

Acute Effects of Ambient Air Pollution on Lower Respiratory Infections in Guangzhou Children of China

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Abstract

Daily concentrations of air pollution are associated with lower respiratory diseases. We investigated the short-term association of ambient air pollution with daily hospital admissions due to pneumonia among children aged 0–17 in Guangzhou city of China. Ambient air pollutants were all positively associated with children hospital admissions due to pneumonia of all ages. Significant associations were found for air pollutants except for inhalable particulate matter (PM) $\leq 10 \mu\text{m}$ in aerodynamic diameter (PM₁₀) in children of all ages. Increments of an interquartile range (IQR) (279.10 $\mu\text{g}/\text{m}^3$ and 28.42 $\mu\text{g}/\text{m}^3$, respectively) in the 7-day-average level of carbon monoxide (CO) and nitrogen dioxide (NO₂) were associated with a 26.17% (95% confidence interval (CI) 1.40%-56.98%) and 25.09% (95%CI 0.54%-55.64%) increase in pneumonia hospitalizations for children aged 6–17, respectively. An IQR increase in CO concentrations was associated with a 15.15% (95%CI 4.34%-27.08%) increase in pneumonia hospitalizations for children aged 1–5. Daily cases of microbial detection for pneumonia were positively associated with daily NO₂ concentration. The pneumonia hospitalizations due to *Mycoplasma pneumoniae*, *Flu A virus* and *Flu B virus*, the predominant pathogenic microorganisms detected in children aged 0–5 are apparently associated with levels of PMs, CO, NO₂ and O₃.

Introduction

Pneumonia in children refers to pulmonary inflammation in the population aged less than 18 years caused by different pathogenic or other factors. It easily occurs in all seasons, mainly in spring and winter^[1]. Severe pneumonia is the major cause of death of children under 5 years old in China, in which, most of patient die of various kinds of pneumonia. Pneumonia pathogens include bacteria, virus and atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* etc. The Western Pacific region had an estimated 0.11 pneumonia episodes per child-year with 61,900 pneumonia-related deaths in children less than 5 years of age in 2011^[2]. Furthermore, family jam^[3] and malnutrition^[4] also result in pulmonary inflammation. Time series analysis shows that pneumonia hospitalizations in children are associated with ambient air pollution level^[5-8]. A child's respiratory system is susceptible to the adverse health effects of air pollution due to lower immunity.

The association between air pollution and hospitalization for acute respiratory infection (ARI) has been investigated worldwide^[9]. Increased concentrations of nitrogen dioxide (NO₂) and sulfur dioxide (SO₂) were associated with increased admissions of pneumonia in Vietnamese children in the dry season (November-April), with excess risks of 8.50% (95% confidence interval (CI) 0.80-16.79) and 5.85% (95%CI 0.44-11.55), respectively. Daily concentrations of particulate matter (PM) $\leq 10 \mu\text{m}$ in aerodynamic diameter (PM₁₀) could be positively associated with increased pneumonia admissions in children in the dry season. Negative associations between air pollutants and pneumonia admissions in children were observed in the rainy season (May-October) in Vietnam^[10]. Daily concentrations of PM₁₀ and ozone (O₃) were strongly associated with hospitalizations of lower respiratory tract infection in children aged 2-5^[11]. In the meantime, a report from Malaysia pointed out that increased acute lower respiratory tract infection admissions in children under 18 were associated with low rainfall but not PM₁₀ nor air pollutant index^[12].

The air quality is getting worse in the progress of industrialization and urbanization process in China, which increases the disease burden of respiratory system^[13]. The air pollutants are acutely and chronically associated with number of hospitalization, morbidity, mortality, clinical symptoms and pulmonary function change for various diseases in China^[14]. If the total suspended particles (TSP) in the atmosphere reached to 184 $\mu\text{g}/\text{m}^3$ in Northern China, life time of local people would be reduced by 5.5 years^[15]. Daily concentration of PM $\leq 2.5 \mu\text{m}$ in aerodynamic diameter (PM_{2.5}) was associated with all-cause mortality in Shanghai city (risk ratio (RR) 1.0068, for time lag0, 95%CI 1.0013-1.0123)^[16]. PM_{2.5} concentration was positively associated with daily hospital admissions for disease of respiratory system in Ji'nan, a provincial capital city in Northern China^[17]. Elevated PM_{2.5} and PM₁₀ were significantly associated with increased emergency department (ED) visits for pneumonia, respiratory tract infection (RTI) and coronary heart disease at both lag0 and lag0-3 in Guangzhou city. A 10 $\mu\text{g}/\text{m}^3$ increment of PM_{2.5-10} (PM_c) was estimated to increase ED visits for pneumonia by 6.32% (95% CI 4.19%-8.49%) and for RTI by 4.72% (95% CI 3.81%-5.63%), respectively. PM_c showed stronger cumulative effects on asthma in children than elderly^[18]. Daily concentration of SO₂ was apparently associated with respiratory mortality in Xi'an (RR 1.4200, 95%CI 0.8270-2.8540), a provincial capital city in Western China^[19]. The air pollutant levels in Wuhan city of Central China and Lanzhou city of Western China were obviously and positively correlated to pneumonia hospitalizations in children^[20].

Guangzhou is the first-tier city in Southern China, covering 7, 434.4 km². Guangzhou had about 14. 90 million inhabitants in 2018 with an average population density of about 2, 005 people/km². Children accounted for 19.11% of the total population here^[21]. The concrete population density and geography location are shown in the additional file 1. The air was seriously polluted by vehicle tail gas, industrial pollution, raised dust of construction sites in Guangzhou city. The proportion of days with Air Quality Index (AQI) levels greater than 100 (unhealthy level to sensitive group) ranged from 4.66% to 41.54% of total monitoring days between 2013 and 2018, according to 2018 year-book of Air Quality in Guangzhou issued by the National Bureau of Statistics of China^[22]. The risk assessment of ambient air pollutants on the daily hospital admissions of pneumonia in Guangzhou children remains sparse. Therefore, this study investigated the short-term effects of exposure to ambient air pollution on hospital admissions due to pneumonia in Guangzhou children under 17 years old. We also explored the impact of age, gender, season and pathogenic microorganism detected results on these associations.

