



Article

Association of Exposure to Fine-Particulate Air Pollution and Acidic Gases with Incidence of Nephrotic Syndrome

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Abstract: *Background:* Air pollution has been associated with autoimmune diseases. Nephrotic syndrome is a clinical manifestation of immune-mediated glomerulopathy. However, the association between nephrotic syndrome and air pollution constituents remains unknown. We conducted this nationwide retrospective study to investigate the association between PM_{2.5} and nephrotic syndrome. *Methods:* We used the Longitudinal Health Insurance Database (LHID) and the Taiwan Air Quality-Monitoring Database (TAQMD). We combined and stratified the LHID and the TAQMD data by residential areas of insurants linked to nearby air quality-monitoring stations. Air pollutant concentrations were grouped into four levels based on quartile. Univariable and multivariable Cox proportional hazard regression models were applied. *Findings:* Relative to Q1-level SO₂, subjects exposed to the Q4 level were associated with a 2.00-fold higher risk of nephrotic syndrome (adjusted HR = 2.00, 95% CI = 1.66–2.41). In NO_x, relative to Q1 NO_x concentrations, the adjusted HRs of nephrotic syndrome risk were 1.53 (95% CI = 1.23–1.91), 1.30 (95% CI = 1.03–1.65), and 2.08 (95% CI = 1.69–2.56) for Q2, Q3, and Q4 levels, respectively. The results revealed an increasing trend for nephrotic syndrome risk correlating with increasing levels of NO, NO₂, and PM_{2.5} concentrations. *Interpretation:* High concentrations of PM_{2.5}, NO, NO₂, and SO₂ are associated with increased risk of nephrotic syndrome.

Keywords: air pollution; PM_{2.5}; nephrotic syndrome; retrospective study

1. Introduction

Nephrotic syndrome—massive proteinuria as a result of heterogeneous dysfunction of the glomerulus—has detrimental effects on long-term renal function [1]. Although nephrotic syndrome has been divided into mechanistic categories, the majority of nephrotic syndrome remains idiopathic

and multifaceted [2]. The estimated annual incidence of nephrotic syndrome in healthy children is two to seven new cases per 100,000 population [3,4]. Both racial and environmental factors have been hypothesized to be involved in the increased susceptibility to nephrotic syndrome [5]. Studies have shown that black people had more prevalence of focal segmental glomerular sclerosis and Asian people had more chances of minimal change disease, compared with Caucasian population [6,7]. For age classifications, the pathology of nephrotic syndrome differed between childhood and adulthood; meanwhile, nephrotic syndrome in adults had much more diverse group of diseases, less chance of minimal change disease, poor response to steroid treatment, and longer time to remission [8]. Furthermore, neonatal and childhood nephrotic syndrome had been found to be more frequently linked with monogenic defects [9]. Studies have identified potential environmental triggers of nephrotic syndrome, including exposure to mercury and its salts [10], secondary syphilis [11], aminonucleosides [12], and organic chemicals [13]. Genetic and environmental factors might affect phenotypic variability among nephrotic syndrome cases [14]. Thus, properly identifying potential environmental triggers of nephrotic syndrome is a key strategy in preventing the development of nephrotic syndrome.

Most identified environmental pathways of nephrotic syndrome have been through ingestion. However, recent studies have also shown that inhalation may be a potential pathway for nephrotic syndrome [15]. For example, Xu et al. showed that air pollution in Mainland China was associated with risk of membrane nephropathy [15]. Xu et al. found that the adjusted odds for membranous nephropathy increased 13% annually over the 11-year study period, whereas the proportions of other major glomerulopathies remained stable [15]. Furthermore, they reported that each $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration associated with 14% higher odds for MN in regions with $\text{PM}_{2.5}$ concentration $>70 \mu\text{g}/\text{m}^3$ [15]. Although researchers have comparatively analyzed average $\text{PM}_{2.5}$ concentrations and the occurrence of membrane nephropathy, data on the association between the composition of $\text{PM}_{2.5}$ and nephrotic syndrome are lacking. In recent decades, Taiwan has been under a transition period entailing the discovery and implementation of alternative energy resources for nuclear energy [16]. Currently, the majority of resources of electricity in Taiwan are from the Taichung coal-burning power plant, which is the top ten largest power plants in the world [17]. Furthermore, Taiwan has worse air pollution with increasing concentrations of $\text{PM}_{2.5}$ than before [17]. However, the association between air pollution $\text{PM}_{2.5}$ and nephrotic syndrome had not been investigated. Previous study has shown that SO_2 and NO_x acid gases were potential inflammation triggers and associated with autoimmune disease [18]. Since triggering autoimmunity is one of the pathogenic pathways of nephrotic syndrome [19], we used the National Health Insurance Research Database (NHIRD) to conduct a retrospective cohort study investigating whether $\text{PM}_{2.5}$ and acidic gases are associated with the occurrence of nephrotic syndrome in Taiwan.

