Article

Air Pollution Exposure and Risk of Spontaneous Pneumothorax in Children: A Longitudinal, Nationwide Study

Jing-Cheng Wang 1, Cheng-Li Lin 2, Chieh-Ho Chen 1 and Chien-Heng Lin 1,3,*

1 Division of Pediatrics Pulmonology, China Medical University Children’s Hospital, Taichung 404327, Taiwan; fcwelldone@gmail.com (J.-C.W.); d30270@mail.cmuh.org.tw (C.-H.C.)
2 Management Office for Health Data, China Medical University Hospital, Taichung 404327, Taiwan; orangechengli@gmail.com
3 Department of Biomedical Imaging and Radiological Science, College of Medicine, China Medical University, Taichung 404328, Taiwan
* Correspondence: lch227@ms39.hinet.net

Abstract: Spontaneous pneumothorax (SP) involves the spontaneous appearance of air in the pleural space. Atmospheric pressure, temperature change, and seasonal factors may precipitate SP, but its association with air pollution remains unclear. Therefore, we conducted this nationwide, retrospective population-based study to evaluate the risk of SP in Taiwanese children exposed to air pollution. We collected data on SP incidence from the Longitudinal Health Insurance Database; the Taiwan Air Quality-Monitoring Database provided daily concentrations of nitric oxide (NO), nitrogen dioxide (NO$_2$), and hydrocarbons in 2000–2012. SP risk was evaluated for four quartiles (Q1, Q2, Q3, Q4). The NO adjusted hazard ratios (aHRs) for Q2, Q3, and Q4 compared to Q1 were 1.11 (95% confidence interval (CI): 0.77–1.61), 1.24 (95% CI: 0.88–1.76), and 1.66 (95% CI: 1.17–2.34), respectively. The NO$_2$ aHRs for Q2, Q3, and Q4 were 1.12 (95% CI: 0.77–1.64), 1.31 (95% CI: 0.90–1.90), and 1.51 (95% CI: 1.04–2.19), respectively. Hydrocarbons aHRs for Q2, Q3, and Q4 were 0.87 (95% CI: 0.64–1.18), 1.16 (95% CI: 0.90–1.49), and 1.40 (95% CI: 1.06–1.85), respectively. Increased exposure to NO, NO$_2$, and hydrocarbons is associated with increased SP risk in Taiwanese children.

Keywords: air pollution; spontaneous pneumothorax; children; nitric oxides; hydrocarbons

1. Introduction

Long-term ambient air pollution is associated with an increased risk of respiratory, cardiovascular and cerebrovascular diseases [1,2]. Respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma may be exacerbated by air pollution; air pollution may also increase morbidity and mortality associated with respiratory diseases [3]. The health effects of air pollution depend on the components and sources of pollutants, which vary with countries, seasons, and times.

Spontaneous pneumothorax (SP) is defined as the spontaneous appearance of air in the pleural space of a patient. SP is caused by the rupture of blebs or emphysematous bullae that develop just beneath the pulmonary pleura. Although the pathogenic mechanisms of SP remain unclear, there is epidemiological evidence of a significant association between the risk of SP and exposure to environmental factors, such as cigarette smoke and meteorological conditions [4–8]. Some studies have suggested that atmospheric pressure, temperature changes, and specific weather phases may be precipitating factors in the development of SP [9,10]. Han et al. found that air pollution exposure, especially pollution containing particulate matter (PM), increased hospital visits due to SP [11]; however, a recent study by Marx et al. found no connection between exposure to NO$_2$ or PM with diameters ≤10 μm (PM$_{10}$) and primary SP but did identify an association between SP and O$_3$ exposure [12]. In summary, the association between air pollution and SP remains unclear and debatable.
Therefore, we conducted this nationwide, retrospective study to evaluate the effect of air pollution exposure on the risk of SP in Taiwanese children.

2. Patients and Methods

We conducted a population-based cohort study using the file on children (aged < 18 years) that is part of the database of citizens enrolled in the Taiwan National Health Insurance (NHI) program [13] and the Taiwan Air Quality-Monitoring Database (TAQMD), which is released by the Taiwan Environmental Protection Agency. Details on the file on children and the TAQMD have been provided in previous studies [14–16]. We combined the pediatric file and the TAQMD by linking the residential areas of insured with nearby 74 air-quality-monitoring stations. The clinics and hospitals in various residential areas were identified, and the study was based on the records of insured children treated for acute upper respiratory tract infections (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM code 460). This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CRREC-103-048).

