



Article

Effects of Fine Particulate Matter and Its Components on Emergency Room Visits for Pediatric Pneumonia: A Time-Stratified Case-Crossover Study

Ming-Ta Tsai ^{1,2}, Yu-Ni Ho ^{1,2}, Charng-Yen Chiang ^{1,2}, Po-Chun Chuang ^{1,2}, Hsiu-Yung Pan ^{1,2}, I-Min Chiu ^{1,2} , Chih-Min Tsai ^{2,3} and Fu-Jen Cheng ^{1,2,*}

- ¹ Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, No. 123, Ta-Pei Road, Niao-Sung, Kaohsiung 833, Taiwan; kabadada@gmail.com (M.-T.T.); r223054987@cgmh.org.tw (Y.-N.H.); bestmulatto@gmail.com (C.-Y.C.); boggy1102@cgmh.org.tw (P.-C.C.); gettingfat720@gmail.com (H.-Y.P.); outofray@hotmail.com (I.-M.C.)
 - ² College of Medicine, Chang Gung University, No. 259, Wenhua 1st Road, Guishan District, Taoyuan City 333, Taiwan; temnor@cgmh.org.tw
 - ³ Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, No. 123, Ta-Pei Road, Niao-Sung, Kaohsiung 833, Taiwan
- * Correspondence: a0953283092@yahoo.com.tw; Tel.: +886-975-056-646



Citation: Tsai, M.-T.; Ho, Y.-N.; Chiang, C.-Y.; Chuang, P.-C.; Pan, H.-Y.; Chiu, I.-M.; Tsai, C.-M.; Cheng, F.-J. Effects of Fine Particulate Matter and Its Components on Emergency Room Visits for Pediatric Pneumonia: A Time-Stratified Case-Crossover Study. *Int. J. Environ. Res. Public Health* **2021**, *18*, 10599. <https://doi.org/10.3390/ijerph182010599>

Academic Editors: Yu-Hsiang Cheng, Elisabete Carolino and Chi-Chi Lin

Received: 7 August 2021

Accepted: 8 October 2021

Published: 10 October 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Pneumonia, one of the important causes of death in children, may be induced or aggravated by particulate matter (PM). Limited research has examined the association between PM and its constituents and pediatric pneumonia-related emergency department (ED) visits. Measurements of PM_{2.5}, PM₁₀, and four PM_{2.5} constituents, including elemental carbon (EC), organic carbon (OC), nitrate, and sulfate, were extracted from 2007 to 2010 from one core station and two satellite stations in Kaohsiung City, Taiwan. Furthermore, the medical records of patients under 17 years old who had visited the ED in a medical center and had a diagnosis of pneumonia were collected. We used a time-stratified, case-crossover study design to estimate the effect of PM. The single-pollutant model demonstrated interquartile range increase in PM_{2.5}, PM₁₀, nitrate, OC, and EC on lag 3, which increased the risk of pediatric pneumonia by 18.2% (95% confidence interval (CI), 8.8–28.4%), 13.1% (95% CI, 5.1–21.7%), 29.7% (95% CI, 16.4–44.5%), 16.8% (95% CI, 4.6–30.4%), and 14.4% (95% CI, 6.5–22.9%), respectively. After PM_{2.5}, PM₁₀, and OC were adjusted for, nitrate and EC remained significant in two-pollutant models. Subgroup analyses revealed that nitrate had a greater effect on children during the warm season (April to September, interaction $p = 0.035$). In conclusion, pediatric pneumonia ED visit was related to PM_{2.5} and its constituents. Moreover, PM_{2.5} constituents, nitrate and EC, were more closely associated with ED visits for pediatric pneumonia, and children seemed to be more susceptible to nitrate during the warm season.

Keywords: particulate matter; particulate matter component; air pollution; pediatric; pneumonia

1. Introduction

Pneumonia is one of the main infectious diseases that are responsible for childhood morbidity and death, leading to about 1.3 million mortalities among children less than 5 years old in 2010 and 2011 [1]. Pneumonia is an inflammatory condition of the lung, and previous studies have shown a relationship between air pollution and lung inflammation [2,3]. Recently, many epidemiologic studies have demonstrated that PM_{2.5} (particulate matter (PM) with an aerodynamic diameter of <2.5 μm) has a greater hazardous effect than other air pollutants [4,5]. For children, a review article concluded that PM_{2.5} was positively related to child admission due to pneumonia [6]. Furthermore, the health impact of PM_{2.5} seemed to present regional heterogeneity. Bell et al. gathered data from 202 counties in the United States and discovered the strongest relationship between PM_{2.5} and respiratory hospitalizations in the northeast region [7]. Regional variation may be explained by some

community features, such as the prevalence of air conditioning [8], the percentage of elderly residents [9], and weather conditions [10]. Another possible reason for regional heterogeneity was the different PM components in different regions [11]. The PM_{2.5} constituent, nitrate, was found to have a greater influence on asthma emergency department (ED) visits [12], while sulfate was found to be more associated with daily mortality [13]. Limited studies have focused on PM components and pediatric pneumonia, and their results were inconclusive [14].

On the other hand, the health effect of PM_{2.5} seems to have seasonal variation. Lv et al. found that children were more sensitive to pneumonia due to PM_{2.5} during the warm season [15], and Ueda et al. revealed that the influence of PM_{2.5} on daily mortality was more significant during transitional seasons [13]. The combination of climate conditions and PM seemed to enhance the hazardous effect on health [16]. The seasonal effect of PM components on pediatric pneumonia is still obscure. As a result, this present study aimed to (1) assess the impacts of short-period exposure to PM_{2.5} and its components on pediatric pneumonia and (2) reveal the effect of PM constituents on pediatric pneumonia in different seasons.

2. Materials and Methods

2.1. Study Area and Population

A retrospective observational study was conducted between 1 January 2007 and 31 December 2010, in an urban tertiary academic medical center in Kaohsiung, Taiwan, with an average of 72,000 ED visits per year. Kaohsiung is largely populated by heavy industries, including the petrochemical industry and steel corporation situated in southwest Taiwan. This study was approved by the institutional review board of our hospital (no. 202001095B0C501) and was performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, informed consent from the subjects was not required. The ED visit data of non-traumatic pediatric (<17 years) patients with a principal diagnosis of pneumonia (International Classification of Diseases, ninth revision: 480–486) were obtained. According to the ED records, data on demographic factors, such as age, sex, and pre-existing diseases, including cerebral palsy, epilepsy, and respiratory disease (including asthma), were also collected.