Methods

Data source

Data of ambient air pollutants used in this study came from the Guangzhou Municipal Air Quality Real-time Release Platform of the Chinese Environmental Monitoring Center (http://210.72.1.33:8023/gzaqi_new/RealTimeDate.html) [36]. The hourly means of air pollutants combined the data recorded from eleven fixed monitoring stations, which are Guangya Middle School station (113°23'5"E, 23°14'22"N), Guangzhou No. 5 Middle School station (113°26'1"E, 23°10'5"N), Tianhe Vocational and Youth station (113°33'33"E, 23°13'42"N), Guangdong Business School station (113°34'8"E, 23°09'16"N), Guangzhou No. 8 Sixteen Middle School station (113°43'3"E, 23°10'5"N), Panyu Middle School station (113°35'2"E, 22°94'77"N), Huadu Teachers' station (113°21'5"E, 23°39'17"N), Guangzhou station (113°26'E, 23°27'83"N), Jiulong Zhenlong station (113°56'8"E, 23°27'83" N), Wuhu station (113°28'1"E, 23°15'69"N) and Maofengshan Forest Park station (113°58'9"E, 23 °55'38"N). Data were averaged by station and calendar day to provide 24-h means of PM_{2.5}, PM₁₀, SO₂, NO₂, O₃ and carbon monoxide (CO). The missing data was estimated by linear interpolation, and a total of 1, 707 days from October 28, 2013 to June 30, 2018 of air quality data was obtained.

Data of meteorological factors were collected for the same period from Reliable Prognosis website (<http://rp5.ru/docs/about/cn>) [37], which provides every three hours recording of temperature (in °C), relative humidity (in percent), wind speed (in m/s), rainfall (in mm), atmospheric pressure (in mmHg) and horizontal visibility (in km) at the Guangzhou Airport Meteorological station (113°30'97"E, 23°39'29"N). Data were averaged by calendar day to provide 24-h means of these meteorological data.

Children hospital admission records of pneumonia (International Classification Diseases 11th revision (ICD11) code CA40) sourced from the Guangdong Maternal and Child Healthcare Hospital (GDMCHH), covering a total of 17, 149 anonymous cases from October 28, 2013 to June 30, 2018. The records include clinical diagnosis, admission number, gender, age and pathogenic microorganism test results of sputum cultivation (including *Chlamydia pneumoniae*, *Haemophilus*, *Mycoplasma pneumoniae*, *Influenza A virus*, *Influenza B virus*, *Parainfluenza virus*, *Adenovirus* and *Respiratory syncytial virus*). GDMCHH is a large-scale tertiary hospital with healthcare, medical, educating, scientific research, training and technical guidance. It is the educating hospital of eight universities including Sun Yat-Sen University, while it also establishes cooperation with Boston Children's Hospital of Harvard Medical School. Having two hospital districts with 1,500 beds and one branch of the Guangdong Cord Blood Bank. GDMCHH is one of the best maternal and child healthcare hospital in Southern China. Its clinical diagnosis records greatly reflect the children incidence of pneumonia in Guangzhou city. This study was conducted on October 1st, 2019.

All of the children patient records were anonymized and de-identified, the study underwent an ethical review by the ethical committee of GDMCHH (Approval number: 201901121, September 2019). All research were performed following the approved guidelines. The study was obtained the informed consent of all participants and their legal guardians.

Data analysis

To study the association between ambient air pollution and daily counts of hospital admissions for pneumonia, we used the semi-parametric generalized additive quasi-Poisson regression models with a log-link function and adjustment for over-dispersion, adjusting for potential confounders. Thin plate spline functions were used to capture the time trends and seasonal variations. The potential confounders were integrated into the models which including daily mean temperature, relative humidity, wind speed, rainfall, day of the week (DOW) and holidays. DOW was treated as a categorical variable with values ranging from 1 (Sunday) to 7 (Saturday). We had adjusted for meteorological factors averaged over the same day and the day before (lag 0-1) and over the five days preceding the period (lag 2-6) and the interaction terms between them. Smoothing spline functions were used to non-parametric smooth of the meteorological data. The time nonlinear independent variables (time=1-1707) in the time series data were fitted and the most suitable smooth spline function degree of freedom was selected by the Generalized Cross-Validation (GCV). When the basic model was established, the air pollutant concentrations were added into the model to be the linear variables, we computed the associations between the two days moving average (lag 0-1), three-day moving average (lag 0-2), and seven-day moving average (lag 0-6) air pollutant concentrations and children hospital admissions. To facilitate comparing the effects of air pollutants, results were reported as RRs of hospital admissions with 95% CI for the one interquartile range (IQR) increment in the level of the respective pollutant variable. Meanwhile, analyses were performed for gender, ages (infants, children aged 1-5, aged 6-17 and children of all ages 0-17) and seasons (spring: March - May, summer: June - August, fall: September - November, winter: December - February). Statistical significance was defined as two-tailed *p*-value < 0.05.

We also built two-pollutant models combining the pollutants which including PM₁₀, PM_{2.5}, SO₂, NO₂, CO and O₃. Variance inflation factor (VIF) was used to evaluate the multicollinearity in these models. All pairs of pollutants had VIF-values maximum of 7.6 that is below the threshold of 10 indicating the strong multicollinearity [38].

However, investigations of associations among meteorological factors, air pollutants and the clinical pathogenic microorganism inspection results for pneumonia in children aged 0-17 in China remain sparse. Because of too many zero-values for the detected results of sputum microbial cultivation which obeyed the zero inflation Poisson distribution, these data were not applicable to the ordinary Poisson regression model. In order to find interpretively independent variables as well as improve the explanatory power and accuracy of the models' prediction, we used Lasso regression model to explore the associations between ambient air pollutants and daily detected results of sputum microbial cultivation after considering the effects of meteorological factors, DOW, holidays and seasons. The initial Lasso regression model was derived for the daily cases of microbial detection for pneumonia, and air pollutants (lag 0-6) as well as meteorological factors. The cross-validation method was used to select the Lambda with the least

average error to optimize the model. Finally, we calculated the root mean-square error (RMSE) which indicated the quality of the models. All statistical analyses were completed using the “mgcv”, “spline” and “glmnet” packages of R language (version 3.5.3, <http://www.r-project.org>).

Results

Descriptive statistics for daily hospital admissions and detected results of sputum cultivation present in Table 1, while Table 2 presents descriptive statistics for daily air pollutant concentrations and meteorological variables. The investigation contained 17,149 hospital admissions for pneumonia (i.e., about average 10.04 cases a day). In daily hospital admissions, the counts of male were about 1.8 times than that of female. Out of all hospital admissions, infants, children aged 1-5 years and 6-17 years accounted for 67.30%, 27.70% and 5.03%, respectively. The daily hospital admissions were maximum in spring. The microbiological detection items for children hospitalizations with pneumonia included *Chlamydia pneumoniae*, *Haemophilus*, *Mycoplasma pneumoniae*, *Influenza A virus*, *Influenza B virus*, *Parainfluenza virus*, *Adenovirus* and *Respiratory syncytial virus*. The daily hospital admissions accounted 46.70% for pulmonary *Mycoplasma pneumoniae*, 21.60% and 9.98% for *Flu A* and *B virus* respectively, but 1.99% for *Haemophilus*. There were seasonal preferences for daily hospital admission counts due to different pathogenic microorganisms.