This study selected a cohort of children younger than 18 years on January 1, 2000 (the index date). We excluded children with a history of pneumothorax (ICD-9-CM codes 512.0, 512.1, 512.2, 512.8) before the index date. The person-years in the follow-up period were counted for each child until they withdrew from the NHI program, expired, developed pneumothorax, or until 31 December 2012. A daily average air pollutant concentration was calculated from 2000 until the end of the observation year for each study subject. Air pollutant concentrations were grouped into four quartiles: nitric oxide (NO) concentration (Q1: <5.18 parts per billion (ppb), Q2: 5.18–8.44 ppb, Q3: 8.44–11.6 ppb, and Q4: >11.6 ppb), nitrogen dioxide (NO\(_2\)) concentration (Q1: <18.2 ppb, Q2: 18.2–23.7 ppb, Q3: 23.7–26.9 ppb, and Q4: >26.9 ppb), and total hydrocarbons concentration (Q1: <2.29 parts per million (ppm), Q2: 2.29–2.37 ppm, Q3: 2.37–2.60 ppm, and Q4: >2.60 ppm). Confounding factors in the study were sex, age, monthly income, and urbanization level.

Age data are presented as mean ± standard deviation and were compared with different air pollutant concentration levels using one-way analysis of variance. Numbers and percentages are presented by air pollutant concentration level for categorical variables such as sex, monthly income, urbanization level, and outcome (pneumothorax); differences were assessed by the Chi-square test. The NHI has stratified all city districts and townships in Taiwan into 7 urbanization levels, based on population density (people/km\(^2\)), proportion of residents with higher education, elderly and agricultural population, and the number of physicians per 100,000 people in each area [17]. Level 1 represented areas with a higher population density and socioeconomic status, and level 7 represented the lowest. As few people lived in the more rural areas of levels 4–7, our study grouped these areas into the level 4 group. The incidence density rate of pneumothorax (per 10,000 person-years) was calculated by air pollutant concentration level.

Univariable and multivariable Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for pneumothorax at Q2–Q4 air pollutant concentrations compared with the reference point (Q1). The multivariable model was adjusted for age, sex, monthly income, and urbanization level. This type of statistical model can be used to assess the relationship between multiple variables, allowing for the assessment of independent relationships while also adjusting for potential confounders. We have used age as a continuous variable in the models, whereas sex, monthly income, and urbanization were applied as categorical variables.

All analyses were conducted using SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA), and the significance level was set at a 2-tailed \( p < 0.05 \).

3. Results

Table 1 presents data for children according to the level of exposure to NO. The daily average NO concentration was 12.7 ± 10.8 ppb (data not shown). The mean age of children located in the highest concentration areas (Q4) of NO was highest at 7.06 ± 3.66 years; 52.1% of children were exposed to Q2 levels of NO. Children exposed to the highest
NO concentrations were more likely to have higher monthly incomes, live in higher urbanization areas, and have higher frequencies of pneumothorax than other groups.

**Table 1.** Characteristics of participants exposed to various annual average concentrations of nitric oxide.

| Nitric Oxide (n = 255,380) | Quartile 1 (Q1) (Lowest) n = 34,316 | Quartile 2 (Q2) n = 56,629 | Quartile 3 (Q3) n = 85,060 | Quartile 4 (Q4) (Highest) n = 79,375 | p-Value |
|-----------------------------|-------------------------------------|-----------------------------|----------------------------|-------------------------------------|---------|
| **Variable**                | n %                                 | n %                         | n %                        | n %                                 |         |
| Age (mean, SD)              | 6.24 3.38                           | 6.03 3.05                   | 6.19 3.25                  | 7.06 3.66                           | <0.001  |
| Boys                        | 17,773 51.8                         | 29,497 52.1                 | 44,085 51.8                | 40,487 51.0                         | <0.001  |
| Monthly income (NTD)        |                                     |                             |                            |                                     | <0.001  |
| <14,400                     | 29,415 85.7                         | 48,268 85.2                 | 72,151 84.8                | 64,004 80.6                         |         |
| 14,400–18,300               | 3308 9.64                           | 5992 10.6                   | 9669 11.4                  | 10,586 13.3                         |         |
| 18,300–21,000               | 722 2.10                            | 1161 2.05                   | 1553 1.83                  | 2151 2.71                           |         |
| ≥21,000                     | 871 2.54                            | 1208 2.13                   | 1687 1.98                  | 2634 3.32                           |         |
| Urbanization level          |                                     |                             |                            |                                     | <0.001  |
| 1 (highest)                 | 4528 13.2                           | 11,994 21.2                 | 30,638 36.0                | 37,804 47.6                         |         |
| 2                           | 12,224 35.6                         | 17,210 30.4                 | 29,413 34.6                | 22,852 28.8                         |         |
| 3                           | 3508 10.2                           | 14,780 26.1                 | 16,822 19.8                | 13,317 16.8                         |         |
| 4 (lowest)                  | 14,056 41.0                         | 12,645 22.3                 | 8187 9.62                  | 5402 6.81                           |         |
| Outcome                     |                                     |                             |                            |                                     | <0.001  |
| Pneumothorax (ICD-9-CM 512.0, 512.8) | 43 0.13                   | 83 0.15                    | 140 0.16                   | 173 0.22                            |         |