2.2. Pollutant and Meteorological Data

We measure hourly mass concentrations of PM₁₀, PM_{2.5}, and four major PM_{2.5} constituents, including elemental carbon (EC), organic carbon (OC), nitrate, and sulfate from the southern PM supersite during the study period. The southern PM monitoring supersite was operated by the Taiwan Environmental Protection Administration from 2006 to 2010. There was one core supersite [Fooyin (latitude 22.60° N, longitude 120.38° E)] and two satellite supersites [Chiautou (To) (22.75° N, 120.29° E) and Qianzhen (22.60° N, 120.30° E)] in Kaohsiung, as described previously [17], as shown in Figure 1. At these supersites, hourly mass concentrations of PM_{2.5} were measured with a tapered element oscillation microbalance (Rupprecht and Patashnick 1400a). Hourly concentrations of OC and EC were detected with Series 5400 Monitor, nitrate was detected with Series 8400N Particulate Nitrate Monitor, and sulfate was detected with Series 8400S Particulate Sulfate Monitor [15]. Climate conditions, such as hourly temperature and humidity, were also recorded at the core station. We measured the daily average of PM₁₀, PM_{2.5}, and PM_{2.5} constituents from each monitoring site, as well as from residential areas of pediatric pneumonia patients. The 24-h mean level of each pollutant and the meteorological data, including mean temperature and mean humidity from the closest monitoring supersites, were also collected for further analysis.

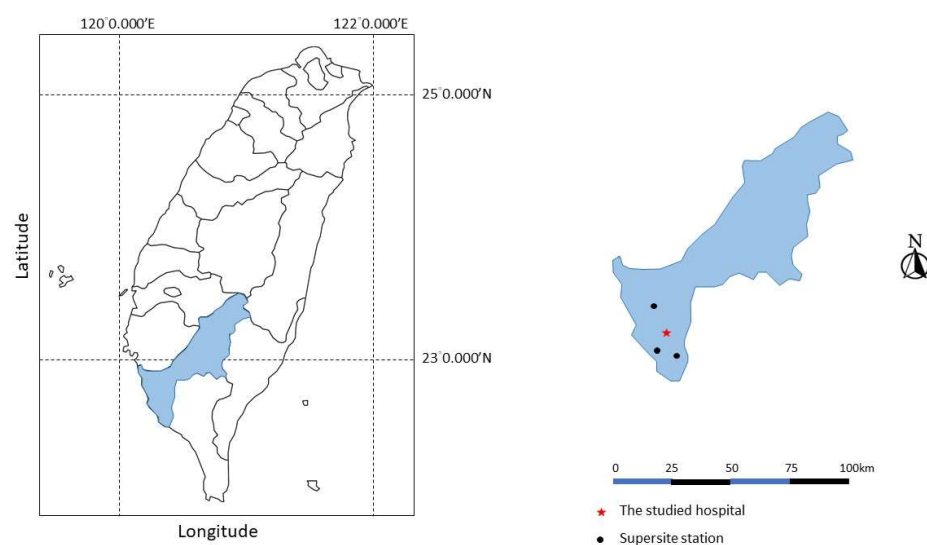


Figure 1. The locations of one core supersite and two satellite supersites in Kaohsiung. Note: the Taiwan map outline was adapted from <https://webvectormaps.com/taiwan-map-outline-free-blank-vector-map/> (accessed on 8 October 2021), which was licensed under the Creative Commons Attribution 4.0 International License.

2.3. Statistics

Both time-stratified and case-crossover techniques were used to analyze the data [18]. The design is a substitute for the Poisson time series regression models for studying the health effect of short-term exposure, such as air pollution [13,19]. In general, the case-crossover design and the time-series approach yielded almost identical results.

The method was described in our previous study [20]. Briefly, we selected referent days as the days falling on the same day of the week within the same month as the index day, in order to adjust for the influences of seasonality, long-term trends, and day of the week [21]. The day on which the pediatric patient visited ED was defined as lag 0, the day before pneumonia event was lag 1, the day before lag 1 was lag 2, and so on. The impact of each lag day was assessed separately. Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of the pneumonia cases associated with $PM_{2.5}$ and its components. Subgroup analyses, including season, temperature, sex, age, and pre-existing diseases, were also carried out to identify the most vulnerable groups.

The levels of each air pollutant and meteorological variables were entered into the models as continuous variables. The baseline model included a linear expression, including each air pollutant and meteorological confounding factors, such as temperature and humidity. Then, plotting univariate restricted cubic splines were used to evaluate the potential non-linear relationships between weather conditions and pediatric pneumonia. We used the Akaike information criterion (AIC) to examine nonlinear effects by introducing temperature and humidity separately in the model, and we compared the goodness-of-fit. SAS macro `lgtphcurv9` (in SAS version 9.4) was used; it implements natural cubic spline methodology to fit a potentially nonlinear response curve in conditional logistic regression models for matched case-control studies [22]. We used both single-pollutant models and multi-pollutant models with different combinations of PM to assess the stability of the effects of PM and its components.

The ORs were calculated on the basis of per interquartile range (IQR) increments in PM_{10} , $PM_{2.5}$, nitrate, sulfate, OC, and EC exposure. Statistical significance was set at $p < 0.05$. Besides the SAS macro `lgtphcurv9`, other statistical analyses were performed with Statistical Product and Service Solutions version 25.0 (IBM Corp, Armonk, NY, USA).

3. Results

During the 4-year study period, data were recorded for 1737 ED patients with pediatric pneumonia. Demographic characteristics are presented in Table 1. In our study, the mean age was 5.1 years, and 921 (53.0%) patients were males. Pre-existing diseases were respiratory disease in 47 (0.3%) patients, cerebral palsy in 48 (0.3%), and epilepsy in 34 (0.2%). Among pediatric pneumonia cases, 867 (49.9%) patients presented during the warm season (April to September), and 801 (46.1%) patients presented on warm days (≥ 26.5 °C).

Table 1. Demographic characteristics of patients.

All	Number = 1737	%
Demographic characteristics of patients		
Age (mean \pm standard deviation)	5.1 \pm 3.6	
Male sex	921	53.0
Respiratory disease	47	0.3
Cerebral palsy	48	0.3
Epilepsy	34	0.2
Warm season	867	49.9
Warm days (≥ 26.5 °C)	801	46.1

The meteorological factors, including the daily mean concentrations of PM and PM components in Kaohsiung during the study period, are presented in Table 2. The average concentrations of PM_{2.5} and PM₁₀ were 32.7 $\mu\text{g}/\text{m}^3$ and 50.3 $\mu\text{g}/\text{m}^3$, respectively, during our study period. The average concentrations of nitrate, sulfate, OC, and EC were 4.4, 9.4, 8.2, and 2.1 $\mu\text{g}/\text{m}^3$, respectively.

Table 2. Meteorological factors during the study period.