Daily mean concentration of PM_{2.5} was 39.80µg/m³, which exceeded the 24-h mean concentration of fine particles (25µg/m³) by 37.19% set in the World Health Organization (WHO) guidelines for air quality. Daily mean concentration of PM₁₀ was 60.80µg/m³, which exceeded the 24-h mean concentration of inhalable particles (50µg/m³) by 17.76% set in WHO guidelines for air quality. Daily mean concentrations of CO, NO₂, O₃ and SO₂ were 935.00µg/m³, 37.30µg/m³, 46.90µg/m³ and 12.90µg/m³, respectively, which were all lower than WHO standards. Daily concentrations of air pollutants were highest in winter and lowest in summer, except for O₃. While, daily concentration of O₃ was highest in autumn and lowest in winter. It indicated that daily mean concentrations of air pollutants were associated with daily mean temperature, relative humidity and rainfall. Daily means of air pollutants were significantly correlated with each other. Daily means of PM_{2.5} was strongly correlated with daily means of PM₁₀ (Spearman rank correlation coefficient, $r=0.97$). Both daily means of PM_{2.5} and PM₁₀ were correlated to daily means of SO₂, NO₂ and CO ($0.50 \leq |r| \leq 0.80$). And as temperature decreased, the correlation coefficients between daily means of SO₂ and PM_{2.5} or PM₁₀ gradually increased. Daily means of O₃ was remarkably correlated to daily means of PM_{2.5} and PM₁₀ in summer and autumn ($0.50 \leq |r| \leq 0.80$) (see additional file 2). Daily mean temperature, relative humidity and rainfall in Guangzhou city were 21.70°C, 78.00% and 6.70mm, respectively.

The RRs of hospital admissions for pneumonia per IQR of the seven-day (lag 0-6) mean concentrations of the pollutants present in Table 3. Daily hospital admissions for pneumonia were positively associated with all pollutants for children of all ages. Statistically significant associations were observed for all pollutants except for PM₁₀ in children aged 0-17 years. The RRs were statistically significant for PM_{2.5} in infants, CO in children aged 1-5 and 6-17 years, while for SO₂, NO₂ and O₃ in children aged 6-17 years. The strongest effect estimation was observed for CO (RR=1.26, 95% CI 1.01-1.57) in children aged 6-17 years. The RRs of 1.15 (95% CI 1.04-1.27) and 1.06 (95% CI 0.95-1.18) corresponded to about one additional case for short term increments in CO and NO₂ respectively of one IQR (i.e. 279.10 µg/m³, 28.42µg/m³, respectively) in children aged 1-5 years.

The RRs for pneumonia hospitalization were higher among children aged 1–5 and 6-17 years as compared to infants, except for PM_{2.5}. For example, the RR for an IQR increase in CO was highest among children aged 6-17 years and lower in infants (RR=0.97, 95% CI 0.89-1.05). Similar modes were found for lag 0, lag 0-1 and lag 0-2 (see additional file 3, additional file 4 and additional file 5). The RRs per IQR ranged from 0.97 to 1.05 for lag 0, from 0.99 to 1.05 for lag 0-1, from 1.00 to 1.06 for lag 0-3 and from 0.95 to 1.06 for lag 0-6 means for all pollutants in children under 17 years.

The season-specific RRs of pneumonia hospitalizations per IQR increase in the seven-day (lag 0-6) moving average concentrations of ambient air pollutants present in Fig 1. Daily hospital admissions for pneumonia were positively associated with PM_{2.5} and PM₁₀ in gender and all age groups. Daily hospital admissions for pneumonia were statistically significant for all pollutants in children aged 6-17 years, except for PM_{2.5} and PM₁₀. Associations with pneumonia hospitalizations were significantly different for pollutants in different seasons. For example, the RR for an IQR increase in SO₂ was higher among children aged 6-17 years in the winter (RR=1.43, 95% CI 1.09-1.87). The RR per IQR for NO₂ was higher in the summer (RR=3.99, 95% CI 1.42-11.26). And the RR per IQR for CO was higher in the spring (RR=1.60, 95% CI 1.08-2.37). Similar modes were found for lag 0, lag 0-1 and lag 0-2 (see additional file 3, additional file 4 and additional file 5).

Two-pollutant models presented in Fig 2 and additional file 6. Estimates for NO₂ were the largest (per IQR) after inclusion of PM_{2.5} and PM₁₀, but stable after inclusion of SO₂ and CO. Effects of CO were higher after inclusion of PM_{2.5} and PM₁₀, but stable after inclusion of other pollutants. In contrast, effects of O₃ all dropped or lost statistical significance after inclusion of PM_{2.5}, PM₁₀, SO₂ or NO₂ in children aged 6-17 years. Results for pneumonia and O₃ were also insensitive to the inclusion of other pollutants in other age groups (see additional file 6).

The season-specific two-pollutant models of NO₂ and CO for age groups presented in Fig 3. Daily hospital admissions for pneumonia were statistically significant difference in different seasons. Effects of NO₂ were higher in summer and autumn after inclusion of PM_{2.5}, PM₁₀, SO₂, CO and O₃. Furthermore, estimates for NO₂ were the larger with the increase of age. Estimates for CO were somewhat less sensitive to seasonal variation. Effects of CO were statistically significant among children under 5 years old in summer. But, effects of CO were significantly higher in spring after inclusion of PM_{2.5}, PM₁₀, SO₂ or NO₂ in children aged 6-17 years.

The descriptive statistics of the clinical pathogenic microorganism inspection results for pneumonia presents in additional file 7. The detected cases of pulmonary *Mycoplasma pneumoniae* were the most predominant. The positive rate of detection for female was higher than that for male, and the positive rate was the largest in the age group 1–5 year. The positive rate minimized in winter for all kinds of pathogenic microorganisms, except that for *Chlamydia pneumoniae* and *Hemophilus*. The cases of microbial detection due to pneumonia increased initially, but decreased during 2014 to 2018.