2. Materials and Methods

2.1. Data Source

We conducted a population-based cohort study using the Longitudinal Health Insurance Database (LHID) and the Taiwan Air Quality-Monitoring Database (TAQMD). The details of the LHID and TAQMD have been well documented in previous studies [20,21]. We combined and stratified the LHID and the TAQMD by residential areas of insurants linked to nearby air quality-monitoring stations. Diagnoses associated with hospital use were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The participants were assigned to residential districts based on the clinic from where they most frequently sought treatment for acute upper respiratory infection. Thus, residential area was determined based on the clinic and hospital of the insurant when treated for acute upper respiratory tract infections (ICD-9-CM code 460). This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH104-REC2-115-CR2).

2.2. Sampled Participants

This study cohort was selected based on where the insureds lived on 1 January 2000, which was designated as the study's index date. We excluded insureds with a history of nephrotic syndrome (ICD-9-CM code 581) before the index date. The endpoint for follow-up was the date of withdrawal from the program, development of nephrotic syndrome (ICD-9-CM code 581), or 31 December 2011. A daily average air pollutant concentration was calculated from 1998 until the end of the observation year for each study subject. Air pollutant concentrations were grouped into four levels based on quartile: SO₂ concentration (first quartile [Q1]: <3.38, second quartile [Q2]: 3.38–4.31, third quartile [Q3]: 4.32–6.03, and fourth quartile [Q4]: >6.03 ppb), NO_x concentration (Q1: <23.4, Q2: 23.4–31.9, Q3: 32.0–38.6, and Q4: >38.6 ppb), NO concentration (Q1: <5.16, Q2: 5.16–8.57, Q3: 8.58–11.5, and Q4: >11.5 ppb), NO₂ concentration (Q1: <18.2, Q2: 18.2–23.6, Q3: 23.7–27.5, and Q4: >27.5 ppb), and PM_{2.5} concentration (Q1: <29.5, Q2: 29.5–33.2, Q3: 33.3–41.2, and Q4: >41.2 µg/m³). The confounding factors considered in this study were gender, age, monthly income, and urbanization level. The Institutes stratified Taiwan into 7 urbanization levels, based on not only scores of population density (people/km²) but also proportion of higher education, elderly and agricultural population, and the number of physicians per 100,000 people in each area. In our study, Level 1 represents areas with a higher population density and socioeconomic status, and Level 7 the lowest. Because few people lived in more rural areas of Levels 4–7, we therefore grouped these 4 types of areas into a Level “4”.

2.3. Statistical Analysis

Category variables, such as sex, monthly income, urbanization level, and outcome, are presented as numbers and percentages, and differences were assessed using a chi-squared test. The incidence density rate of nephrotic syndrome (per 10,000 person-years) was calculated at different air pollutant concentration levels. Univariable and multivariable Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for nephrotic syndrome in Levels Q2–Q4 for air pollutant concentration relative to the lowest level (Q1). The multivariable model was adjusted for age, sex, monthly income, and urbanization level. To address the concern of constant proportionality, we examined the proportional hazard model assumption using a test of scaled Schoenfeld residuals. There was no significant relationship between Schoenfeld residuals for SO₂, NO_x, NO, and NO₂ and follow-up time (*p*-value = 0.75, 0.48, 0.48, 0.66, respectively) in the model evaluating the nephrotic syndrome. In the model evaluating the nephrotic syndrome risk throughout overall follow-up period, results of the test revealed a significant relationship between Schoenfeld residuals for PM_{2.5} and follow-up time (*p*-value < 0.001), suggesting the proportionality assumption was violated. In the subsequent analyses, we stratified the follow-up duration to deal with the violation of proportional hazard assumption. Variables found to be significant in the univariable analysis were further included in the multivariable analysis. We further tested the interaction between air pollutant and confounders by including a cross-product term in the model. If the interaction was significant, we also put in the model for adjustment. All analyses were conducted using SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA), and the significance level was set at a two-tailed *P* less than 0.05.