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; NTD: new Taiwan dollar; SD: standard deviation.

The average daily NO\textsubscript{2} concentration was 24.4 ± 5.57 ppb (data not shown). The mean age was highest (6.70 ± 3.55 years) among children exposed to Q4 levels of NO\textsubscript{2} (Table 2). Boys accounted for 52.3% of children exposed to Q1 NO\textsubscript{2} concentrations. Children exposed to Q1 levels of NO\textsubscript{2} had the highest percentage of children in the lowest income group. Children exposed to Q4 NO\textsubscript{2} concentrations had the highest percentage of children living in highly urbanized areas, as well as the highest frequency of pneumothorax.

**Table 2.** Characteristics of participants exposed to various annual average concentrations of nitrogen dioxide.

| Nitric Dioxide (n = 255,380) | Quartile 1 (Q1) (Lowest) n = 29,082 | Quartile 2 (Q2) n = 70,475 | Quartile 3 (Q3) n = 72,168 | Quartile 4 (Q4) (Highest) n = 83,655 | p-Value |
|-----------------------------|-------------------------------------|-----------------------------|----------------------------|-------------------------------------|---------|
| **Variable**                | n %                                 | n %                         | n %                        | n %                                 |         |
| Age (mean, SD)              | 6.05 3.12                           | 6.24 3.33                   | 6.46 3.31                  | 6.70 3.55                           | <0.001  |
| Boys                        | 15,221 52.3                         | 36,631 52.0                 | 37,315 51.7                | 42,675 51.0                         | <0.001  |
| Monthly income (NTD)        |                                     |                             |                            |                                     | <0.001  |
| <14,400                     | 24,975 85.9                         | 59,736 84.8                 | 60,077 83.3                | 69,050 82.5                         |         |
| 14,400–18,300               | 2909 10.0                           | 7594 10.8                   | 8986 12.5                  | 10,066 12.0                         |         |
| 18,300–21,000               | 587 2.02                            | 1435 2.04                   | 1533 2.12                  | 2032 2.43                           |         |
| ≥21,000                     | 611 2.10                            | 1710 2.43                   | 1572 2.18                  | 2507 3.00                           | <0.001  |
| Urbanization level          |                                     |                             |                            |                                     | <0.001  |
| 1 (highest)                 | 3740 12.9                           | 14,772 21.0                 | 23,335 32.3                | 43,117 51.5                         |         |
| 2                           | 7652 26.3                           | 25,083 35.6                 | 26,300 36.4                | 22,664 27.1                         |         |
| 3                           | 4730 16.3                           | 14,864 21.1                 | 16,454 22.8                | 12,379 14.8                         |         |
| 4 (lowest)                  | 12,960 44.6                         | 15,756 22.4                 | 6079 8.42                  | 5495 6.57                           |         |
| Outcome                     |                                     |                             |                            |                                     |         |
| Pneumothorax (ICD-9-CM 512.0, 512.8) | 39 0.13                   | 103 0.15                    | 127 0.18                   | 170 0.20                            | <0.001  |

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; NTD: new Taiwan dollar; SD: standard deviation.
The average daily total hydrocarbons concentration was 2.42 ± 0.23 ppm (data not shown). The mean age was highest (7.74 ± 3.84 years) among children exposed to Q4 concentrations of hydrocarbons, as was the percentage of girls (49.5%) (Table 3). Among children exposed to Q4 hydrocarbon levels, 49.9% lived in the most highly urbanized areas, as opposed to 6.43% in the least urbanized areas. Children exposed to Q1 levels of hydrocarbons reported a lower monthly income. Children exposed to the Q4 levels of total hydrocarbons had the highest frequency of pneumothorax among all groups.

