal deficiency includes oxidative stress, activation of cell signaling and transcription factors, release of pro-inflammatory mediators, and apoptosis [54,55]. These reactions further prompted the development of tissue inflammation and fibrosis [54,56].

Moreover, the interaction between ozone and air pollution particles has been proposed to further impact the effects of iron sequestration, disruption of cellular metal homeosta-
sis, and tissue inflammation [57,58]. Apart from inflammatory reactions induced by air pollutants and cigarette smoke, pathogenic organisms also take part in the progression of periodontal disease. Porphyromonas gingivalis has been implicated as a major etiological component in the initiation and progression of periodontitis [59]. The ability of the pathogen to colonize and proliferate within the human periodontal pocket depends in part upon the acquisition of iron due to its inability to synthesize the protoporphyrin ring [39]. Characteristic secretions of surface-associated proteases and hemagglutinins have been demonstrated to be capable of degrading structural and defense mechanisms and harvesting heme, iron-containing proteins [39]. The virulence of \( P. \) gingivalis can be augmented in the presence of cigarette smoke and hydrogen sulfide, which are commonly seen aerosol particles [60,61]. Laboratory research and animal studies have revealed that purified gingipains and trypsin-like proteinase from \( P. \) gingivalis can promote MMP-8 and MMP-3 expression in rat mucosal epithelial cells and upregulate the collagen-degrading ability of some human gingival fibroblasts, causing an imbalance in the proliferative and catalytic activity of human gingival fibroblasts [40].

Eventually, tooth-supporting structures and alveolar bone are destroyed. At the cellular level, many studies have reported excessive release of matrix metalloproteinases, degradation of connective tissue and bone matrix, induction of RANKL, and increased levels of various cytokines (IL-8, IL-6, TNF-\( \alpha \), IL-1\( \beta \), etc.) from peripheral blood polymorphonuclear neutrophils [37,62–65]. This pathognomonic reaction cascade has been found in several other disorders, such as diabetes mellitus, smoking, obesity, and rheumatoid arthritis [27,66–69]. We postulated that a similar inflammatory pathway underlies the connection between air pollution and periodontitis.

The present study has several advantages over previous studies. First, we used a nationwide database and recruited a relatively large sample size over an 11-year follow-up period, which yielded strong evidence regarding long-term outcomes in the observed Taiwanese population. Second, as 99% of the Taiwanese population is enrolled in the NHIRD, the bias associated with data collection, region, age, and institution was minimized. The use of the NHIRD also eliminated loss to follow-up and enabled the gathering of data from participants with varied demographic characteristics who were geographically dispersed [70]. Relatedly, the long follow-up period prevented any potential bias. Third, population density was incorporated to demonstrate the geographic connection between the severity of air pollution and periodontitis. However, the present study had some limitations. First, although this study merged two nationwide databases, the exposure levels of indoor air pollutants were not available [71]. Evidence has shown that buildings cannot block outdoor NO\(_2\) molecules efficiently. Thus, it is worthwhile to clarify the impact of indoor and outdoor air pollutants in future studies. Second, two large databases were combined: the NHIRD and TAQMD. The pollution levels in the residential areas of the NHIRD insurers were determined based on the location of their most common clinic or hospital for cold diagnosis (ICD-9-CM 460). Therefore, residents without a cold diagnosis during the study period were not enrolled in this study. Most likely they lived in areas with low levels of pollutants. This may have resulted in an underestimation of PD risk. Third, the NHIRD does not record detailed information on other potential confounders, such as socioeconomic status, family history, systemic comorbidities, smoking or alcohol consumption, and diet factors, which could be considered risk factors for periodontitis. Fourth, we conducted this retrospective nationwide cohort study using random sampling. Although this study had a long follow-up period, underdiagnosis due to PD development after the study period may have resulted in an underestimation of PD risk. Fifth, one of the limitations of LGTD is the lack of SES information. Tobacco abuse/dependence cannot completely reflect light smoking behavior and second-hand smoking. Thus, we considered COPD and asthma as the smoking status of the participants [72–74]. However, the covariates included are likely inadequate to control for socioeconomic position, which is a primary confounding factor in this analysis. Sixth, the NHIRD was established in early 1996 and was initially incomplete. Thus, only longitudinal data from January 2005 to
December 2016 were selected and analyzed. Bias due to miscoding and misclassification of the ICD may have occurred during the transition phase from paper-based to electronic medical records. Additionally, the ICD-9 information used in this study was restricted to the ICD code only. The definitions of periodontitis and gingivitis have varied significantly between different specialties and timing. Since there were no objective image records, photos of the periodontal disease, or other laboratory data in the NHIRD, we relied on the professional judgment and accurate diagnosis of board-certified dentists. We did not determine the validity of the diagnosis in the present study. Furthermore, there are three sources for potential measurement error: (1) only 74 monitors in the whole study area without research enhanced monitors, and no information about the monitor locations; (2) no detailed residential addresses and moving history available; and (3) only raw measurements without temporal and spatial resolutions from advanced prediction models. Despite all these drawbacks, the data were examined carefully.