3. Results

The present study included the follow-up data on 161,970 residents. After the 12-year follow-up, 776 participants developed nephrotic syndrome (Table 1). The mean age at enrollment was 40.5 ± 14.6, and men accounted for 43.8% of all participants. Most participants lived in moderately urbanized areas (32.5%). The daily average SO₂, NO_x, NO, NO₂, and PM_{2.5} concentrations were 4.98 ± 2.41 ppb, 36.3 ± 35.1 ppb, 11.0 ± 10.2 ppb, 22.6 ± 6.57 ppb, and 34.8 ± 8.76 µg/m³.

Table 1. Baseline demographics and exposure of air pollutants in Taiwan.

| N = 161,970 | | n | % |
|--|--|----------|------|
| Gender | Men | 70,948 | 43.8 |
| | Women | 91,022 | 56.2 |
| Age, years | mean, SD | 40.5 | 14.6 |
| Urbanization level | 1 (highest) | 55,898 | 34.5 |
| | 2 | 52,644 | 32.5 |
| | 3 | 27,407 | 16.9 |
| | 4 (lowest) | 26,020 | 16.1 |
| Exposure of air pollutants SO ₂ level (daily average, ppb) | mean, SD | 4.98 | 2.41 |
| | Min | 0.44 | |
| | Lower quartile | 3.38 | |
| | Median | 4.32 | |
| | Upper quartile | 6.03 | |
| | 90th percentile | 8.68 | |
| | Maximum | 14.1 | |
| | NO _x level (daily average, ppb) | mean, SD | 36.3 |
| | Min | 1.65 | |
| | Lower quartile | 23.4 | |
| | Median | 32.0 | |
| | Upper quartile | 38.6 | |
| | 90th percentile | 54.8 | |
| | Maximum | 426.7 | |
| NO level (daily average, ppb) | mean, SD | 11.0 | 10.2 |
| | Min | 0.32 | |
| | Lower quartile | 5.16 | |
| | Median | 8.58 | |
| | Upper quartile | 11.5 | |
| | 90th percentile | 24.1 | |
| NO ₂ level (daily average, ppb) | mean, SD | 22.6 | 6.57 |
| | Min | 0.85 | |
| | Lower quartile | 18.2 | |
| | Median | 23.7 | |
| | Upper quartile | 24.5 | |
| | 90th percentile | 30.6 | |
| PM _{2.5} level (daily average, µg/m ³) | mean, SD | 34.8 | 8.76 |
| | Min | 1.00 | |
| | Lower quartile | 29.5 | |
| | Median | 33.3 | |
| | Upper quartile | 41.2 | |
| | 90th percentile | 47.7 | |
| | Maximum | 113.2 | |
| Outcome | | | |
| Nephrotic syndrome | Yes | 776 | 0.48 |
| Follow-up time, years | mean, SD | 11.7 | 0.99 |

The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized. SO₂, sulfur dioxide; NO_x, nitrogen oxides; NO, nitrogen monoxide; NO₂, nitrogen dioxide; PM, particulate matter; PM_{2.5}, particles with aerodynamic diameter < 2.5 µm; SD, standard deviation.

Participants resided in the most highly urbanized towns exposed to the Q4 level including SO₂, NO_x, NO, NO₂, and PM_{2.5} (Table 2).