	Minimum	Percentiles			Maximum	Mean	IQR
		25%	50%	75%			
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	6.9	18.9	31.6	43.0	119.5	32.7	24.1
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	10.7	29.7	46.6	66.9	449.5	50.3	37.2
Nitrate ($\mu\text{g}/\text{m}^3$)	0.3	1.4	3.9	6.6	20.7	4.4	5.2
Sulfate ($\mu\text{g}/\text{m}^3$)	1.1	5.6	9.1	12.5	33.7	9.4	6.9
Organic carbon ($\mu\text{g}/\text{m}^3$)	1.4	5.4	7.5	10.6	27.8	8.2	5.2
Elemental carbon ($\mu\text{g}/\text{m}^3$)	0.5	1.5	2.0	2.6	16.5	2.1	1.1
Temperature (°C)	13.4	22.6	26.5	28.8	31.6	25.5	6.2
Humidity (%)	44.0	69.0	73.4	77.3	95.3	73.2	8.3

IQR, interquartile range; PM, particulate matter.

The Pearson's correlation coefficients for PM₁₀, PM_{2.5}, each PM_{2.5} chemical constituent, and weather conditions are presented in Table 3. PM_{2.5} was significantly correlated with PM₁₀ ($r = 0.909$; $p < 0.001$), nitrate ($r = 0.793$, $p < 0.001$), sulfate ($r = 0.908$, $p < 0.001$), and OC ($r = 0.822$, $p < 0.001$) and moderately correlated with EC ($r = 0.669$, $p < 0.001$).

Table 3. Pearson's correlation coefficients between air pollutants and weather conditions in the study period.

	PM ₁₀	PM _{2.5}	Nitrate	Sulfate	Organic Carbon	Elemental Carbon	Temperature (°C)	Humidity (%)
PM ₁₀		0.909	0.669	0.774	0.731	0.568	−0.493	−0.410
PM _{2.5}			0.793	0.908	0.822	0.669	−0.504	−0.406
Nitrate				0.680	0.833	0.643	−0.580	−0.269
Sulfate					0.673	0.592	−0.403	−0.359
Organic carbon						0.732	−0.536	−0.377
Elemental carbon							−0.376	−0.277
Temperature (°C)								0.315
Humidity (%)								

PM, particulate matter.

Conditional regression was performed to evaluate the influence of $PM_{2.5}$ and its constituents on pediatric pneumonia. When the environmental temperature was set as a continuous linear term, the AIC value for the linear model (4816.364) was better than that of the spline model (4817.46), and the curvature test (nonlinear relationship) was non-significant ($p = 0.306$). As shown in Figure 2, with humidity, the spline model (AIC = 4788.325) was better than the linear model (AIC = 4793.54), and the curvature test was significant ($p < 0.001$). Therefore, the spline model was used to create five categorical variables according to knots for humidity (Figure 2) using AIC [23]. When the conditional logistic regression model was included in this categorical representation of relative humidity, the AIC value was 4788.032, which was better than the linear model.

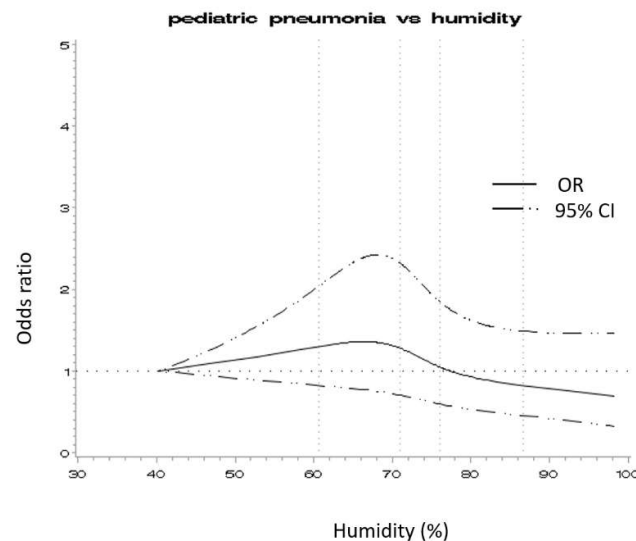


Figure 2. Restricted cubic spline for humidity. This figure displays a restricted cubic spline from conditional logistic regression with relative humidity as the predictor and pediatric pneumonia ED visit as the outcome. The reference exposure value was set at a relative humidity of 40%, including 4 knots.

Figure 3 shows the 95% CIs, excess rates (%), and the probability that the value is different from 0 for pediatric pneumonia ED visits that are related to each IQR increase in $PM_{2.5}$, PM_{10} , and $PM_{2.5}$ constituents after adjusting for humidity and temperature as previously described. IQR increases in $PM_{2.5}$, PM_{10} , nitrate, and OC concentrations on lag 2 were related to an increased risk of pediatric pneumonia ED visits by 11.5% (95% CI, 2.9–20.9%), 6.6% (95% CI, 1.1–12.3%), 25.0% (95% CI, 12.2–39.2%), and 12.9% (95% CI, 0.7–26.5%), respectively. IQR increases in $PM_{2.5}$, PM_{10} , nitrate, OC, and EC levels on lag 3 were related to an increased risk of pediatric pneumonia ED visits by 18.2% (95% CI, 8.8–28.4%), 13.1% (95% CI, 5.1–21.7%), 29.7% (95% CI, 16.4–44.5%), 16.8% (95% CI, 4.6–30.4%), and 14.4% (95% CI, 6.5–22.9%), respectively. On the other hand, IQR increase in sulfate level was not significantly related to pediatric ED visits.

A two-pollutant model was designed to offer insight into which sole component, independent of the effects of the other $PM_{2.5}$ components, may enhance the risk of pediatric pneumonia ED visits (Table 4). In the multi-pollutant models, we concurrently included $PM_{2.5}$, PM_{10} , nitrate, OC, and EC on lag 3, according to the results of the single-pollutant model. As presented in Table 4, the risk of ED visits for pediatric pneumonia was significantly associated with an IQR increase in nitrate after adjusting for $PM_{2.5}$ (OR = 1.230; 95% CI: 1.064–1.442), PM_{10} (OR = 1.250; 95% CI: 1.104–1.416), OC (OR = 1.299; 95% CI: 1.136–1.485), and EC (OR = 1.231; 95% CI: 1.095–1.384). The risk of pediatric pneumonia ED visits was significantly associated with an IQR increment in EC after adjusting for $PM_{2.5}$ (OR = 1.091; 95% CI: 1.014–1.175), PM_{10} (OR = 1.108; 95% CI: 1.030–1.193), nitrate (OR = 1.083; 95% CI: 1.010–1.162), and OC (OR = 1.130; 95% CI: 1.029–1.242). The risk

of PM_{2.5}, PM₁₀, and OC for pediatric pneumonia was not statistically significant after adjustment for nitrate.

