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Effects of fine particulate matter and its chemical constituents on influenza-like illness in Guangzhou, China

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ABSTRACT

Background: Although the link between fine particulate matter ($PM_{2.5}$) and influenza-like illness (ILI) is well established, the effect of the chemical constituents of $PM_{2.5}$ on ILI remains unclear. This study aims to explore this effect in Guangzhou, China.
Methods: Daily data on ILI cases, $PM_{2.5}$ levels, and specific $PM_{2.5}$ constituents (black carbon [BC], chlorine [Cl^-], ammonia [NH_4^+], nitrate [NO_3^-], and sulfate [SO_4^{2-}]) in Guangzhou, China, were collected for the period of 2014–2019. Additionally, data on gaseous pollutants and meteorological conditions were obtained. By using quasi-Poisson regression models, the association between exposure to $PM_{2.5}$ and its constituents and ILI risk was estimated. Stratified subgroup analyses were performed by gender, age, and season to explore in depth the effects of these factors on disease risk.
Results: Single-pollutant modeling results showed that an increase of one interquartile range (IQR) in Cl^-, SO_4^{2-}, $PM_{2.5}$, NH_4^+, BC, and NO_3^- corresponded to relative risks of ILI of 1.046 (95 % CI: 1.004, 1.090) (lag03), 1.098 (95 % CI: 1.058, 1.139) (lag01), 1.091 (95 % CI: 1.054, 1.130) (lag02), 1.093 (95 % CI: 1.049, 1.138) (lag02), 1.111 (95 % CI: 1.074, 1.150) (lag03), and 1.103 (95 % CI: 1.061, 1.146) (lag03), respectively. Notably, the association between ILI and BC remained significant even after adjusting for $PM_{2.5}$ mass. Subgroup analyses indicated that individuals aged 5–14 and 15–24 years may exhibit higher sensitivity to BC and Cl^- exposure than other individuals. Furthermore, stronger associations were observed during the cold season than during the warm season.
Conclusions: Results showed that the mass and constituents of $PM_{2.5}$ were significantly correlated with ILI. Specifically, the carbonaceous fractions of $PM_{2.5}$ were found to have a pronounced effect on ILI. These findings underscore the importance of implementing effective measures to reduce the emission of specific sources of $PM_{2.5}$ constituents to mitigate the risk of ILI. Nevertheless, limitations such as potential exposure misclassification and regional constraints should be considered.

1. Introduction

Influenza-like illness (ILI) refers to fever (body temperature ≥ 38 °C) accompanied with either coughing or sore throat. It is a common respiratory syndrome that is caused by various pathogens and is used globally as an indicator of influenza activity (Ng and Gordon, 2015; Su et al., 2019). ILI exerts a substantial adverse effect on public health, contributing considerably to annual morbidity and mortality rates (Paget et al., 2019; Iuliano et al., 2018). Specifically, in China, influenza was linked to an additional 2.5 ILI consultations per 1000 individuals

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across 30 provinces (Feng et al., 2020). A large body of evidence shows that exposure to air pollutants is associated with a remarkably increased risk of ILI (Huang et al., 2016; Feng et al., 2016; Lindner-Cendrowska and Brode, 2021; Toczylowski et al., 2021; Lu et al., 2022).

According to the 2019 Global Burden of Disease Study, air pollution ranks fourth in terms of the global burden of disease and has a severe global impact. Air pollution is responsible for approximately 4.14 million deaths and 181 million disability-adjusted life years (Lancet, 2020). Among the adverse effects of various pollutants, those of ambient particulate matter (PM) have attracted considerable attention. PM can be categorized into PM_{10} (≤10 μm), $PM_{2.5}$ (≤2.5 μm), and PM_1 (≤1 μm) on the basis of aerodynamic diameter. $PM_{2.5}$ is the main air pollutant in China and is characterized by a complex chemical composition that includes carbon constituents, organic compounds, water-soluble ions, and inorganic elements (Pateraki et al., 2020; Son et al., 2012). The composition of $PM_{2.5}$ is highly variable and influenced by factors, such as combustion sources, seasonal variations, climate, and industrial or urban pollution type. $PM_{2.5}$ is hypothesized to exert different health effects depending on its chemical composition (Li et al., 2015; Bachwenkizi et al., 2021; Samoli et al., 2016).

Previous studies have identified correlations between specific chemical constituents of $PM_{2.5}$ and various health outcomes (Lin et al., 2016a; Zhou et al., 2022; Masselot et al., 2022), particularly those affecting the respiratory system (Hwang et al., 2017; Wang et al., 2022; Jones et al., 2015). For example, organic carbon (OC), black carbon (BC), sulfate (SO_4^{2-}), ammonia (NH_4^+), and nitrate (NO_3^-) have been associated with increased asthma incidence (Hwang et al., 2017; Wang et al., 2022; Khreis et al., 2017). Furthermore, a positive correlation has been observed among OC, elemental carbon (EC), and high respiratory mortality (Zhou et al., 2022). Although numerous studies have linked short-term $PM_{2.5}$ exposure to ILI, the health effects of the chemical composition of $PM_{2.5}$ on ILI have not been investigated.

In this study, we conducted a time-series analysis covering the period of 2014–2019 in Guangzhou, a megacity located in southern China. Our main objective is to identify the specific constituents of $PM_{2.5}$ with the greatest effect on ILI. By employing statistical analysis, this study provides epidemiological evidence for exploring the biological mechanisms linking $PM_{2.5}$ constituents to ILI. This study aims to deepen the understanding of the health effects of $PM_{2.5}$ on ILI to support the development of effective air pollution control strategies.