Table 3. Characteristics of participants exposed to various annual average concentrations of total hydrocarbons.

| Variable                        | Quartile 1 (Q1) (Lowest) n = 67,078 | Quartile 2 (Q2) n = 50,365 | Quartile 3 (Q3) n = 85,457 | Quartile 4 (Q4) (Highest) n = 52,480 | p-Value |
|---------------------------------|--------------------------------------|---------------------------|---------------------------|--------------------------------------|---------|
| Age (mean, SD)                  | 5.51 ± 2.60                          | 5.54 ± 2.73               | 6.88 ± 3.62               | 7.74 ± 3.84                          | <0.001  |
| Boys                            | 35,017 (52.2%)                       | 26,114 (51.9%)            | 44,211 (51.7%)            | 26,500 (50.5%)                       | <0.001  |
| Monthly income (NTD)            | <0.001                               |                           |                           |                                      |         |
| <14,400                         | 59,734 (89.1%)                       | 44,650 (88.7%)            | 69,566 (81.4%)            | 39,888 (76.0%)                       |         |
| 14,400–18,300                   | 5685 (8.48%)                         | 4133 (8.21%)              | 11,170 (13.1%)            | 8567 (16.3%)                         |         |
| 18,300–21,000                   | 885 (1.32%)                          | 769 (1.53%)               | 2126 (2.49%)              | 1807 (3.44%)                         |         |
| ≥21,000                         | 774 (1.15%)                          | 813 (1.61%)               | 2595 (3.04%)              | 2218 (4.23%)                         | <0.001  |
| Urbanization level              |                                      |                           |                           |                                      | <0.001  |
| 1 (highest)                     | 18,901 (28.2%)                       | 11,346 (22.5%)            | 28,534 (33.4%)            | 21,683 (49.9%)                       |         |
| 2                               | 16,335 (24.4%)                       | 19,771 (39.3%)            | 29,906 (35.0%)            | 15,669 (29.9%)                       |         |
| 3                               | 15,490 (23.1%)                       | 8003 (15.9%)              | 17,680 (20.7%)            | 7254 (13.8%)                         |         |
| 4 (lowest)                      | 16,334 (24.4%)                       | 11,245 (22.3%)            | 9337 (10.9%)              | 3374 (6.43%)                         |         |
| Pneumothorax (ICD-9-CM 512.0, 512.8) | 106 (0.16%)                         | 68 (0.14%)                | 153 (0.18%)               | 112 (0.21%)                         | <0.01   |

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; NTD: new Taiwan dollar; SD: standard deviation.

Table 4 presents the risks of pneumothorax by the level of air pollutant concentration. The incidence rate of pneumothorax increased with increasing NO and NO2 concentrations. The NO adjusted hazard ratios (aHRs) for Q2, Q3, and Q4, when compared with Q1, were 1.11 (95% confidence interval CI: 0.77–1.61), 1.24 (95% CI: 0.88–1.76), and 1.66 (95% CI: 1.17–2.34), respectively. The NO2 aHRs for Q2, Q3, and Q4 were 1.12 (CI: 0.77–1.64), 1.31 (95% CI: 0.90–1.90), and 1.51 (95% CI: 1.04–2.19), respectively. Hydrocarbons aHRs for Q2, Q3, and Q4 were 0.87 (95% CI: 0.64–1.18), 1.16 (95% CI: 0.90–1.49), and 1.40 (95% CI: 1.06–1.85), respectively.

Participants exposed to Q4 levels of NO had a 1.66-fold higher risk of pneumothorax than those exposed to Q1 levels, while those exposed to Q4 levels of NO2 were 1.51 times more likely than those exposed to Q1 levels to suffer a pneumothorax. Those exposed to Q4 hydrocarbon levels had a 1.40-fold higher risk of pneumothorax than those exposed to Q1 levels.
Table 4. Comparisons of pneumothorax incidence and associated hazard ratios by average annual concentration of air pollutants.