OR (95% CI) of ED visits for pneumonia associated with an IQR increase of PM components after adjusting for temperature and humidity

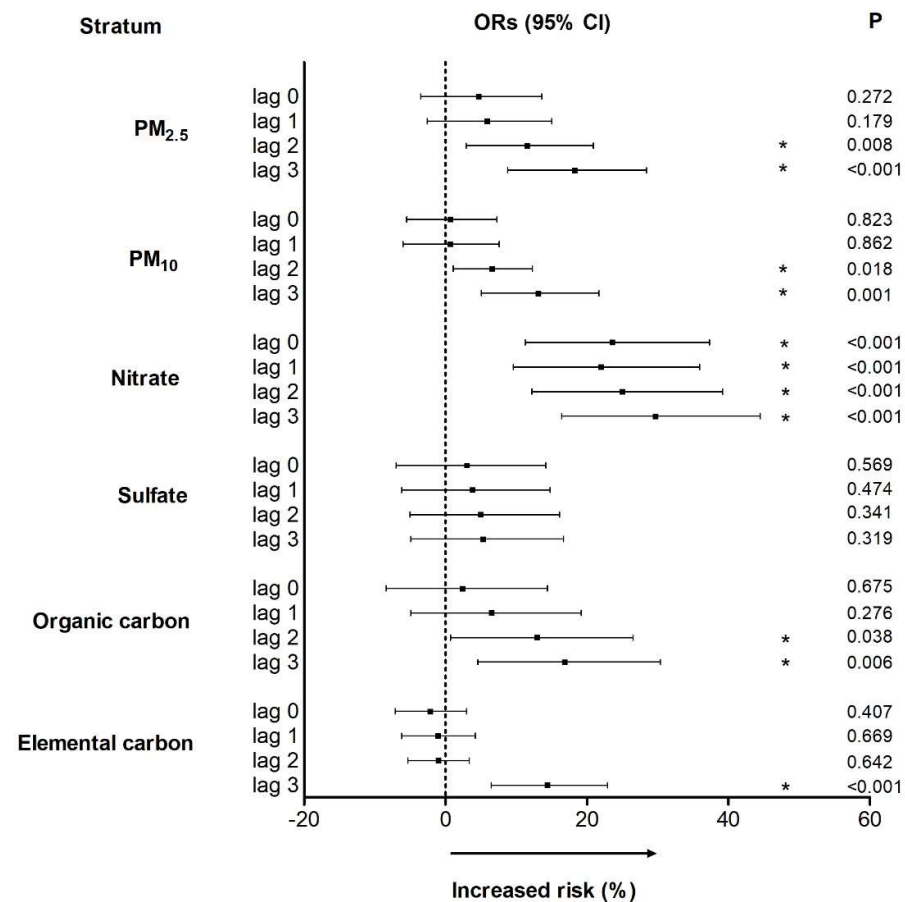


Figure 3. Odds ratios and 95% confidence intervals for pediatric pneumonia ED visits. The values are presented according to IQR increments in the levels of PM_{2.5} and its constituents, with adjustment for temperature and humidity. ED, emergency department; OR, odds ratio; CI, confidence interval; IQR, interquartile range; PM, particulate matter. * *p* < 0.05.

Table 4. OR (95% CI) of pneumonia ED visits for each interquartile range change in two-pollutant models, adjusted for temperature, relative humidity, and pollutant.

	Adjusted for PM _{2.5}	Adjusted for PM ₁₀	Adjusted for Nitrate	Adjusted for Organic Carbon	Adjusted for Elemental Carbon
PM _{2.5}		1.160 (1.011–1.331)	1.063 (0.951–1.189)	1.168 (1.050–1.300)	1.124 (1.024–1.233)
PM ₁₀	1.019 (0.903–1.150)		1.051 (0.966–1.144)	1.102 (1.012–1.199)	1.084 (1.002–1.173)
Nitrate	1.230 (1.064–1.442)	1.250 (1.104–1.416)		1.299 (1.136–1.485)	1.231 (1.095–1.384)
Organic carbon	1.024 (0.889–1.181)	1.081 (0.951–1.229)	0.997 (0.870–1.143)		1.028 (0.887–1.192)
Elemental carbon	1.091 (1.014–1.175)	1.108 (1.030–1.193)	1.083 (1.010–1.162)	1.130 (1.029–1.242)	

CI, confidence interval; ED, emergency department; OR, odds ratio; PM, particulate matter.

Figure 4a,b shows the results of the stratified analysis used to evaluate the effects of nitrate and EC on pediatric pneumonia based on different age groups, environmental temperature, seasons, and underlying physical conditions on lag 3. As shown in Figure 4a, after adjusting for temperature and humidity, patients were more susceptible to nitrate during the warm season (OR = 1.469; 95% CI, 1.211–1.781; interaction *p* = 0.035). The results were not significantly different for nitrate in subgroups of different ages and underlying diseases.

Figure 4b demonstrates that the effect estimates for EC were higher in male patients, in older patients (≥ 4 years), during the cold season, and during cold days ($< 26.5^\circ\text{C}$), but the results were not statistically significant.