The Lasso regression model was derived for the daily cases of microbial detection due to pneumonia and air pollutants (lag 0-6), combined with meteorological factors. Regression coefficients (RCs) and root mean square errors (RMSEs) of models present in Table 4. RCs of NO₂ were always positive which indicated that NO₂ had positive effects on the daily cases of microbial detection for pneumonia. RCs of O₃ were almost positive except for *Flu B virus*, *Chlamydia pneumoniae* and *Adenovirus*. While RCs of SO₂ were almost negative, except for *Adenovirus*, which indicated that SO₂ had negative effects on the daily cases of microbial detection. Detailed estimates present in additional file 8 and additional file 9. RCs of O₃, PM_{2.5} and PM₁₀ were mainly positive for children less than 5 years-old. RCs of SO₂, NO₂ and CO were mainly positive for children aged 6-17 years-old (see additional file 10).

Discussion

We finished a time-series larger population-based study on the acute effects of ambient air pollution on children's health in Guangzhou city of China. Overall, associations with pneumonia hospital admissions were strongest for CO and NO₂. Increments of an IQR (279.10 µg/m³ and 28.42µg/m³ respectively) in the 7-day-average level of CO and NO₂ were associated with a 26.17% (95%CI 1.40%-56.98%) and 25.09% (95%CI 0.54%-55.64%) increase in pneumonia hospitalizations for children aged 6-17, respectively. An IQR increase in CO concentrations (279.10 µg/m³) was associated with a 15.15% (95%CI 4.34%-27.08%) increase in pneumonia hospitalizations for children aged 1-5. These results are basically consistent with the previous conclusions which showing children hospital admissions for ARI associated with markers of primary traffic pollutants such as CO or NO₂ [23].

In this study, parts of ambient air pollutions levels were relatively higher than WHO standards, especially in winter. During 2013 and 2018, daily mean PM_{2.5} levels ranged from 4.61µg/m³ to 155.00µg/m³ which exceeded the WHO guideline value (24-h mean is 25µg/m³) on 1184 days (69.36%), while daily mean PM₁₀ levels ranged from 9.96µg/m³ to 208.29µg/m³ which exceeded recommended levels on 931 days (54.54%). Daily mean CO levels ranged from 479.30µg/m³ to 2610.00µg/m³ which exceeded the WHO guideline value (24-h mean is 2000µg/m³) on 5 days, daily mean NO₂ levels ranged from 0.55µg/m³ to 163.25µg/m³ which exceeded the WHO guideline value (24-h mean is 40µg/m³) on 751 days, daily mean SO₂ levels ranged from 2.00µg/m³ to 53.00µg/m³ which exceeded the WHO guideline value (24-h mean is 20µg/m³) on 190 days, and daily mean O₃ levels ranged from 3.46µg/m³ to 139.21µg/m³ which exceeded the WHO guideline value (8-h mean is 100µg/m³) on 59 days.

Lots of epidemiological and clinical studies indicated that ambient particulate matter (PM) in air pollution was strongly associated with increased cardiovascular disease, respiratory disease, chronic obstructive pulmonary disease and heart disease in urban residents [24]. PM₁₀ could be positively associated with increased pneumonia admissions in children in the dry season [10]. Daily mean PM₁₀ levels were associated with prolonged hospitalizations in children aged 2–5 years in Vietnam [11]. Unexpectedly, we find that the associations between daily mean PM₁₀ levels and pneumonia hospitalizations of children were not statistically significant in all age groups. Although, a study showed positive associations between ARI and both NO₂ and PM₁₀ during the dry season 2003-2005 [25], but the results were not statistically significant given the rather short series and limited statistical power [26]. Another report pointed out that increased acute lower respiratory tract infection admissions in children under 18 were associated with low rainfall but not PM₁₀ nor air pollutant index [12]. So, why are the effects of PM₁₀ completely different in different regions? Is it possible that the effect of PM₁₀ is mainly related to climate factor, immunity and age? Sure, the differences of the effect of PM₁₀ may also be determined by genetic predisposition. We interestingly find that air pollutants might exacerbate genetic variations associated with asthma, including *GLUTATHIONE-S-TRANSFERASE M1 (GSTM1)* and *GLUTATHIONE-S-TRANSFERASE P1 (GSTP1)* gene. Among them, *GSTP1* modified the delayed effects of PM₁₀ and Consistent with previous studies, early living in polluted atmospheric can damage lung function on an average of 24-h for three days, and enhanced the lung respiratory function of carriers. Individuals carrying G allele could reduce the adverse effects of air pollutant in children of South Africa [27]. The gene expression level of white blood cells in Ostrava area polluted by high PM concentration had been measured. It was found that the cellular immune response pathway was affected by higher PM concentration. The expression of *APURINIC/APYRIMIDINIC ENDONUCLEASE (APEX)*, *ATAXIA-TELANGIECTASIA MUTATED (ATM)*, *FAS CELL SURFACE DEATH RECEPTOR (FAS)*, *GLUTATHIONE S-TRANSFERASE MU1 (GSTM1)*, *INTERLEUKIN1 BETA (IL1B)* and *RAD21 HOMOLOG (Schizosaccharomyces pombe) (RAD21)* decreased significantly in Ostrava subjects, and the pathways related to neurodegenerative diseases were significantly correlated with PM_{2.5} exposure in Prague subjects of the Czech Republic [28]. In addition, there have been relatively few researchers studied on the gene-PM exposure interactions, and most have done on a small number of loci for genetic polymorphisms. The possible underlying molecular mechanisms for PM exposure induced increases of acute lower respiratory infections in children remain the mystery.

About 95% of children in this study population are under 5 years of age. And a larger proportion (e.g. 67.31%) of children are infants. Hence, our results mainly reflect the effects of air pollutants in children under 5 years of age. Generally, the tertiary general hospital has a Pediatric Department in China. But hospital beds for children and the numbers of pediatric doctors are limited almost in all hospitals. Guangzhou is a super city with a population of more than 10 million. Therefore, most children with conditions requiring hospitalization are likely admitted to GDMCHH. Normally, GDMCHH is the most crowded specialist children's hospital in Guangzhou city, and children under 5 years of age are prioritized. And older children are preferably transferred to

other local hospitals. Our results showed that the RR was statistically significant only for PM_{2.5} in infants (RR =0.90, 95%CI 0.82-0.99). And a study findings suggested that parental exposure to PM_{2.5} could increase infant mortality differently by the timing of exposure and gender, which suggested a relation to fetal development in South Korea [29]. Zwodziazak et al. reported a decrease in lung function parameters with increasing exposure of indoor PM₁ in school children [30]. This may be an indication that smaller size PMs induce stronger inflammatory responses, particularly the ultrafine particles that can penetrate deeply into lung alveoli or be transported to other organs [31,32]. These results also suggested that high smaller size PMs exposures might adversely influence both development of the innate immune system and development of lung function of infants. Hence, to protect infancy vulnerability of the rapid lung and immune system development from high levels of air pollution exposure is very important during the early months of life.