Table 2. Baseline urbanization level among quartiles of daily average concentration of air pollutants in Taiwan.

| Air Pollutant Concentration | Quartile 1 (Q1) (lowest) | | Quartile 2 (Q2) | | Quartile 3 (Q3) | | Quartile 4 (Q4) (highest) | | * <i>p</i> -Value |
|--|--------------------------|--------|-----------------|--------|-----------------|--------|---------------------------|--------|-------------------|
| N = 161,970 | n | (%) | n | (%) | n | (%) | n | (%) | |
| Sulfur dioxide (SO₂) | | | | | | | | | <0.001 |
| Urbanization level | | | | | | | | | |
| 1 (highest) | 12,662 | (29.9) | 13,928 | (36.4) | 19,315 | (41.6) | 9993 | (28.6) | |
| 2 | 13,428 | (31.7) | 11,114 | (29.1) | 13,820 | (29.8) | 14,282 | (40.8) | |
| 3 | 4829 | (11.4) | 5479 | (14.3) | 8887 | (19.2) | 8212 | (23.5) | |
| 4 (lowest) | 11,411 | (27.0) | 7721 | (20.2) | 4389 | (9.46) | 2499 | (7.14) | |
| Nitrogen oxides (NO_x) | | | | | | | | | <0.001 |
| Urbanization level | | | | | | | | | |
| 1 (highest) | 8667 | (22.4) | 10,836 | (25.2) | 10,950 | (32.5) | 25,445 | (54.6) | |
| 2 | 13,095 | (33.9) | 15,717 | (36.5) | 12,480 | (37.0) | 11,352 | (24.4) | |
| 3 | 4777 | (12.4) | 8540 | (19.9) | 7358 | (21.8) | 6732 | (14.5) | |
| 4 (lowest) | 12,101 | (31.3) | 7932 | (18.4) | 2934 | (8.70) | 3053 | (6.55) | |
| Nitrogen monoxide (NO) | | | | | | | | | <0.001 |
| Urbanization level | | | | | | | | | |
| 1 (highest) | 8329 | (21.0) | 9967 | (24.3) | 16,250 | (45.0) | 21,352 | (47.4) | |
| 2 | 13,887 | (35.0) | 13,634 | (33.2) | 11,368 | (31.5) | 13,755 | (30.5) | |
| 3 | 4255 | (10.7) | 10,186 | (24.8) | 5471 | (15.2) | 7495 | (16.6) | |
| 4 (lowest) | 13,244 | (33.4) | 7261 | (17.7) | 3035 | (8.40) | 2480 | (5.50) | |
| Nitrogen dioxide (NO₂) | | | | | | | | | <0.001 |
| Urbanization level | | | | | | | | | |
| 1 (highest) | 8313 | (23.1) | 11,056 | (23.4) | 21,609 | (45.0) | 14,920 | (48.7) | |
| 2 | 10,953 | (30.4) | 18,620 | (39.4) | 14,202 | (29.6) | 8869 | (29.0) | |
| 3 | 5454 | (15.1) | 7740 | (16.4) | 9075 | (18.9) | 5138 | (16.8) | |
| 4 (lowest) | 11,308 | (31.4) | 9850 | (20.8) | 3152 | (6.56) | 1710 | (5.58) | |
| Particulate matter (PM_{2.5}) | | | | | | | | | <0.001 |
| Urbanization level | | | | | | | | | |
| 1 (highest) | 22,062 | (47.4) | 14,301 | (40.2) | 10,754 | (27.5) | 8781 | (21.6) | |
| 2 | 13,032 | (28.0) | 10,350 | (29.1) | 13,593 | (34.7) | 15,669 | (38.5) | |
| 3 | 5443 | (11.7) | 6153 | (17.3) | 5749 | (14.7) | 10,062 | (24.7) | |
| 4 (lowest) | 6054 | (13.0) | 4733 | (13.3) | 9063 | (23.1) | 6170 | (15.2) | |

* Chi-square test. The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized. The daily average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant.

Table 3 shows the risk of nephrotic syndrome among levels of air pollutant concentrations. Relative to Q1-level SO₂, the subjects exposed at the Q4 level were associated with a 2.00-fold higher risk of nephrotic syndrome (adjusted HR = 2.00, 95% CI = 1.66–2.41). For NO_x, relative to Q1 NO_x concentrations, the adjusted HRs of nephrotic syndrome risk were 1.32 (95% CI = 1.00–1.73) for Q2 levels. For NO, relative to Q1 NO concentrations, the adjusted HRs of nephrotic syndrome risk were 1.34 (95% CI = 1.02–1.77) for Q2 levels. The data revealed an increasing trend for nephrotic syndrome risk correlating with increasing levels of PM_{2.5} concentrations. The adjusted HRs of nephrotic syndrome risk were 1.33 (95% CI = 0.91–1.93), 1.96 (95% CI = 1.08–3.55), and 2.53 (95% CI = 1.08–5.94) for subjects exposed to Q1-level PM_{2.5}, Q2-level PM_{2.5}, and Q3-level PM_{2.5}, respectively.