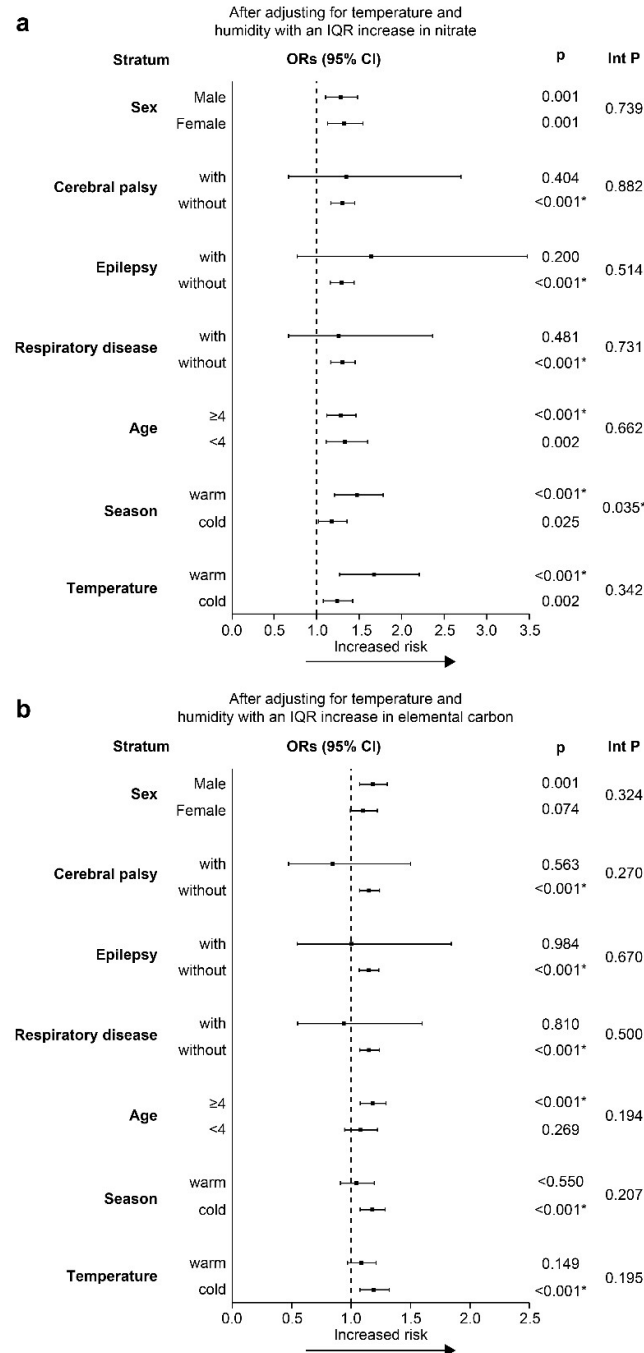


Figure 4. Adjusted ORs and CI of subgroup analysis for $\text{PM}_{2.5}$ constituents on lag 3: (a) nitrate, (b) elemental carbon. The X-axis represents percentage of excess risk with 95% confidence intervals. Warm season was defined as April through September; cold season as October through March. Warm temperature, $\geq 26.5^\circ\text{C}$; cold temperature, $< 26.5^\circ\text{C}$. CI, confidence intervals; Int P, interaction p value; IQR, interquartile range; OR, odds ratio; PM, particulate matter. * $p < 0.05$.

4. Discussion

Our study demonstrated that both $\text{PM}_{2.5}$ concentration and its chemical components are related to pediatric ED visits. Among the four $\text{PM}_{2.5}$ components that we evaluated in the study (i.e., nitrate, sulfate, OC, and EC), the estimated effects of nitrate and EC on pedi-

atric pneumonia were more robust after adjusting for $PM_{2.5}$, PM_{10} , and OC. Furthermore, children were more susceptible to nitrate during the warm season.

Many epidemiologic studies have revealed that $PM_{2.5}$ is related to cardiovascular diseases, respiratory diseases, and daily mortality [4,9,24], but few studies have focused on $PM_{2.5}$ and pediatric pneumonia, and even the results of these few studies are controversial. Lv et al. and Xiao et al. demonstrated that elevated $PM_{2.5}$ was related to pediatric hospital admission for pneumonia and ED visits for pediatric pneumonia [14,15], but some studies did not conclude on a positive correlation between ED visits for pediatric pneumonia and $PM_{2.5}$ exposure [25,26]. The following may be explanations for this dissimilarity. First, the lag times of the studies were different. Strickland et al. collected their data up to lag 1, and Malig et al. collected their data up to lag 2. Lv et al. revealed that $PM_{2.5}$ was associated with pediatric pneumonia admission on lag 4. Xiao et al. indicated that the 3-day moving average $PM_{2.5}$ was related to pediatric pneumonia ED visits. The present study showed that $PM_{2.5}$ was associated with pediatric ED visits on lag 2 and lag 3. That is to say, the studies did not find statistical significance probably due to fewer lag days traced. Second, the source and composition of $PM_{2.5}$ may have seasonal and regional variations [11], and different constituents may cause different health impacts. Among $PM_{2.5}$ components, chloride, EC, and OC were found to be related to cardiovascular mortality, and ammonia and potassium were related to respiratory mortality [13]. A systemic review/meta-analysis enrolled 17 studies and concluded on a positive association between hospitalization of children due to pneumonia and daily levels of $PM_{2.5}$ [6]. Our study showed a positive relationship between $PM_{2.5}$ and ED visits for pediatric pneumonia, which is similar to the results of previous studies.

Limited studies have focused on PM components and health hazards. Nitrate and EC were found to be related to hemorrhagic stroke, while OC and EC were found to be related to ischemic stroke [27]. EC, OC, sulfate, selenium, and silicon are associated with cardiovascular disease mortality [28]. Sanart et al. showed that EC and OC were related to ED visits for cardiovascular diseases, and $PM_{2.5}$ was associated with ED visits for asthma/wheeze [29]. For respiratory diseases, Hwang et al. conducted a population-based study by collecting data from the National Health Insurance Research Database and concluded that $PM_{2.5}$ was related to pediatric asthma ED visits, and asthma ED visits were significantly associated with concentrations of nitrate [12]. Furthermore, limited studies have focused on PM components and the risk of pediatric pneumonia. Xiao et al. found that $PM_{2.5}$ and $PM_{2.5}$ constituents (EC, OC, sulfate, and ammonium) were associated with a higher risk of ED visits for pediatric pneumonia [14]. Our study presented similar results. Our single-pollutant model revealed that $PM_{2.5}$, EC, OC, and nitrate were related to pediatric ED visits. Furthermore, our study showed that nitrate and EC were independently associated with pediatric pneumonia, even after adjusting for $PM_{2.5}$ and other $PM_{2.5}$ constituents in the two-pollutant model. On the other hand, another study revealed that OC was positively related to ED visits for pediatric pneumonia, but $PM_{2.5}$ and its components (EC, nitrate, and sulfate) were not related to pediatric ED visits [30]. This conclusion is different from our study's and that of Xiao et al. Only patients < 4 years old were enrolled in Darrow's study, and the difference in study groups may be the cause of the different results. Therefore, our study suggests that nitrate and EC have more hazardous effects than other PM constituents. However, the results should be interpreted with caution. Although inorganic water-soluble ionic species, such as nitrate and sulfate, and carbonaceous species, EC and OC, are the major components of PM [31], there are elemental components of $PM_{2.5}$, such as nickel and zinc, and organic components, such as polycyclic aromatic hydrocarbons (PAHs), which were not monitored in the present study. In animal experiments, the water extracts of PM, mainly elemental components, led to an inflammatory response of the lungs and increased production of reactive oxygen species in the lungs [32]. PAHs in urban air PM may lead to persistent activation of DNA damage signaling [33]. Thus, our results demonstrate that nitrate and EC have more significant effects among PM components (EC, OC, nitrate, and sulfate)

on pediatric pneumonia, but further study is needed to clarify the elemental and organic components of PM and their hazardous effect on pediatric health.