| Pollutant | Levels  | Event | PY    | IR   | cHR   | 95% CI          | aHR   | 95% CI          |
|-----------|---------|-------|-------|------|-------|-----------------|-------|-----------------|
| NOQ1: <5.18 ppb | 34,316  | 43    | 375,702 | 1.14 | Ref.  | Ref.            | Ref.  | Ref.            |
| Q2: 5.18–8.44 ppb | 56,629  | 83    | 634,501 | 1.31 | 1.14  | (0.79, 1.64)    | 1.11  | (0.77, 1.61)    |
| Q3: 8.44–11.6 ppb | 85,060  | 140   | 939,106 | 1.49 | 1.30  | (0.93, 1.83)    | 1.24  | (0.88, 1.76)    |
| Q4: >11.6 ppb | 79,375  | 173   | 816,112 | 2.12 | 1.99  | (1.42, 2.78)**  | 1.66  | (1.17, 2.34)**  |
| NO2Q1: <18.2 ppb | 29,082  | 39    | 324,172 | 1.20 | Ref.  | Ref.            | Ref.  | Ref.            |
| Q2: 18.2–23.7 ppb | 70,475  | 103   | 773,695 | 1.33 | 1.11  | (0.77, 1.60)    | 1.12  | (0.77, 1.64)    |
| Q3: 23.7–26.9 ppb | 72,168  | 127   | 781,264 | 1.63 | 1.39  | (0.97, 1.99)    | 1.31  | (0.90, 1.90)    |
| Q4: >26.9 ppb | 83,655  | 170   | 886,289 | 1.92 | 1.66  | (1.17, 2.35)**  | 1.51  | (1.04, 2.19)*   |
| Hydrocarbons | Total |       |       |      |       |                 |       |                 |
| Q1: <2.29 ppm | 67,078  | 106   | 782,116 | 1.36 | Ref.  | Ref.            | Ref.  | Ref.            |
| Q2: 2.29–2.37 ppm | 50,365  | 68    | 584,105 | 1.16 | 0.86  | (0.63, 1.17)    | 0.87  | (0.64, 1.18)    |
| Q3: 2.37–2.60 ppm | 85,457  | 153   | 890,724 | 1.72 | 1.40  | (1.09, 1.79)**  | 1.16  | (0.90, 1.49)    |
| Q4: >2.60 ppm | 52,480  | 112   | 508,476 | 2.20 | 1.95  | (1.49, 2.54)**  | 1.40  | (1.06, 1.85)*   |

*: <0.05; **: <0.01; ***: <0.001.

4. Discussion

In this nationwide retrospective cohort study, the participants exposed to increasing levels of nitric oxides (NOx) and total hydrocarbons were at increased risk of spontaneous pneumothorax.

Pneumothorax is due to the spontaneous rupture of subpleural blebs or bullae [18]. Subpleural blebs and bullae are found in the lung apices at thoracoscopy and on computed tomography scanning in up to 90% of cases of SP [19], compared with 20% of controls matched for age and smoking status [20]. Even among nonsmokers with a history of pneumothorax, 81% have bullae [21]. The development of blebs or bullae may be linked to a variety of factors, including distal airway inflammation [22], hereditary predisposition [23], anatomical abnormalities of the bronchial tree [24], apical ischemia at the apices [25,26], low body mass index and caloric restriction [27], and abnormal connective tissue [28]. Air pollution contributes to worsening chronic inflammation of the lung and may eventually lead to SP. Rapid changes in environmental conditions may be a precipitating factor in the development of SP. Previous studies have suggested an association between SP and changes in meteorological conditions. One study reported increases in SP were associated with days having significantly higher wind speeds and lower atmospheric pressures [29]. In Japan, the temperature was linked to SP events [30,31]. Environmental factors such as NO2, ozone (O3), and carbon dioxide concentrations are reported to influence the onset of SP, as are viral epidemics occurring in autumn or spring (adenovirus, rhinovirus, etc.) that may increase the frequency of SP by inducing hyperreactivity cough [10,32]. Bertolaccini et al. found that SP (first episode or relapse, without age selection) occurs in clusters and is significantly more likely on warm, windy days with low atmospheric pressure and high mean NO2 concentrations [33,34]. However, those studies had potential limitations, such as a small study size and lack of age selection.

The term NOx describes a mixture of nitric oxide (NO) and NO2. Most NOx is present as NO, but this species is readily oxidized to NO2 by reaction with O3, so NOx levels are similar to standard values for NO2. Nitric oxides in the air can irritate the eyes, nose, throat, and lungs. It inflames the lining of the lungs, and it can reduce immunity to lung infections. This may worsen cough and wheezing, reduce lung function, and increase asthma attacks [33]. Moreover, it may also result in fluid build-up in the lungs 1 or 2 days after exposure. The health effects of hydrocarbons have been noted in occupational exposures to tetra methyl lead, benzene, and other substances. Inhalation of hydrocarbons...
can also cause irritation, and hydrocarbons are major contributors to eye and respiratory irritation caused by photochemical smog. A study of rats exposed to hydrocarbons revealed a history of lung edema and hemorrhagic necrosis of lung alveoli and parenchyma [34]. The evidence suggested that this was the result of damage to the antioxidant defense system with consequential loss of cell and tissue surfactant. Further animal evidence of lung pathology associated with exposure to hydrocarbons revealed the rupture of alveoli and terminal bronchioles [35]. It is not clear whether this pathology is related to hydrocarbon toxicity, the consequence of increased intraluminal pressure, or both. Both NOx and hydrocarbons in the air can damage the lung and cause bullae to rupture more easily, thereby increasing the risk of SP.