Table 4 shows the risk of nephrotic syndrome among levels of PM_{2.5} concentrations stratified by follow-up period. Relative to Q1-level PM_{2.5}, the subjects exposed at the Q4 level were associated with a 4.23-fold higher risk of nephrotic syndrome (adjusted HR = 4.23, 95% CI = 1.02–1.76) for the follow-up period ≤6 years. For PM_{2.5}, relative to Q1 PM_{2.5} concentrations, the adjusted HRs of nephrotic syndrome risk were 1.65 (95% CI = 1.04–2.61), 2.16 (95% CI = 1.02–4.55) for Q2 level and Q3 level.

Table 3. Differences in nephrotic syndrome incidences and associated HRs in participants exposed to various daily average concentrations of air pollutants.

| Pollutant Levels | N | Event | PY | IR | cHR | 95%CI | aHR | 95%CI |
|--------------------------------|--------|-------|---------|------|------|------------------|------|------------------|
| SO ₂ ¹ | | | | | | | | |
| Q1 | 42,331 | 184 | 493,552 | 3.73 | Ref. | | Ref. | |
| Q2 | 38,242 | 129 | 448,116 | 2.88 | 0.77 | (0.62, 0.97) | 0.80 | (0.64, 1.00) |
| Q3 | 46,411 | 179 | 543,975 | 3.29 | 0.88 | (0.72, 1.08) | 0.97 | (0.79, 1.20) |
| Q4 | 34,986 | 284 | 407,059 | 6.98 | 1.87 | (1.56, 2.25) *** | 2.00 | (1.66, 2.41) *** |
| NO _x ² | | | | | | | | |
| Q1 | 38,640 | 126 | 451,937 | 2.79 | Ref. | | Ref. | |
| Q2 | 43,026 | 207 | 503,906 | 4.11 | 1.47 | (1.18, 1.84) *** | 1.32 | (1.00, 1.73) * |
| Q3 | 33,722 | 154 | 395,166 | 3.90 | 1.40 | (1.10, 1.77) ** | 1.15 | (0.79, 1.68) |
| Q4 | 46,582 | 289 | 541,693 | 5.34 | 1.91 | (1.55, 2.36) *** | 1.41 | (0.89, 2.22) |
| NO ³ | | | | | | | | |
| Q1 | 39,715 | 127 | 465,107 | 2.73 | Ref. | | Ref. | |
| Q2 | 41,048 | 201 | 480,251 | 4.19 | 1.66 | (1.33, 2.07) *** | 1.34 | (1.02, 1.77) * |
| Q3 | 36,125 | 151 | 423,750 | 3.56 | 1.64 | (1.28, 2.09) *** | 1.12 | (0.76, 1.64) |
| Q4 | 45,082 | 297 | 523,594 | 5.67 | 2.49 | (2.01, 3.09) *** | 1.47 | (0.92, 2.35) |
| NO ₂ ⁴ | | | | | | | | |
| Q1 | 36,028 | 127 | 421,548 | 3.01 | Ref. | | Ref. | |
| Q2 | 47,267 | 228 | 553,336 | 4.12 | 1.37 | (1.10, 1.70) ** | 1.23 | (0.94, 1.61) |
| Q3 | 48,038 | 208 | 563,416 | 3.69 | 1.23 | (0.98, 1.53) | 1.02 | (0.69, 1.51) |
| Q4 | 30,637 | 213 | 354,402 | 6.01 | 2.00 | (1.61, 2.49) *** | 1.35 | (0.78, 2.33) |
| PM _{2.5} ⁵ | | | | | | | | |
| Q1 | 46,591 | 129 | 545,526 | 2.36 | Ref. | | Ref. | |
| Q2 | 35,537 | 126 | 416,539 | 3.02 | 1.28 | (1.00, 1.64) * | 1.33 | (0.91, 1.93) |
| Q3 | 39,160 | 212 | 457,761 | 4.63 | 1.96 | (1.57, 2.44) *** | 1.96 | (1.08, 3.55) * |
| Q4 | 40,682 | 309 | 472,877 | 6.53 | 2.77 | (2.26, 3.40) *** | 2.53 | (1.08, 5.94) * |