Previous studies revealed that the adverse effects of PM on human health varied with the season: Cheng et al. revealed that PM_{2.5} was positively associated with ED visits for pneumonia during the warm season [4]; Hsu et al. discovered that PM_{2.5} was related to cardiovascular hospitalization, especially in winter [34]. Few studies have focused on the seasonal effect of PM on pediatric pneumonia. A previous study demonstrated that children seemed to be more susceptible to pneumonia caused by PM_{2.5} on warm days (>23 °C); however, interaction *p* was not analyzed in the study [15]. Our previous study revealed that PM_{2.5} was related to pediatric pneumonia ED visits, but there was no discernible seasonal difference [35]. In the present study, a strong association was found between nitrate and pediatric pneumonia during the warm season, and there was no evident effect of seasonality between EC and pediatric pneumonia. That is to say, in different studies, the varying compositions of PM_{2.5} in different seasons and regions may lead to distinct results.

Many toxicological studies have shown the adverse health effects of PM. In animal studies, PM exposure was found to probably contribute to sinonasal inflammation, accompanied by eosinophilic inflammation, an increase in inflammatory cytokines, and eosinophil accumulation [36]. On the other hand, PM_{2.5} exposure has been explored to reduce phagocytosis of alveolar macrophages by activating proinflammatory cytokines, such as tumor necrosis factor- α , interleukin (IL)-1 β , and IL-6 [37]. Human studies have also demonstrated that PM is related to systemic inflammation. Hassanvand et al. showed that there were positive associations between PM exposure and elevated white blood cells (WBCs), high-sensitivity C-reactive protein, and other pro-inflammatory cytokines, such as IL-6 and tumor necrosis factor-soluble receptor-II [38]. Pneumonia is recognized as an inflammatory condition in the lungs, and PM exposure may trigger or exacerbate lung inflammation. The current study also supports this hypothesis, and we found a positive association between PM exposure and the risk of pediatric pneumonia.

In different age groups, PM_{2.5} has been noted to have different human health effects. Lv et al. discovered that children younger than 1 year old were more susceptible to PM_{2.5} and had a higher risk of pneumonia compared to children over 1 year old [15]. On the contrary, another study revealed that children aged 1–4 years were more susceptible to PM_{2.5} and more easily had pneumonia and upper airway infection than children less than 1 year old [30]. However, interaction *p* was not calculated in either study. Our previous study showed that older children (aged ≥ 4 years, interaction *p* = 0.024) were more susceptible to PM_{2.5} [35]. The present study found that older children seemed more susceptible to EC, but the association did not reach statistical significance (interaction *p* = 0.194). Children of different ages may have a variation in outdoor activity and staying time in different studies. This variation may lead to distinct exposure to PM_{2.5}, with different results. Additionally, the composition of PM_{2.5} may differ in seasons and regions [39], contributing to the diversity of its health effects.

Many previous epidemiologic studies have shown that the interval for the health effect of PM ranged from 0 to 3 days. Pan et al. found that PM_{2.5} concentration increases the risk of ST-segment elevation myocardial infarction on lag 0 [40]; Cheng et al. revealed a positive association between out-of-hospital cardiac arrest and PM_{2.5} concentration on lag 1 [20]. For pediatric pneumonia, Lv et al. found that PM_{2.5} was positively correlated with hospital admissions on lag 2 [15]. Xiao et al. found the joint effect of O₃ and PM_{2.5} components (sulfate, nitrate, and ammonium) on pediatric pneumonia ED visits on lag 0–2 [14]. In the present study, we revealed a positive association between ED visits for pediatric pneumonia and PM_{2.5} on lag 2 and lag 3. There may be several possible reasons for the different time windows. First, we discovered a positive correlation between nitrate and pediatric pneumonia on lag 0 to lag 3, a positive correlation between OC and pediatric pneumonia on lag 2 to lag 3, and a positive correlation between EC and pediatric pneumonia on lag 3. Different components of PM_{2.5} seem to have different time windows for

the risk of pediatric pneumonia. This is because constitutions of PM_{2.5} vary with seasons and regions, resulting in distinct time windows. Second, Hassanvand et al. revealed that exposure to PM_{2.5} was related to elevation of WBCs and IL-6; for healthy young adults, the elevation of WBC and IL-6 was on lag 1, while for the elderly (>65 years of age), WBC and IL-6 were elevated on lag 0 to lag 4. In other words, different patient groups may have different reactions and response times to PM exposure, and this may lead to diversity in study results [38].

5. Limitation

There are several limitations to the present study. First, our study was conducted in a single tertiary medical center located in tropical metropolitan and industrial city. The results may, therefore, not be generalizable to other areas that have different meteorological and regional characteristics. Second, factors such as the usage of personal protective equipment, time spent outdoors, and use of air purification devices may influence people's exposure to PM, and the observed results may vary under different conditions. Further studies should be conducted in regions with diversity, and the use of air purification devices or personal protective equipment should be factored into the analysis.

6. Conclusions

We discovered that PM₁₀, PM_{2.5}, and PM_{2.5} constituents (EC, OC, and nitrate) were positively associated with ED visits for pediatric pneumonia in Kaohsiung, Taiwan. The influences of nitrate and EC were strong after adjusting for PM₁₀, PM_{2.5}, and OC. Children were more susceptible to pediatric pneumonia due to nitrate during the warm season.

Author Contributions: Conceptualization, M.-T.T. and F.-J.C.; methodology, Y.-N.H. and F.-J.C.; formal analysis, P.-C.C., C.-Y.C. and H.-Y.P.; resources, C.-M.T.; data curation, I.-M.C.; writing—original draft preparation, M.-T.T. and F.-J.C. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported in part by research grants from the Kaohsiung Chang Gung Memorial Hospital (grant number CMRPG8K1481).

Institutional Review Board Statement: This study was approved by the institutional review board of our hospital (no. 202001095B0C501) and was performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Statement: The need for informed consent was waived owing to the retrospective nature of the study.

Data Availability Statement: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments: We appreciate the statistical support provided by the Biostatistics Center of Kaohsiung Chang Gung Memorial Hospital.

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

Bullet Point::

- PM_{2.5} was significantly associated with pediatric pneumonia.
- ED visits for pediatric pneumonia were more directly related to nitrate and EC.
- Children were more susceptible to nitrate during the warm season.