5. Conclusions
The present retrospective cohort study demonstrated an association between air pollution and periodontitis. In particular, residents in Taiwan with long-term exposure to higher levels of air pollutants had a greater risk of periodontitis. However, additional studies are required to investigate whether reduced exposure to air pollutants can lower the risk of periodontitis and to elucidate the underlying mechanism.

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Data Availability Statement: Data are available from the NHIRD published by Taiwan National Health Insurance Bureau. Due to the ‘Personal Information Protection Act’, data cannot be made publicly available (http://nhird.nhri.org.tw/en/index.html).

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Appendix A
In the Cox proportional hazard regression (pollutant levels as continuous variables), subjects who were exposed to higher concentrations of SO\textsubscript{2} (adjusted hazard ratio [aHR] = 1.42, 95% CI = 1.41–1.42), CO (aHR = 2.73, 95% CI = 2.66–2.80), NO (aHR = 1.01, 95% CI = 1.013–1.014), NO\textsubscript{x} (aHR = 1.01, 95% CI = 1.013–1.014), NO\textsubscript{2} (aHR = 1.05, 95% CI = 1.045–1.048), PM\textsubscript{2.5} (aHR = 1.14, 95% CI = 1.13–1.14), and PM\textsubscript{10} (aHR = 1.04, 95% CI = 1.038–1.04) developed a significantly higher risk of PD.
Table A1. The risk of Periodontitis in patients exposed to various air pollutants daily average concentration in Cox proportional hazard regression.

| Pollutants | cHR (95% CI) | aHR † (95% CI) |
|------------|--------------|-----------------|
| SO$_2$     | 1.42 (1.41, 1.43) *** | 1.42 (1.41, 1.42) *** |
| CO         | 2.66 (2.59, 2.73) *** | 2.73 (2.66, 2.80) *** |
| NO         | 1.013 (1.012, 1.014) *** | 1.01 (1.013, 1.014) *** |
| NO$_x$     | 1.013 (1.013, 1.014) *** | 1.01 (1.013, 1.014) *** |
| NO$_2$     | 1.045 (1.044, 1.046) *** | 1.05 (1.045, 1.048) *** |
| PM$_{2.5}$ | 1.141 (1.14, 1.142) *** | 1.14 (1.13, 1.14) *** |
| PM$_{10}$  | 1.038 (1.038, 1.039) *** | 1.04 (1.038, 1.04) *** |

IR, incidence rate (per 1000 person-years); cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; Adjusted HR †, adjusted for age, sex, population density, monthly income and comorbidities of alcohol abuse/dependence, tobacco abuse/dependence, chronic obstructive pulmonary disease asthma, diabetes, obesity, and rheumatoid arthritis; *** p < 0.001.

Appendix B

The adjusted HR (95 CI%) for periodontitis in Q2–Q4 increased with increased exposure to SO$_2$, CO, NO, NO$_x$, NO$_2$, PM$_{2.5}$, and PM$_{10}$ from 1.27 (1.24–1.30) to 3.33 (3.25–3.41); from 1.67 (1.63–1.72) to 2.97 (2.90–3.04); from 1.43 (1.39–1.46) to 2.48 (2.42–2.54); from 1.73 (1.68–1.77) to 2.96 (2.89–3.03); from 1.71 (1.67–1.75) to 3.27 (3.19–3.35); from 1.25 (1.22–1.29) to 3.98 (3.88–4.08, and from 1.65 (1.61–1.70) to3.00 (2.93–3.08), respectively, compared to Q1.