Several previous studies have indicated that exposure to air pollutants such as NO\textsubscript{2}, PM and O\textsubscript{3} might induce systemic inflammation [11,12]. Air pollutants such as NO and hydrocarbon may enter the pleural space through various mechanisms: direct alveolar rupture (as in emphysema or necrotic pneumonia) via the lung interstitium or backward via the bronchovascular bundle and mediastinal pleura (pneumomediastinum).

In our study, we assessed participants who were younger than 18 years. To the best of our knowledge, our study is the first study in the literature to evaluate the link between childhood SP and air pollution. As COPD does not occur in individuals in this age group, and these participants had no history of asthma, confounding factors associated with these two diseases were excluded. The confounding factors considered in this study were age, sex, monthly income, and urbanization level. We used a multivariable model to assess the relationships between multiple variables, which allowed us to assess independent relationships while adjusting for these four confounders. Our findings showed that these confounding factors rarely influenced the outcomes of our study, with male adolescence (age of 10–18 years) identified as the only factors likely to increase the risk of subsequent SP events, which has been previously identified.

We defined the areas of the subjects according to the location of the clinics where they most frequently sought treatment for acute upper respiratory tract infections. Furthermore, we used urbanization as a covariate in a multivariate analysis model, in addition to controlling for the influences of available medical resources and social status. Although differences in urbanization levels among towns throughout Taiwan were considered, potential bias may have resulted from defining the active area according to the location of medical institutions where residents sought acute upper respiratory tract infection treatment. Healthy residents are more likely to be exposed to the lowest levels of air pollution, and this may have led to the underestimation of SP risk.

The main limitation of this study was the lack of detail on the clinical histories, including body weight, height, and smoking history. It is known that smoking is a risk factor for SP, but we were unable to determine if these patients had a smoking history or if they had been exposed to smoking environments. The severity of SP was also unknown in our study, or if it was related to the severity of air pollution. Meteorological conditions such as temperature, atmospheric pressure, and rainfall may be related to the onset of SP but were not recorded in the LHID. Therefore, further investigation is warranted.

5. Conclusions

In summary, we observed an increasing trend in the relationship between air pollution levels and the risk of SP among children. Exposure to the highest level of NOx and hydrocarbons may increase the risk of SP in the Taiwanese pediatric population. Comparisons of the impacts of air pollution between children and adults represent a potential direction for future study.

**Author Contributions:** Conceptualization, J.-C.W. and C.-H.L.; Methodology, C.-L.L.; Software, C.-L.L. and C.-H.C.; Validation, J.-C.W. and C.-L.L.; Formal Analysis, C.-L.L.; Investigation, C.-H.L.; Resources, J.-C.W. and C.-H.C.; Data Curation, C.-H.C.; Writing—Original Draft Preparation, J.-C.W.; Writing—Review and Editing, C.-H.L.; Visualization, J.-C.W.; Supervision, C.-H.L.; Project Administration, C.-H.L. All authors have read and agreed to the published version of the manuscript.
**Funding:** This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW108-TDU-B-121-133004), China Medical University Hospital, Academia Sinica Stroke Biosignature Project (BM1070101021), MOST Clinical Trial Consortium for Stroke (MOST 107-2321-B-039 -004 -Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

**Institutional Review Board Statement:** After a full description of the study, written informed consent of participation was obtained from the legal guardians. The study protocol was approved by the Ethics Review Board of the China Medical University ethics committee (Approval # CRREC-103-048).

**Informed Consent Statement:** Patient consent was waived due to the retrospective nature of this study.

**Data Availability Statement:** The data are not publicly available due to ethical restrictions.

**Acknowledgments:** We would like to thank the China Medical University Hospital Medical Research Department (DMR-111-070) for providing support and assistance for this work.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Alamanos, Y.; Drosos, A.A. Epidemiology of adult rheumatoid arthritis. *Autoimmun. Rev.* 2005, 4, 130–136. [CrossRef]

2. Beckerman, B.S.; Jerrett, M.; Finkelstein, M.; Kanaroglou, P.; Brook, J.R.; Arain, M.A.; Sears, M.R.; Stieb, D.; Balmes, J.; Chapman, K. The association between chronic exposure to traffic-related air pollution and ischemic heart disease. *J. Toxicol. Environ. Health Part A* 2012, 75, 402–411. [CrossRef]