Abbreviations

AIC	Akaike information criterion
CI	confidence interval
EC	elemental carbon
ED	emergency department
IL	interleukin

IQR	interquartile range
OC	organic carbon
OR	odds ratio
PAH	polycyclic aromatic hydrocarbons
PM	particulate matter
WBC	white blood cell

References

- Walker, C.L.F.; Rudan, I.; Liu, L.; Nair, H.; Theodoratou, E.; Bhutta, Z.A.; O'Brien, K.L.; Campbell, H.; Black, R.E. Global burden of childhood pneumonia and diarrhoea. *Lancet* **2013**, *381*, 1405–1416. [\[CrossRef\]](#)
- Chen, Y.; Luo, X.S.; Zhao, Z.; Chen, Q.; Wu, D.; Sun, X.; Wu, L.; Jin, L. Summer-winter differences of PM_{2.5} toxicity to human alveolar epithelial cells (A549) and the roles of transition metals. *Ecotoxicol. Environ. Saf.* **2018**, *165*, 505–509. [\[CrossRef\]](#) [\[PubMed\]](#)
- Huang, K.L.; Liu, S.Y.; Chou, C.C.; Lee, Y.H.; Cheng, T.J. The effect of size-segregated ambient particulate matter on Th1/Th2-like immune responses in mice. *PLoS ONE* **2017**, *12*, e0173158. [\[CrossRef\]](#) [\[PubMed\]](#)
- Cheng, F.J.; Lee, K.H.; Lee, C.W.; Hsu, P.C. Association between Particulate Matter Air Pollution and Hospital Emergency Room Visits for Pneumonia with Septicemia: A Retrospective Analysis. *Aerosol Air Qual. Res.* **2019**, *19*, 345–354. [\[CrossRef\]](#)
- Liu, H.; Tian, Y.; Cao, Y.; Song, J.; Huang, C.; Xiang, X.; Li, M.; Hu, Y. Fine particulate air pollution and hospital admissions and readmissions for acute myocardial infarction in 26 Chinese cities. *Chemosphere* **2018**, *192*, 282–288. [\[CrossRef\]](#)
- Nhung, N.T.T.; Amini, H.; Schindler, C.; Kutlar Joss, M.; Dien, T.M.; Probst-Hensch, N.; Perez, L.; Kunzli, N. Short-term association between ambient air pollution and pneumonia in children: A systematic review and meta-analysis of time-series and case-crossover studies. *Environ. Pollut.* **2017**, *230*, 1000–1008. [\[CrossRef\]](#) [\[PubMed\]](#)
- Bell, M.L.; Ebisu, K.; Peng, R.D.; Walker, J.; Samet, J.M.; Zeger, S.L.; Dominici, F. Seasonal and regional short-term effects of fine particles on hospital admissions in 202 US counties, 1999–2005. *Am. J. Epidemiol.* **2008**, *168*, 1301–1310. [\[CrossRef\]](#)
- Bell, M.L.; Ebisu, K.; Peng, R.D.; Dominici, F. Adverse health effects of particulate air pollution: Modification by air conditioning. *Epidemiology* **2009**, *20*, 682–686. [\[CrossRef\]](#)
- Kim, T.-Y.; Kim, H.; Yi, S.-M.; Cheong, J.-P.; Heo, J. Short-term Effects of Ambient PM_{2.5} and PM_{2.5–10} on Mortality in Major Cities of Korea. *Aerosol Air Qual. Res.* **2018**, *18*, 1853–1862. [\[CrossRef\]](#)
- Cheng, M.H.; Chiu, H.F.; Yang, C.Y. Coarse Particulate Air Pollution Associated with Increased Risk of Hospital Admissions for Respiratory Diseases in a Tropical City, Kaohsiung, Taiwan. *Int. J. Environ. Res. Public Health* **2015**, *12*, 13053–13068. [\[CrossRef\]](#)
- Grivas, G.; Cheristanidis, S.; Chaloulakou, A.; Koutrakis, P.; Mihalopoulos, N. Elemental Composition and Source Apportionment of Fine and Coarse Particles at Traffic and Urban Background Locations in Athens, Greece. *Aerosol Air Qual. Res.* **2018**, *18*, 1642–1659. [\[CrossRef\]](#)
- Hwang, S.L.; Lin, Y.C.; Lin, C.M.; Hsiao, K.Y. Effects of fine particulate matter and its constituents on emergency room visits for asthma in southern Taiwan during 2008–2010: A population-based study. *Environ. Sci. Pollut. Res. Int.* **2017**, *24*, 15012–15021. [\[CrossRef\]](#) [\[PubMed\]](#)
- Ueda, K.; Yamagami, M.; Ikemori, F.; Hisatsune, K.; Nitta, H. Associations between Fine Particulate Matter Components and Daily Mortality in Nagoya, Japan. *J. Epidemiol.* **2016**, *26*, 249–257. [\[CrossRef\]](#) [\[PubMed\]](#)
- Xiao, Q.; Liu, Y.; Mulholland, J.A.; Russell, A.G.; Darrow, L.A.; Tolbert, P.E.; Strickland, M.J. Pediatric emergency department visits and ambient Air pollution in the U.S. State of Georgia: A case-crossover study. *Environ. Health* **2016**, *15*, 115. [\[CrossRef\]](#)
- Lv, C.; Wang, X.; Pang, N.; Wang, L.; Wang, Y.; Xu, T.; Zhang, Y.; Zhou, T.; Li, W. The impact of airborne particulate matter on pediatric hospital admissions for pneumonia among children in Jinan, China: A case-crossover study. *J. Air Waste Manag. Assoc.* **2017**, *67*, 669–676. [\[CrossRef\]](#)
- Huang, C.H.; Lin, H.C.; Tsai, C.D.; Huang, H.K.; Lian, I.B.; Chang, C.C. The Interaction Effects of Meteorological Factors and Air Pollution on the Development of Acute Coronary Syndrome. *Sci. Rep.* **2017**, *7*, 44004. [\[CrossRef\]](#)
- Ho, Y.N.; Cheng, F.J.; Tsai, M.T.; Tsai, C.M.; Chuang, P.C.; Cheng, C.Y. Fine particulate matter constituents associated with emergency room visits for pediatric asthma: A time-stratified case-crossover study in an urban area. *BMC Public Health* **2021**, *21*, 1593. [\[CrossRef\]](#)
- Peng, R.D.; Bell, M.L.; Geyh, A.S.; McDermott, A.; Zeger, S.L.; Samet, J.M.; Dominici, F. Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. *Environ. Health Perspect.* **2009**, *117*, 957–963. [\[CrossRef\]](#)
- Levy, D.; Sheppard, L.; Checkoway, H.; Kaufman, J.; Lumley, T.; Koenig, J.; Siscovick, D. A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. *Epidemiology* **2001**, *12*, 193–199. [\[CrossRef\]](#)
- Cheng, F.J.; Wu, K.H.; Hung, S.C.; Lee, K.H.; Lee, C.W.; Liu, K.Y.; Hsu, P.C. Association between ambient air pollution and out-of-hospital cardiac arrest: Are there potentially susceptible groups? *J. Expo. Sci. Environ. Epidemiol.* **2020**, *30*, 641–649. [\[CrossRef\]](#) [\[PubMed\]](#)
- Peng, R.D.; Dominici, F.; Pastor-Barriuso, R.; Zeger, S.L.; Samet, J.M. Seasonal analyses of air pollution and mortality in 100 US cities. *Am. J. Epidemiol.* **2005**, *161*, 585–594. [\[CrossRef\]](#)
- DeVries, R.; Kriebel, D.; Sama, S. Low level air pollution and exacerbation of existing copd: A case crossover analysis. *Environ. Health* **2016**, *15*, 98. [\[CrossRef\]](#)