Table A2. Comparisons of different periodontal disease incidences and associated hazard ratios among 4 levels of air pollutants.

| Pollutant | Levels | Event | IR | cHR (95% CI) | aHR † (95% CI) |
|-----------|--------|-------|----|--------------|----------------|
| SO$_2$    | Q1     | 11,335| 12.8| Reference group | Reference group |
|           | Q2     | 12,828| 15.5| 1.26 (1.23,1.30) | 1.27 (1.24, 1.30) |
|           | Q3     | 12,699| 13.5| 1.06 (1.03, 1.09) | 1.07 (1.04, 1.09) |
|           | Q4     | 20,300| 30.2| 3.32 (3.24, 3.40) | 3.33 (3.25, 3.41) |
| CO        | Q1     | 9828  | 10.6| Reference group | Reference group |
|           | Q2     | 14,183| 16.6| 1.68 (1.63, 1.72) | 1.67 (1.63, 1.72) |
|           | Q3     | 14,170| 17.7| 1.83 (1.78, 1.88) | 1.84 (1.79, 1.88) |
|           | Q4     | 18,957| 25.5| 2.96 (2.89, 3.03) | 2.97 (2.90, 3.04) |
| NO        | Q1     | 10,999| 11.9| Reference group | Reference group |
|           | Q2     | 13,384| 16.1| 1.42 (1.39, 1.46) | 1.43 (1.39, 1.46) |
|           | Q3     | 13,986| 17.2| 1.54 (1.50, 1.57) | 1.55 (1.51, 1.58) |
|           | Q4     | 18,793| 24.7| 2.46 (2.41, 2.52) | 2.48 (2.42, 2.54) |
| NO$_2$    | Q1     | 9794  | 10.7| Reference group | Reference group |
|           | Q2     | 15,188| 17.0| 1.71 (1.66, 1.75) | 1.73 (1.68, 1.77) |
|           | Q3     | 14,041| 16.5| 1.63 (1.59, 1.67) | 1.64 (1.60, 1.68) |
|           | Q4     | 18,139| 27.2| 3.25 (3.17, 3.33) | 3.26 (3.19, 3.35) |
| NO$_x$    | Q1     | 10,050| 11.1| Reference group | Reference group |
|           | Q2     | 14,395| 17.6| 1.72 (1.68, 1.77) | 1.71 (1.67, 1.75) |
|           | Q3     | 13,393| 15.4| 1.44 (1.40, 1.48) | 1.64 (1.60, 1.68) |
|           | Q4     | 19,324| 26.3| 2.94 (2.87, 3.02) | 3.27 (3.19, 3.35) |
| PM$_{2.5}$| Q1     | 8956  | 10.0| Reference group | Reference group |
|           | Q2     | 11,486| 12.0| 1.25 (1.22, 1.29) | 1.25 (1.22, 1.29) |
|           | Q3     | 18,081| 22.5| 2.90 (2.83, 2.98) | 2.91 (2.84, 2.98) |
|           | Q4     | 18,493| 27.6| 3.97 (3.87, 4.08) | 3.98 (3.88, 4.08) |
Table A2. Cont.

| Pollutant | Levels | Event IR | cHR (95% CI) | aHR † (95% CI) |
|-----------|--------|----------|--------------|-----------------|
| PM$_{10}$ | Q1     | 9294     | 10.4         | Reference group  |
|           | Q2     | 14,349   | 15.6         | 1.65 (1.61, 1.69)| 1.65 (1.61, 1.70) |
|           | Q3     | 14,576   | 20.2         | 2.34 (2.28, 2.40)| 2.34 (2.28, 2.40) |
|           | Q4     | 18,943   | 24.0         | 3.01 (2.94, 3.09)| 3.00 (2.93, 3.08) |

IR, incidence rate (per 1000 person-years); cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval. The two-year average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant; Adjusted HR †, adjusted for age, sex, population density, monthly income and comorbidities of alcohol abuse/dependence, tobacco abuse/dependence, chronic obstructive pulmonary disease asthma, diabetes, obesity, and rheumatoid arthritis.

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