Q1 = first quartile. Q2 = second quartile. Q3 = third quartile. Q4 = fourth quartile. PY = person-years. IR = incidence rate, (per 10,000 person-years). cHR = crude hazard ratio. aHR = adjusted hazard ratio. CI = confidence interval. Ref. = reference group. ¹ Adjusted HR was calculated by Cox proportional hazard regression and adjusted for age, sex, monthly income, and urbanization level. ² Adjusted HR was calculated by Cox proportional hazard regression and adjusted for age, sex, monthly income, and urbanization level, and interaction of NO_x and monthly income. ³ Adjusted HR was calculated by Cox proportional hazard regression and adjusted for age, sex, monthly income, urbanization level, and interaction of NO and urbanization level. ⁴ Adjusted HR was calculated by Cox proportional hazard regression and adjusted for age, sex, monthly income, urbanization level, and interaction of NO₂ and monthly income. ⁵ Adjusted HR was calculated by Cox proportional hazard regression and adjusted for age, sex, monthly income, urbanization level, interaction of PM_{2.5} and age, interaction of PM_{2.5} and sex, interaction of PM_{2.5} and monthly income, and interaction of PM_{2.5} and urbanization level. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 4. Differences in nephrotic syndrome incidences and associated HRs in participants exposed to daily average concentrations of PM_{2.5} stratify by follow-up period.

| | cHR | 95%CI | aHR | 95%CI |
|-------------------------|------|------------------|------|----------------|
| PM_{2.5} | | | | |
| Follow-up period ≤ 6 | | | | |
| Q1 | Ref. | | Ref. | |
| Q2 | 0.63 | (0.38, 1.03) | 0.73 | (0.36, 1.44) |
| Q3 | 1.19 | (0.80, 1.78) | 1.53 | (0.55, 4.22) |
| Q4 | 3.31 | (2.38, 4.59) *** | 4.23 | (1.02, 17.6) * |
| Follow-up period > 6 | | | | |
| Q1 | Ref. | | Ref. | |
| Q2 | 1.67 | (1.25, 2.23) *** | 1.65 | (1.04, 2.61) * |
| Q3 | 2.42 | (1.85, 3.15) *** | 2.16 | (1.02, 4.55) * |
| Q4 | 2.45 | (1.88, 3.19) *** | 1.93 | (0.66, 5.68) |

Q1 = first quartile. Q2 = second quartile. Q3 = third quartile. Q4 = fourth quartile. cHR = crude hazard ratio. aHR = adjusted hazard ratio of a multivariate analysis, after adjustment for age, sex, monthly income, urbanization level, interaction of PM_{2.5} and age, interaction of PM_{2.5} and sex, interaction of PM_{2.5} and monthly income, and interaction of PM_{2.5} and urbanization level. CI = confidence interval. Ref. = reference group. * $p < 0.05$; *** $p < 0.001$.

4. Discussion

This study clearly demonstrated that increased exposure to increasing quartile concentrations of PM_{2.5}, SO₂, NO_x, and NO were associated with increased risk of nephrotic syndrome in Taiwan. However, the underlying mechanism remains to be investigated; nevertheless, several pathways might explain this finding. First, whatever the pathologic pattern of nephrotic syndrome is, the mechanism of nephrotic syndrome is believed to be associated with autoimmunity [22]. Autoimmunity triggers the production of circulating autoantibodies. Such autoantibodies may target either the components of the glomerulus directly, forming the immune complex in situ, or ubiquitous antigens of systemic autoimmune disease, forming circulating complexes that are deposited in the glomerulus [23]. A previous study found that changes to the charge of the immune complex altered the glomerulus barrier and may contribute to nephrotic syndrome [24]. Air pollution has been closely related to chronic airway diseases, including asthma and chronic obstructive pulmonary disease [25]. Air pollution has recently also been associated with systemic autoimmune diseases [26], intestinal diseases [27], and diabetes mellitus [28], in which alterations in autoimmunity play a role. Air pollution has been found to induce oxidative-stress DNA damage [29], and such DNA damage could contribute to the development of autoimmunity [30]. Van Eeden et al. found that air pollution increased levels of interleukin (IL)-6, IL-1 β , macrophage inflammatory protein-1 α (MIP-1 α), granulocyte macrophage colony-stimulating factor (GM-CSF), and circulating levels of IL-1 β , IL-6, and GM-CSF [31]. These cytokines have previously been associated with the development of nephrotic syndrome [32–34]. Thus, air pollution PM_{2.5} might increase systemic oxidative-stress [18] and inflammatory response, triggering autoimmunity and thus altering the barrier of the glomerulus to increase occurrences of nephrotic syndrome.