23. Aho, K.; Derryberry, D.; Peterson, T. Model selection for ecologists: The worldviews of AIC and BIC. *Ecology* **2014**, *95*, 631–636. [[CrossRef](#)]
24. Bañeras, J.; Ferreira-González, I.; Marsal, J.R.; Barrabés, J.A.; Ribera, A.; Lidón, R.M.; Domingo, E.; Martí, G.; García-Dorado, D. Short-term exposure to air pollutants increases the risk of ST elevation myocardial infarction and of infarct-related ventricular arrhythmias and mortality. *Int. J. Cardiol.* **2018**, *250*, 35–42. [[CrossRef](#)]
25. Malig, B.J.; Green, S.; Basu, R.; Broadwin, R. Coarse particles and respiratory emergency department visits in California. *Am. J. Epidemiol.* **2013**, *178*, 58–69. [[CrossRef](#)] [[PubMed](#)]
26. Strickland, M.J.; Hao, H.; Hu, X.; Chang, H.H.; Darrow, L.A.; Liu, Y. Pediatric Emergency Visits and Short-Term Changes in PM_{2.5} Concentrations in the U.S. State of Georgia. *Environ. Health Perspect.* **2016**, *124*, 690–696. [[PubMed](#)]
27. Chen, S.Y.; Lin, Y.L.; Chang, W.T.; Lee, C.T.; Chan, C.C. Increasing emergency room visits for stroke by elevated levels of fine particulate constituents. *Sci. Total Environ.* **2014**, *473–474*, 446–450. [[CrossRef](#)] [[PubMed](#)]
28. Ito, K.; Mathes, R.; Ross, Z.; Nadas, A.; Thurston, G.; Matte, T. Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. *Environ. Health Perspect.* **2011**, *119*, 467–473. [[CrossRef](#)]
29. Sarnat, S.E.; Winqvist, A.; Schauer, J.J.; Turner, J.R.; Sarnat, J.A. Fine particulate matter components and emergency department visits for cardiovascular and respiratory diseases in the St. Louis, Missouri-Illinois, metropolitan area. *Environ. Health Perspect.* **2015**, *123*, 437–444. [[CrossRef](#)]
30. Darrow, L.A.; Klein, M.; Flanders, W.D.; Mulholland, J.A.; Tolbert, P.E.; Strickland, M.J. Air pollution and acute respiratory infections among children 0–4 years of age: An 18-year time-series study. *Am. J. Epidemiol.* **2014**, *180*, 968–977.
31. Kumar, P.; Kumar, S.; Yadav, S. Seasonal variations in size distribution, water-soluble ions, and carbon content of size-segregated aerosols over New Delhi. *Environ. Sci. Pollut. Res. Int.* **2018**, *25*, 6061–6078. [[CrossRef](#)] [[PubMed](#)]
32. Pardo, M.; Shafer, M.M.; Rudich, A.; Schauer, J.J.; Rudich, Y. Single Exposure to near Roadway Particulate Matter Leads to Confined Inflammatory and Defense Responses: Possible Role of Metals. *Environ. Sci. Technol.* **2015**, *49*, 8777–8785. [[CrossRef](#)] [[PubMed](#)]
33. Jarvis, I.W.; Bergvall, C.; Bottai, M.; Westerholm, R.; Stenius, U.; Dreij, K. Persistent activation of DNA damage signaling in response to complex mixtures of PAHs in air particulate matter. *Toxicol. Appl. Pharmacol.* **2013**, *266*, 408–418. [[CrossRef](#)] [[PubMed](#)]
34. Hsu, W.H.; Hwang, S.A.; Kinney, P.L.; Lin, S. Seasonal and temperature modifications of the association between fine particulate air pollution and cardiovascular hospitalization in New York state. *Sci. Total Environ.* **2017**, *578*, 626–632. [[CrossRef](#)]
35. Cheng, C.-Y.; Cheng, S.-Y.; Chen, C.-C.; Pan, H.-Y.; Wu, K.-H.; Cheng, F.-J. Ambient air pollution is associated with pediatric pneumonia: A time-stratified case–crossover study in an urban area. *Environ. Health* **2019**, *18*, 77. [[CrossRef](#)]
36. Ramanathan, M., Jr.; London, N.R., Jr.; Tharakan, A.; Surya, N.; Sussan, T.E.; Rao, X.; Biswal, S. Airborne Particulate Matter Induces Nonallergic Eosinophilic Sinonasal Inflammation in Mice. *Am. J. Respir. Cell Mol. Biol.* **2017**, *57*, 59–65. [[CrossRef](#)]
37. Miyata, R.; van Eeden, S.F. The innate and adaptive immune response induced by alveolar macrophages exposed to ambient particulate matter. *Toxicol. Appl. Pharmacol.* **2011**, *257*, 209–226. [[CrossRef](#)]
38. Hassanvand, M.S.; Naddafi, K.; Kashani, H.; Faridi, S.; Kunzli, N.; Nabizadeh, R.; Momeniha, F.; Gholampour, A.; Arhami, M.; Zare, A.; et al. Short-term effects of particle size fractions on circulating biomarkers of inflammation in a panel of elderly subjects and healthy young adults. *Environ. Pollut.* **2017**, *223*, 695–704. [[CrossRef](#)]
39. Wu, Y.; Lu, B.; Zhu, X.; Wang, A.; Yang, M.; Gu, S.; Wang, X.; Leng, P.; Zierold, K.M.; Li, X.; et al. Seasonal Variations, Source Apportionment, and Health Risk Assessment of Heavy Metals in PM_{2.5} in Ningbo, China. *Aerosol Air Qual. Res.* **2019**, *19*, 2083–2092. [[CrossRef](#)]
40. Pan, H.-Y.; Cheung, S.-M.; Chen, F.-C.; Wu, K.-H.; Cheng, S.-Y.; Chuang, P.-C.; Cheng, F.-J. Short-Term Effects of Ambient Air Pollution on ST-Elevation Myocardial Infarction Events: Are There Potentially Susceptible Groups? *Int. J. Environ. Res. Public Health* **2019**, *16*, 3760. [[CrossRef](#)]