Our results demonstrated that the association of CO with hospital admissions due to pneumonia reached statistical significance in children aged 1-5 (RR =1.15, 95%CI 1.04–1.27). And the RR per IQR for CO was higher in the spring (RR=1.60, 95% CI 1.08-2.37). Estimates for CO were statistically significant among children aged 1-5 years in summer. While there was a diametrically opposite conclusion for CO in Hanoi, Vietnam [33]. How to explain this contradiction is a vexed one. Although, daily mean CO levels just exceeded the WHO guideline value on 5 days in Guangzhou during October 28, 2013 to June 30, 2018. But, effects of CO were significantly higher in spring after inclusion of PM_{2.5}, PM₁₀, SO₂ or NO₂ in children aged 6-17 years.

We find that associations between air pollutants (CO, SO₂, NO₂ and O₃) and pneumonia hospitalizations of children aged 6-17 years were statistically significant in Guangzhou city. Generally, Guangzhou children living in a super city should spend more time for going to schools and coming back home, the primary traffic pollutants concentrations such as PMs, CO or NO₂ were the highest during that time. No doubt the timing of air pollutants exposure increased. An investigation showed that acute lower respiratory infection admissions among children under 5 years of age were generally positively associated with ambient levels of PM₁₀, NO₂, and SO₂ during the dry season, but not the rainy season, and negative results in the rainy season could be driven by residual confounding present from May to October in Ho Chi Minh City, Vietnam [10]. Daily concentration of SO₂ was apparently associated with respiratory mortality in Xi'an city [19]. Daily concentrations of CO, NO₂, SO₂, and PM₁₀ were significantly associated with increased risk of both cardiovascular and respiratory hospital admissions, whereas O₃ was associated with only respiratory hospital admission [33,34]. The observed seasonal difference in hospital admissions is larger than what one expects based on the difference in air pollution alone. The latter is though only one out of many determinants of hospital admissions.

The results of two pollutant models are presented in Fig 2 and additional file 6. Basically, two-pollutant models could be used to evaluate the possible roles of single pollutants. Pneumonia related estimates for NO₂ were higher after inclusion of PM_{2.5} and PM₁₀ in summer and autumn, but stable after inclusion of SO₂ and CO. Estimates for CO were statistically significant among children aged 1-5 years in summer. The two-pollutant models revealed consistent patterns across all outcomes luckily as shown in additional file 6.

Another feature of this study is to demonstrate associations between air pollutants and the clinical pathogenic microorganism inspection results in the cases of hospitalization due to pneumonia among Guangzhou children. The clinical pathogenic microorganism inspection results for pneumonia are shown in additional file 7. The detected cases of pulmonary *Mycoplasma pneumoniae* were the most predominant, accounting for 37.28% of total detected cases of microorganism inspection (TDCMI). The positive rate was the largest in the age group 1-5 years. The positive rate minimized in winter for all kinds of pathogenic microorganisms, except that for *Chlamydia pneumoniae* and *Hemophilus*. The Lasso regression model was derived for the daily cases of microbial detection due to pneumonia and air pollutants (lag 0-6), combined with meteorological factors. RCs of daily mean NO₂ levels were always positive which indicated that NO₂ had significantly positive effects on the daily cases of microbial detection for pneumonia. RCs of daily mean O₃ levels were almost positive except for *Flu B virus*, *Chlamydia pneumoniae* and *Adenovirus*. While RCs of daily mean SO₂ levels were almost negative, except for *Adenovirus*, which indicated that daily mean SO₂ levels had negative effects on the daily cases of microbial detection. We find out that RCs of daily mean PM₁₀ levels were positive for *Mycoplasma pneumoniae*, *Parainfluenza virus* and *Haemophilus*, which accounting for 37.27%, 6.65% and 1.62% of TDCMI in children aged 0-17, respectively; the detected cases of these three kinds of pathogenic microorganisms accounted for 45.56% of TDCMI in whole children population. RCs of daily mean PM_{2.5} levels were both positive for *Flu A virus* which accounting for 4.61% only in infants and 15.64% among the 1-5 year age group, and *Flu B virus* which accounting for 10.68% only in infants and 32.60% among the 1-5 year age group; the detected cases of these two kind of pathogenic microorganisms accounted for 25.74%. RCs of daily mean PM₁₀, NO₂, CO and O₃ levels were positive to *Mycoplasma pneumoniae* which accounting for 24.89% in infants and 63.36% among the 1-5 year age group simultaneously. RCs of daily mean PM_{2.5} and NO₂ levels were positive to *Influenza A and B virus* simultaneously. RCs of daily mean O₃, PM_{2.5} and PM₁₀ levels were mainly positive for children less than 5 years-old. RCs of daily mean SO₂, NO₂ and CO levels were mainly positive for children aged 6-17 years. The pneumonia hospitalizations due to *Mycoplasma pneumoniae*, *Flu A virus* and *Flu B virus* in children aged 0-5 are apparently associated with the levels of air pollutants (i.e. PMs, NO₂, CO and O₃). And pathogenic microorganisms, such as *Mycoplasma pneumoniae*, *Flu A virus* and *Flu B virus*, might be possibly carried by PMs, which increased risks of the acute lower respiratory infections in children aged 0-5 years. We fortunately found a study from Urumqi city of Western China, which reported that the microorganisms responsible for human allergy and respiratory disease carried by PM₁₀ and PM₁ had been analyzed during winter. Their results showed that the bacterial community was mainly composed of *Proteobacteria*, *Firmicutes* and *Actinobacteria*. The sequences of several pathogenic bacteria and opportunistic pathogens were also detected, such as *Acinetobacter*, *Delftia*, *Serratia*, *Chryseobacterium*, which might impact on immunocompromised populations (elderly, children and postoperative convalescence patients) [35]. However, to our knowledge, no previous study has studied the association between outdoor air pollutants and daily cases of microbial detection for pneumonia in children. Nowadays, further investigations are warranted.

This study has some limitations. The GDMCHH is the tertiary hospital, children with severe diseases might make up a larger proportion than in other hospitals. No doubt, outpatients were excluded from our study. Therefore, to obtain a more convincing explanation of the effects of air pollutants among children aged 6-17 years, the data from other local tertiary hospitals would be used to analyze. The effect estimates in our model are based on the sample size. If our sample size was large enough, the conclusions should be more accurate.