3. Kelly, F.J.; Fussell, J.C. Air pollution and airway disease. *Clin. Exp. Allergy* 2011, 41, 1059–1071. [CrossRef]

4. Ozpolat, B.; Gozubuyuk, A.; Kocer, B.; Yazkan, R.; Dural, K.; Genc, O. Meteorological conditions related to the onset of spontaneous pneumothorax. *Tohoku J. Exp. Med.* 2009, 217, 329–334. [CrossRef]

5. Smit, H.J.; Deville, W.L.; Schramel, F.M.; Schreurs, J.M.; Sutedja, T.G.; Postmus, P.E. Atmospheric pressure changes and outdoor temperature changes in relation to spontaneous pneumothorax. *Chest* 1999, 116, 676–681. [CrossRef]

6. Bulajich, B.; Subotich, D.; Mandarich, D.; Kljajich, R.V.; Gajich, M. Influence of atmospheric pressure, outdoor temperature, and weather phases on the onset of spontaneous pneumothorax. *Ann. Epidemiol.* 2005, 15, 185–190. [CrossRef]

7. Alifano, M.; Forti Parri, S.N.; Bonfanti, B.; Arab, W.A.; Passini, A.; Boaron, M. Atmospheric pressure influences the risk of pneumothorax: Beware of the storm! *Chest* 2007, 131, 1877–1882. [CrossRef]

8. Bense, L. Spontaneous pneumothorax related to falls in atmospheric pressure. *Eur. J. Resp. Dis.* 1984, 65, 544–546. [CrossRef]

9. Bense, L.; Ecklund, G.; Wiman, L.G. Smoking and the increased risk of contracting spontaneous pneumothorax. *Chest* 1987, 92, 1009–1012. [CrossRef]

10. Bertolaccini, L.; Alemanno, L.; Rocco, G.; Cassardo, C. Air pollution, weather variations and primary spontaneous pneumothorax. *J. Thorac. Dis.* 2010, 2, 9–15. [CrossRef]

11. Han, C.; Lim, Y.H.; Jung, K.; Hong, Y.C. Association between ambient air pollution exposure and spontaneous pneumothorax occurrence. *Epidemiology* 2019, 30 (Suppl. S1), S48–S56. [CrossRef]

12. Marx, T.; Bernard, N.; Parmentie, A.L.; Puyraveau, M.; Martin, B.; Pretalli, J.B.; Dalphin, J.-C.; Mauny, F.; Desmettre, T. Short term association between air pollution (PM_{10}, NO_{2} and O_{3}) and secondary spontaneous pneumothorax. *Sci. Rep.* 2020, 16, 11823. [CrossRef]

13. National Health Research Institute. National Health Insurance Research Database. Available online: http://nhird.nhri.org.tw/en/index.html (accessed on 17 April 2018).

14. Lin, J.N.; Lin, C.L.; Lin, M.C.; Lai, C.H.; Lin, H.H.; Yang, C.H.; Sung, F.C.; Kao, C.H. Risk of leukaemia in children infected with enterovirus: A nationwide, retrospective, population-based, Taiwanese-registry, cohort study. *Lancet Oncol.* 2015, 16, 1335–1343. [CrossRef]

15. Lin, J.N.; Lin, C.L.; Yang, C.H.; Lin, M.C.; Lai, C.H.; Lin, H.H.; Kao, C.H. Risk of nephrotic syndrome following enteroviral infection in children: A nationwide retrospective cohort study. *PLoS ONE* 2016, 11, e0161004. [CrossRef]

16. Chang, K.H.; Hsu, C.C.; Muo, C.H.; Hsu, C.Y.; Liu, H.C.; Kao, C.H.; Chen, C.Y.; Chang, M.; Hsu, Y.C. Air pollution exposure increases the risk of rheumatoid arthritis: A longitudinal and nationwide study. *Environ. Int.* 2016, 94, 495–499. [CrossRef]

17. Liu, C.Y.; Hung, Y.T.; Chuang, Y.L.; Chen, Y.J.; Weng, W.S.; Liu, J.S. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. *J. Healthc. Manag.* 2006, 14, 1–22. [CrossRef]

18. Schramel, F.M.; Postmus, P.E.; Vanderschueren, R.G. Current aspects of spontaneous pneumothorax. *Eur. Respir. J.* 1997, 10, 1372–1379. [CrossRef]