Furthermore, increasing quartile concentrations of SO₂, NO_x, NO₂, and NO were associated with higher incidences of nephrotic syndrome. Bernatsky et al. found that industrial emitters of sulfur dioxide were associated with increased anticitrullinated antibody (ACPA) positivity [35]. In addition, Franze et al. noted that abundant nitrogen oxide air pollutants promoted protein nitration [36]. Nitrated protein, which is an inflammatory-associated product [37], is associated with loss of immune tolerance [38] and triggers autoimmunity [39,40]. We hypothesize that the aforementioned pathways may also contribute to the increased incidences of nephrotic syndrome. This is the first study to examine the association between nephrotic syndrome and increasing quartile concentrations of SO₂, NO_x, NO₂, and NO.

Several similarities and differences should be mentioned between our study and the study of Xu et al. [15]. First, this study is a 12-year nationwide study, which is slightly longer than that of Xu et al. [15]. Second, we used quartile concentrations to examine correlations with the incidence of nephrotic syndrome. This strategy could alleviate possible bias, such as biopsy rates and urbanization. Furthermore, our results are robust irrespective of whether the trends of nephrotic syndrome are increasing or decreasing. Third, because the development of nephrotic syndrome would need an incubation period, correlating the quartile concentrations of air pollution with nephrotic syndrome would be more appropriate to examine the association between air pollution and nephropathy. Fourth, we analyzed the trends for quartile air pollution concentrations with nephrotic syndrome. Our results demonstrate that a clear dose–response relationship exists between air pollution and nephrotic syndrome. Finally, Taiwan researchers have found an association of osteoporosis and rheumatic diseases with air pollution PM_{2.5} [18,19]. Our and the above studies showed that air pollution has threatened the general health of Taiwan citizens [18,19]. Since Taiwan is a country with the top three highest incidence of renal disease in the world [41], our study might provide implications for public health impacts and policy, such as shortening the period of finding alternative power sources and setting national alarm systems for air quality.

Several limitations of this study should also be mentioned. First, the information regarding family history, past atypical infection, viral infection, specific diet preference, over-the-counter medication use (including nonsteroidal anti-inflammatory drugs), and exposure to gold salts, which are potential

risk factors of nephrotic syndrome, are unavailable in the NHIRD. Second, we analyzed the serial concentration of fine-particulate air pollution (PM_{2.5}), but information about individual exposure to fine-particulate PM_{2.5} was unavailable. Some participants may have worn an N95 mask, used an air cleaner while inside, or avoided outdoor activities during periods of serious air pollution, thus lessening personal contact with PM_{2.5}. Additionally, some participants might have had increased PM_{2.5} exposure due to their occupations and working environments. Because there would be variations in pollutant levels among these cities, bias from regional differences would exist and possible baseline bias may also exist in this study. Third, information about single-nucleotide polymorphisms, including variants of the nephrin gene (NPHS1) [42], GPC5 [43], PLCE1 [44], and PLA2R1 [45] are unavailable in NHIRD.

5. Conclusions

In conclusion, this study reported an association between fine-particulate air pollution PM_{2.5} and occurrences of nephrotic syndrome, suggesting that air pollution might cause nephrotic syndrome. Additional studies are required to investigate whether avoiding exposure to PM_{2.5} could lessen the risks or delay the progression of nephrotic syndrome.

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