Conclusion

In summary, we have found the positive associations between children's hospital admissions for lower respiratory infections and air pollutants as well as associations between air pollutants and the clinical pathogenic microorganism inspection results in the cases of hospitalization due to pneumonia among Guangzhou children. Significant associations were found for air pollutants except for PM₁₀ in children aged 0-17 years. Our study suggested that short-term exposures to air pollutions, especially to CO and NO₂, were associated with increased risk of hospital admissions for pneumonia of children under 17 years old. The pneumonia hospitalizations due to *Mycoplasma pneumoniae*, *Flu A virus* and *Flu B virus*, the predominant pathogenic microorganisms detected in children aged 0-5 are apparently associated with levels of smaller size particulate matters, carbon monoxide, nitrogen dioxide and ozone. We suggest the Guangzhou Municipal Government should make more efforts to improve the local air quality.

Abbreviations

ARI: Acute Respiratory Infection

CI: Confidence Interval

ED: Emergency Department

RTI: Respiratory Tract Infection

RR: Risk Ratio

AQI: Air Quality Index

GDMCHH: Guangdong Maternal and Child Healthcare Hospital

DOW: Day of the Week

IQR: Interquartile Range

VIF: Variance Inflation Factor

RMSE: Root Mean-Square Error

RCs: Regression Coefficients

WHO: World Health Organization

TDCMI: Total Detected Cases of Microorganism Inspection

Declarations

Authors' contributions

M. H. conceived the idea of the study, designed the study. HW Z., LL Y., W Q., ZY X., LT W. and JM J. collected and analyzed the data. All authors discussed the results, revised the manuscript and approved the final manuscript.

Additional information

Ethics approval and consent to participate

The study obtained ethical approval from the ethical committee of the Guangdong Maternal and Child Healthcare Hospital (Approval number: 201901121, September 2019).

Availability of data and materials

The datasets of ambient air quality data and meteorological data supporting the conclusions of this article are available in the Guangzhou Municipal Air Quality Real-time [http://210.72.1.33:8023/gzaqi_new/RealTimeDate.html] and Reliable Prognosis website [<http://rp5.ru/docs/about/cn>]

The datasets of daily hospitalized records analyzed during the current study are not publicly available due their containing information that could compromise the privacy of research participants but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Descriptive statistics for daily pneumonia hospital admissions and detected results of sputum cultivation in Guangzhou, 2013-2018

Group	Number of admissions	Daily mean (SD)	Daily mean in spring (SD) (March-May)	Daily mean in summer (SD) (July-August)	Daily mean in fall (SD) (September-November)	Daily mean in winter (SD) (December-February)
By gender						
Boy	10973	6.43(5.10)	7.68(5.54)	5.98(4.33)	5.72(4.96)	6.17(5.18)
Girl	6176	3.62(3.13)	4.37(3.39)	3.14(2.59)	3.38(3.14)	3.49(3.14)
By age						
<1 year	11543	6.76(5.34)	8.47(5.93)	6.21(4.29)	5.83(5.24)	6.33(5.26)
1-5 years	4743	2.78(2.59)	3.13(2.75)	2.38(2.21)	2.84(2.72)	2.71(2.57)
6-17 years	863	0.51(0.87)	0.45(0.79)	0.53(0.91)	0.43(0.74)	0.61(1.01)
All age 0-17	17149	10.10(7.60)	12.10(8.31)	9.12(6.18)	9.10(7.52)	9.66(7.71)
Microbe						
Chlamydia pneumoniae	104	0.06(0.29)	0.08(0.32)	0.07(0.33)	0.04(0.21)	0.06(0.27)
Haemophilus	278	0.16(0.56)	0.30(0.80)	0.09(0.36)	0.08(0.32)	0.16(0.56)
Mycoplasma pneumoniae	6393	3.75(3.64)	4.74(4.41)	3.59(3.16)	3.57(3.41)	3.02(3.13)
Influenza A virus	1397	0.81(1.88)	0.95(1.93)	0.84(1.76)	0.86(2.17)	0.63(1.66)
Influenza B virus	3018	1.77(2.63)	2.66(2.89)	1.77(2.45)	1.36(2.61)	1.21(2.25)
Parainfluenza virus	1142	0.67(1.43)	0.93(1.62)	0.57(1.40)	0.59(1.36)	0.56(1.27)
Adenovirus	627	0.37(0.83)	0.56(0.98)	0.41(0.90)	0.28(0.78)	0.22(0.54)
Respiratory syncytial virus	1042	0.61(1.27)	0.72(1.24)	0.66(1.34)	0.66(1.55)	0.42(0.89)

Table 2. Overall and seasonal distribution of daily pollutant concentrations, Guangzhou, 2013-2018

Variable	Daily mean (SD)	Median	Minimum-maximum	Interquartile range	Daily mean in spring (SD) (March-May)	Daily mean in summer (SD) (July-August)	Daily mean in fall (SD) (September-November)	Daily mean in winter (SD) (December-February)
Pollutants ($\mu\text{g}/\text{m}^3$)								
24h PM _{2.5}	39.80(22.90)	34.00	4.61-155.00	27.20	37.00(17.60)	26.80(12.90)	40.70(19.00)	53.10(29.50)
24h PM ₁₀	60.80(30.10)	53.00	9.96-208.00	37.30	58.00(24.60)	44.50(16.60)	64.00(27.50)	75.30(38.10)
24h SO ₂	12.90(5.89)	11.50	2.00-53.00	6.50	12.60(4.91)	11.60(3.98)	13.00(5.38)	14.30(7.97)
24h NO ₂	37.30(25.70)	37.60	0.55-163.00	28.40	40.80(24.30)	27.70(16.90)	34.80(23.90)	44.60(31.60)
24h CO	935.00(238.00)	890.00	479.00-2610.00	279.00	922.00(218.00)	788.00(128.00)	934.00(153.00)	1080.00(303.00)
8h O ₃	46.90(25.20)	43.60	3.46-139.00	35.80	43.10(26.10)	52.20(25.40)	52.60(27.00)	41.00(19.80)
Meteorological factors								
Temperature (°C)	21.70(6.27)	23.10	3.46-31.40	23.70	21.90(4.57)	28.20(1.70)	23.50(4.17)	14.20(3.73)
Pressure (mm/Hg)	758.00(24.70)	760.00	380.00-778.00	8.10	754.00(40.90)	753.00(17.21)	760.00(12.30)	765.00(11.30)
Relative Humidity (%)	77.90(11.20)	79.10	29.60-99.80	13.50	81.80(9.73)	81.40(7.75)	77.10(9.67)	71.70(13.30)
Wind speed (m/s)	2.31(0.95)	2.13	0.50-6.75	1.25	2.19(0.83)	2.05(0.76)	2.27(0.95)	2.68(1.09)
Horizontal visibility (km)	12.60(5.93)	11.70	0.68-30.00	8.05	11.10(5.93)	15.00(5.79)	12.40(5.56)	12.10(5.75)
Precipitation (mm)	6.70(18.00)	0.00	0.00-222.00	4.10	9.10(21.90)	12.30(23.80)	3.16(9.48)	2.40(9.63)