19. Lesur, O.; Delorme, N.; Fromaget, J.M.; Bernadac, P. Computed tomography in the etiologic assessment of idiopathic spontaneous pneumothorax. *Chest* 1999, 98, 341–347. [CrossRef]

20. Mitlehner, W.; Friedrich, M.; Dissmann, W. Value of computer tomography in the detection of bullae and blebs in patients with primary spontaneous pneumothorax. *Respiration* 1992, 59, 221–227. [CrossRef]
21. Bense, L.; Lewander, R.; Eklund, G.; Hedenstierna, G.; Wiman, L.G. Nonsmoking, non-alpha1-antitrypsin deficiency-induced emphysema in nonsmokers with healed spontaneous pneumothorax, identified by computed tomography of the lungs. *Chest* **1993**, *103*, 433–438. [CrossRef]  
22. Horio, H.; Nomori, H.; Kobayashi, R.; Naruke, T.; Suemasu, K. Impact of additional pleurodesis in video-assisted thoracoscopic bullectomy for primary spontaneous pneumothorax. *Surg. Endosc.* **2002**, *16*, 630–634. [CrossRef]  
23. Morrison, P.J.; Lowry, R.C.; Nevin, N.C. Familial primary spontaneous pneumothorax consistent with true autosomal dominant inheritance. *Thorax* **1998**, *53*, 151–152. [CrossRef]  
24. Bense, L.; Eklund, G.; Wiman, L.G. Bilateral bronchial anomaly. A pathogenetic factor in spontaneous pneumothorax. *Am. Rev. Respir. Dis.* **1992**, *146*, 513–516. [CrossRef] [PubMed]  
25. Withers, J.N.; Fishback, M.E.; Kiehl, P.V.; Hannon, J.L. Spontaneous pneumothorax: Suggested etiology and comparison of treatment methods. *Am. J. Surg.* **1964**, *108*, 772–776. [CrossRef]  
26. Kawakami, Y.; Irie, T.; Kamishima, K. Stature, lung height, and spontaneous pneumothorax. *Respiration* **1982**, *43*, 35–40. [CrossRef]  
27. Coxson, H.O.; Chan, I.H.T.; Mayo, J.R.; Hlynsky, J.; Nakano, Y.; Birmingham, C.L. Early emphysema in patients with anorexia nervosa. *Am. J. Respir. Crit. Care Med.* **2004**, *170*, 748–752. [CrossRef]  
28. Neptune, E.R.; Frischmeyer, P.A.; Arking, D.E.; Myers, L.; Bunton, T.E.; Gayraud, B.; Ramirez, F.; Sakai, L.Y.; Dietz, H.C. Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. *Nat. Genet.* **2003**, *33*, 407–411. [CrossRef]  
29. Schieman, C.; Graham, A.; Gelfand, G.; McFadden, S.P.; Tiruta, C.; Hill, M.D.; Grondin, S.C. Weather and chinook winds in relation to spontaneous pneumothoraces. *Can. J. Surg.* **2009**, *52*, E151–E155. [CrossRef]  
30. Motono, N.; Maeda, S.; Honda, R.; Tanaka, M.; Machida, Y.; Usuda, K.; Uramoto, H. Atmospheric temperature and pressure influence the onset of spontaneous pneumothorax. *Clin. Resp. J.* **2016**, *12*, 557–562. [CrossRef]  
31. Bertolaccini, L.; Viti, A.; Boschetto, L.; Pasini, A.; Attanasio, A.; Terzi, A.; Cassardo, C. Analysis of spontaneous pneumothorax in the city of Cuneo: Environmental correlations with meteorological and air pollutant variables. *Surg. Today* **2015**, *45*, 625–629. [CrossRef] [PubMed]  
32. Brauer, M.; Hoek, G.; Van Vliet, P.; Meliefste, K.; Fischer, P.H.; Wijga, A.; Koopman, L.P.; Neijens, H.J.; Gerritsen, J.; Kerkhof, M.; et al. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am. J. Respir. Crit. Care Med.* **2002**, *166*, 1092–1098. [CrossRef]  
33. Azeez, O.M.; Akhigbe, R.E.; Anigbogu, C.N. Exposure to petroleum hydrocarbon: Implications in lung lipid peroxidation and antioxidant defense system in rat. *Toxicol. Int.* **2012**, *19*, 306–309. [PubMed]  
34. Lipscomb, T.P.; Harris, R.K.; Moeller, R.B.; Pletcher, J.M.; Haebler, R.J.; Ballachey, B.E. Histopathologic lesions in sea otters exposed to crude oil. *Vet. Pathol.* **1993**, *30*, 1–11. [CrossRef]