Article

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 SO_2, CO, NO, NO_2, NO_X, $PM_{2.5}$, and PM_{10} 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 (1.49–1.55); 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-αmay 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 *Porphyromasgingivalis* [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 SO_2, CO, NO, NO_X, NO_2, $PM_{2.5}$, and 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: SO_2 concentration (Q1: <2.71 ppb, Q2: 2.71–3.26 ppb, Q3: 3.26–3.79 ppb, and Q4: >3.79 ppb); CO concentration (Q1: <0.38 ppm, Q2: 0.38–0.46 ppm, Q3: 0.46–0.56 ppm, and Q4: >0.56 ppm); NO concentration (Q1: <2.74 ppm, Q2: 2.74–4.24 ppm, Q3: 4.24–6.65 ppm, and Q4: >6.65 ppm); NO_2 concentration (Q1: <13.6 ppm, Q2: 13.6–17.2 ppm, Q3: 17.2–20.8 ppm, and Q4: >20.8 ppm); NO_X concentration (Q1: <16.3 ppm, Q2: 16.3–21.6 ppm, Q3: 21.6–27.3 ppm, and Q4: >27.3 ppm); $PM_{2.5}$ concentrations (Q1: <17.5 $\mu g/m^3$, Q2: 17.5–206 $\mu g/m^3$, Q3: 3, 20.6–27.2 $\mu g/m^3$, and Q4: >27.2 $\mu g/m^3$); and PM_{10} concentrations (Q1: <36.5 $\mu g/m^3$, Q2: 36.5–42.9 $\mu g/m^3$, 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, 30300, 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 code J45), 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 $\mu g/m^3$ and 54.3 ± 12.8 $\mu g/m^3$, 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. Characteristics of participants in this study.

N = 292,263		*n*	%
Gender	Female	160,985	55.1
	Male	131,278	44.9
Age, years	mean, SD	41.1	16.2
Population density †	1 (highest)	174,977	59.9
	2	95,730	32.8
	3	18,721	6.41
	4 (lowest)	2835	0.97
Monthly income(NTD)			
<20,000		54,397	18.6
20,000–40,000		148,121	50.7
≥40,000		89,745	30.7
Comorbidity			
Alcohol abuse/dependence		4512	1.54
Tobacco abuse/dependence		11,474	3.93
Chronic obstructive pulmonary disease		47,458	16.2
Asthma		43,818	15.0
Diabetes		52,884	18.1
Obesity		5262	1.80
Rheumatoid arthritis		858	0.29

Table 1. *Cont.*

N = 292,263		*n*	%
Exposure of air pollutants			
SO_2 level (two-year average, ppb)		4.42	1.68
CO level (two-year average, ppm)	mean, SD	0.60	0.23
NO level (two-year average, ppm)	mean, SD	8.69	8.77
NO_2 level (two-year average, ppm)	mean, SD	17.3	5.74
NO_X level (two-year average, ppm)	mean, SD	28.6	14.0
$PM_{2.5}$ (two-year average, $\mu g/m^3$)	mean, SD	30.2	7.88
PM_{10} (two-year average, $\mu g/m^3$)	mean, SD	54.3	12.8
Outcome			
Periodontitis	Yes	126,167	56.8
Follow-up time, years	mean, SD	11.4	2.80
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_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-yearaverage concentrations of SO_2, CO, NO, NO_2, NO_X, $PM_{2.5}$, and PM_{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_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*	(%)	
SO_2									<0.001
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)									<0.001
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_2									<0.001
Population density level									
1	39,621	22.6	41,999	24.0	47,193	27.0	46,164	26.4	
2	30,102	31.4	29,494	30.8	19,328	20.2	16,806	17.6	
3	4679	25.0	4755	25.4	5775	30.9	3512	18.8	
4	1108	39.1	583	20.6	624	22.0	520	18.3	

Table 2. *Cont.*

Air Pollutant Concentration	Q1 (Lowest)		Q2		Q3		Q4 (Highest)		*p*-Value *
N = 292,263	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	
NO$_X$									<0.001
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	
PM$_{2.5}$									<0.001
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	
PM$_{10}$									<0.001
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% to53.0%, 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	(1.25, 1.29)	1.28	(1.26, 1.30)
	Q3	28,342	30.2	1.09	(1.07, 1.11)	1.11	(1.09, 1.13)
	Q4	45,178	67.2	3.37	(3.32, 3.42)	3.39	(3.34, 3.44)
CO	Q1	22,740	24.6	Reference group		Reference group	
	Q2	30,904	36.3	1.58	(1.55, 1.60)	1.58	(1.55, 1.61)
	Q3	31,484	39.4	1.75	(1.72, 1.78)	1.78	(1.75, 1.81)
	Q4	40,976	55.1	2.75	(2.71, 2.80)	2.77	(2.73, 2.82)
NO	Q1	25,583	27.8	Reference group		Reference group	
	Q2	29,243	35.3	1.34	(1.31, 1.36)	1.34	(1.32, 1.36)
	Q3	30,915	38.1	1.46	(1.43, 1.48)	1.48	(1.46, 1.51)
	Q4	40,426	53.0	2.27	(2.23, 2.31)	2.30	(2.26, 2.33)

Table 3. *Cont.*

Pollutant	Levels	Event	IR	cHR	(95% CI)	aHR †	(95% CI)
NO$_2$	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)
NO$_X$	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)
PM$_{2.5}$	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)
PM$_{10}$	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; The annual average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant; 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. Porphyromonasgingivalis 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-α, IL-1β, 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 insurants 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.

Appendix A

In the Cox proportional hazard regression (pollutant levels as continuous variables), subjects who were exposed to higher concentrations of SO_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), NOx (aHR = 1.01, 95% CI = 1.013–1.014), NO_2 (aHR = 1.05, 95% CI = 1.045–1.048), $PM_{2.5}$ (aHR = 1.14, 95% CI = 1.13–1.14), and PM_{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) ***
NOx	1.013	(1.013, 1.014) ***	1.01	(1.013, 1.014) ***
$NO2$	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_2, NO_X, $PM_{2.5}$, 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) to 3.00 (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)	1.45	(1.41, 1.49)
	Q4	18,139	27.2	3.25	(3.17, 3.33)	2.96	(2.89, 3.03)
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		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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