Table 3. RR for an IQR increase in the 7-day moving average (lag 0-6) of ambient air pollution concentrations and children pneumonia hospital admissions

Daily hospital admissions and interquartile range units presented in Table 2. Risk ratios (RR) estimated from Quasi-Poisson regression models, adjusting for secular trends and seasonal variation, day of the week, holiday, influenza epidemic, and meteorological factors including temperature, relative humidity, pressure, horizontal visibility, precipitation and wind speed average. * $p < 0.05$. ** $p < 0.01$ (Wald χ^2 test).

Outcome by pollutant	All ages (0-17)			< 1 Years of age			1-5 Years old			6-17 Years old		
	RR	95%CI		RR	95%CI		RR	95%CI		RR	95%CI	
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
PM _{2.5}	0.95	0.87	1.03	0.90*	0.82	0.99	1.07	0.97	1.18	1.11	0.90	1.37
PM ₁₀	0.97	0.90	1.05	0.93	0.86	1.02	1.06	0.97	1.17	1.09	0.90	1.35
SO ₂	1.00	0.94	1.07	0.98	0.91	1.05	1.03	0.94	1.13	1.21*	1.02	1.45
NO ₂	1.06	0.98	1.14	1.03	0.95	1.12	1.06	0.95	1.18	1.25*	1.01	1.56
CO	1.02	0.94	1.11	0.97	0.89	1.05	1.15**	1.04	1.27	1.26*	1.01	1.57
O ₃	0.98	0.91	1.06	1.01	0.93	1.10	0.94	0.85	1.04	0.81*	0.66	1.00

Table 4. Regression coefficients of the 7-day moving average ambient air pollutants in Lasso regression models with cases of pneumonia microbial detection

	PM _{2.5}	PM ₁₀	SO ₂	NO ₂	CO	O ₃	RMSE
<i>Chlamydia pneumoniae</i>	-1.46×10 ⁻²	0	-1.47×10 ⁻¹	4.00×10 ⁻²	-1.20×10 ⁻³	0	0.28
<i>Haemophilus</i>	-4.36×10 ⁻²	8.40×10 ⁻³	-1.19×10 ⁻¹	1.48×10 ⁻²	3.32×10 ⁻³	9.50×10 ⁻³	0.51
<i>Mycoplasma pneumoniae</i>	-3.48×10 ⁻²	2.00×10 ⁻²	-3.15×10 ⁻²	8.50×10 ⁻³	7.00×10 ⁻⁴	4.00×10 ⁻⁴	2.85
<i>Influenza A virus</i>	2.67×10 ⁻²	-9.50×10 ⁻³	-2.31×10 ⁻¹	7.15×10 ⁻²	-5.91×10 ⁻³	4.80×10 ⁻³	1.50
<i>Influenza B virus</i>	3.69×10 ⁻²	-2.36×10 ⁻²	-2.87×10 ⁻²	2.17×10 ⁻²	-2.32×10 ⁻³	-7.00×10 ⁻⁴	2.17
<i>Parainfluenza virus</i>	-6.74×10 ⁻²	2.01×10 ⁻²	-8.15×10 ⁻²	4.10×10 ⁻²	1.31×10 ⁻³	3.90×10 ⁻³	1.29
<i>Adenovirus</i>	-2.30×10 ⁻²	-5.70×10 ⁻³	0	3.16×10 ⁻²	0	0	0.76
<i>Respiratory syncytial virus</i>	-1.20×10 ⁻²	-6.10×10 ⁻³	-1.80×10 ⁻¹	5.59×10 ⁻²	-1.71×10 ⁻³	1.16×10 ⁻²	1.07

Figures

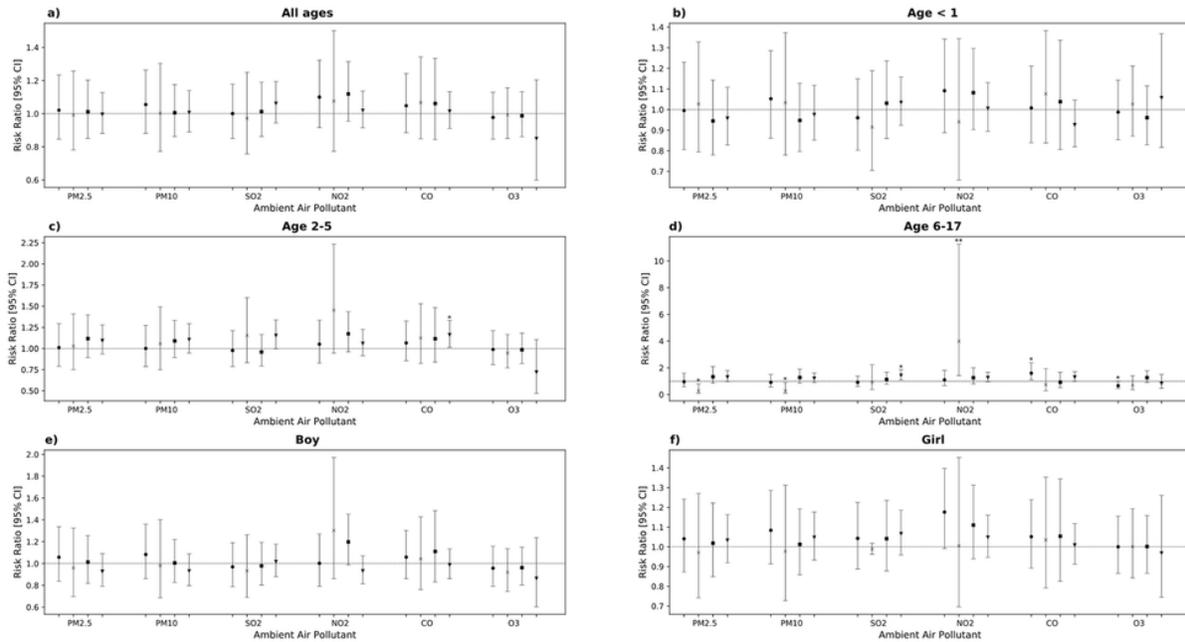


Figure 1
 Season-specific RR per IQR increment in the seven-day moving average (lag 0-6) ambient air pollutant concentrations for a) all ages, b) infants, c) age 1-5, d) age 6-17, e) boys, f) girls, in Guangzhou. Circle dot: Spring (March-May), cross symbol: Summer (June-August), square: Fall (September-November), triangle point down: Winter (December-February). Bar: 95% confidence intervals, *p < 0.05. **p < 0.01.

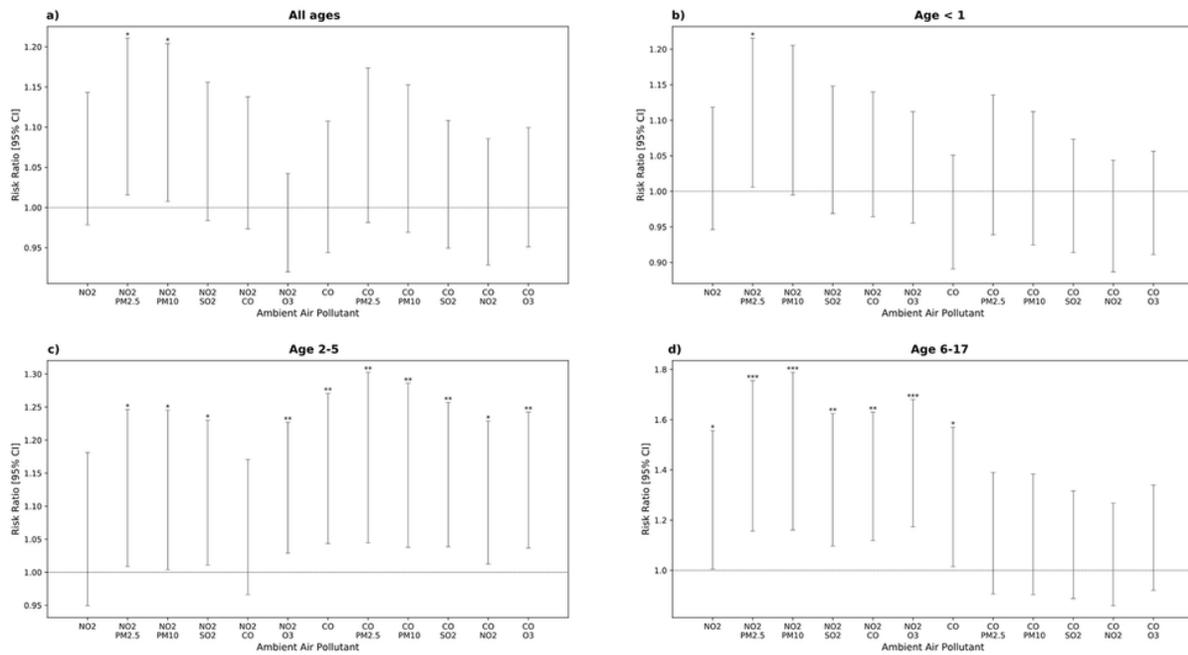


Figure 2

RR per IQR increment of NO₂ and CO respectively, from single pollutants models (left most estimated) and two pollutant models with adjustment for PM_{2.5}, PM₁₀, SO₂, NO₂, CO and O₃, for a) all ages, b) age < 1, c) age 1-5, d) age 6-17, Guangzhou. Bar: 95% confidence intervals, *p < 0.05. **p < 0.01. ***p < 0.001.

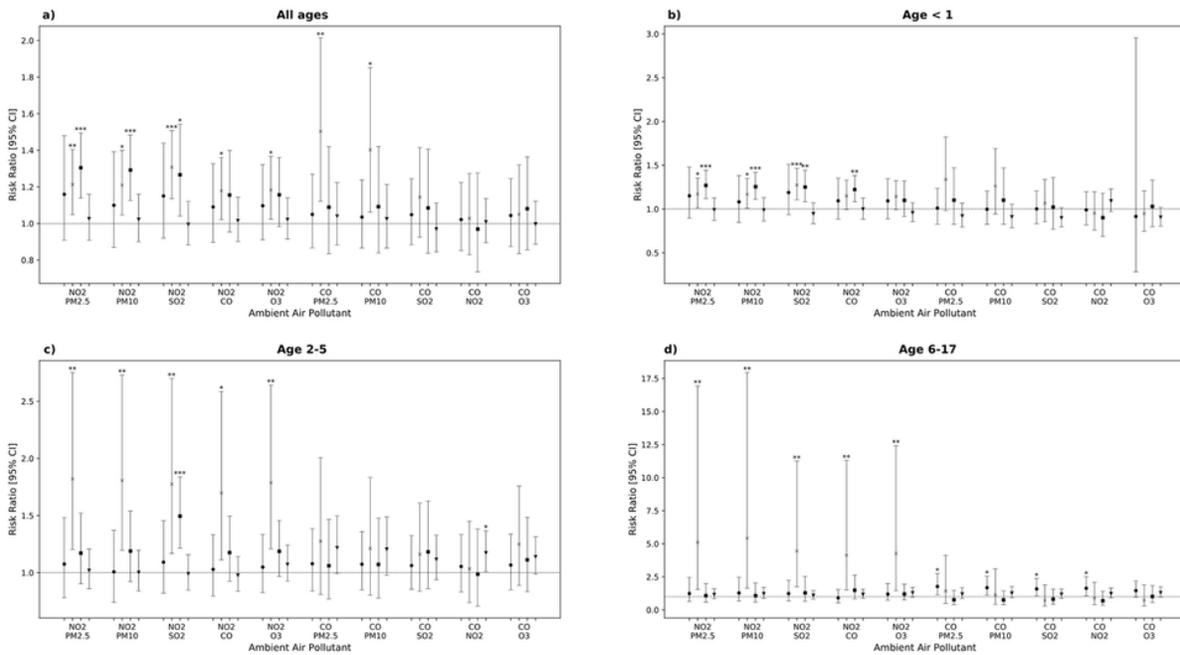


Figure 3

Season-specific estimated RR per IQR increment of NO₂ and CO respectively, two pollutant models with adjustment for PM_{2.5}, PM₁₀, SO₂, NO₂, CO and O₃, for a) all ages, b) age < 1, c) age 1-5, d) age 6-17, Guangzhou. Circle dot: Spring (March-May), cross symbol: Summer (June-August), square: Fall (September-November), triangle point down: Winter (December-February). Bar: 95% confidence intervals, *p < 0.05. **p < 0.01. ***p < 0.001.

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