2. Materials and methods

2.1. Data collection

2.1.1. Data of ILI cases

We used the China National Notifiable Diseases Reporting System to obtain data on daily ILI cases in Guangzhou between 2014 and 2019. ILI cases were identified on the basis of symptoms of acute respiratory infection, a body temperature above 38 °C, and other undiagnosed symptoms. Influenza, a class C infectious disease, was confirmed via virus isolation and identification from nasopharyngeal swabs collected at sentinel hospitals, with results reported online within 24 h. ILI cases were categorized into five age groups: 0–4, 5–14, 15–24, 25–59, and ≥ 60 years old.

2.1.2. Air pollution data

We used the China High Air Pollutants (CHAP, available at https://weijing-rs.github.io/product.html) grid dataset for Guangzhou City. This dataset includes the daily average concentrations of $PM_{2.5}$ and its constituents (BC, Cl^-, NH_4^+, NO_3^-, and SO_4^{2-}), as well as gaseous pollutants (NO_2, SO_2, and O_3) (Wei et al., 2021a, 2019, 2021b); (Wei et al., 2022a, 2022b, 2022c). The CHAP dataset, known for its broad coverage, high resolution (1 km × 1 km), long-term data, and high quality, is generated by using artificial intelligence that accounts for the spatial and temporal heterogeneity of air pollution. It integrates multiple data sources, including satellite remote sensing data, ground-based measurements, atmospheric reanalysis, and model simulations. The calculation model has been extensively validated and has a high prediction accuracy with a coefficient of determination between 0.74 and 0.77.

2.1.3. Meteorological data

During the study, we obtained daily average ambient temperature (°C) and relative humidity (%) data from the China Meteorological Data Sharing Service System (http://data.cma.cn) of the China Meteorological Administration.

2.2. Statistical analysis

Descriptive statistics analyses were performed on the distributions of ILI, meteorological data, and $PM_{2.5}$ and its constituents. Variables were tested for normality, and the resulting P values were all less than 0.001. Therefore, we applied Spearman correlation analysis to evaluate the relationship between air pollutants and meteorological variables.

The generalized additive model (GAM) is a nonparametric extension of the traditional generalized linear model. GAM can effectively handle complex nonlinear relationships between explanatory and effect variables, and it has been widely used in epidemiological studies on air pollution mainly for analyzing the short-term effects of atmospheric pollutants or meteorological factors on health outcomes (Liu et al., 2019; Li et al., 2022; Chen et al., 2017; Wang et al., 2023). The daily count of ILI follows a Poisson distribution. Therefore, we used GAM with quasi-Poisson regression to evaluate the effect of short-term exposure to $PM_{2.5}$ and its constituents on influenza cases. Categorical variables were included to control for public holidays (PH) and days of weeks (DOW). Nonpenalized cubic splines were used to account for non-linear trends in temporality, temperature, and relative humidity. In accordance with the settings of previous studies, we applied an average of 7 degrees of freedom (df) per year for time trends and 3 df per year for temperature and relative humidity (Liu et al., 2019; Chen et al., 2017; Wang et al., 2023; Niu et al., 2018). Considering that ILI may exhibit long-term trends and seasonality, we also applied an average of 12 df per year for time trends. Sensitivity analyses were performed by varying the model's df to confirm the robustness of the results.

The single-pollutant model is specified as follows:

$\log[E(Y_t)] = \beta X_i + \text{ns (time, df)} + \text{ns (temperature, df)} + \text{ns (relative humidity, df)} + PH + DOW + \text{intercept}$,

where $E(Y_t)$ denotes the expected number of daily ILI cases; ns () denotes the smoothing function with df; β is the regression coefficient for atmospheric pollutants (e.g., $PM_{2.5}$ and its constituents); X_i includes $PM_{2.5}$ and its constituents; PH denotes the binary variable for public holidays; and DOW denotes the day of the week.

Single-day lags were used to capture immediate effects, while moving average lags were applied to account for cumulative exposure over multiple days. According to a systematic review (Lessler et al., 2009), the incubation period for most ILI-associated acute respiratory infections is typically within 4 days. Therefore, we fitted models by using single-day lags (lag0–lag4) and moving average lags (lag01–lag04) to investigate the lag effect and understand the temporal relationship between $PM_{2.5}$ and its constituents and ILI onset.

Subgroup analyses were conducted after identifying the lag days with the greatest effect stratified by gender, age group (0–4, 5–14, 15–24, 25–59, and ≥60 years), and season (warm season: April to September, cold season: October to March (Wang et al., 2023, 2021). The intergroup significance test was conducted by using the formula $(Q_1 - Q_2) \pm 1.96\sqrt{SE_1^2 + SE_2^2}$, where Q_1 and Q_2 are the effect estimates for each group, and SE_1 and SE_2 are the associated standard errors (Lin et al., 2016b; Zhang and Zhou, 2020). Relative risks (RRs) were calculated on the basis of the incremental interquartile range (IQR) of $PM_{2.5}$ and its constituents.

In the sensitivity analysis, we employed several approaches to assess the robustness and stability of the findings on the effect of $PM_{2.5}$ and its constituents on ILI. First, we extended the evaluation of temporal trend adjustments by varying the degrees of freedom (df) from 6 to 14 per year. Generalized cross-validation (GCV), a performance metric for generalized additive models (GAM), was reported for each configuration to evaluate model fit. Second, we established two-pollutant models by including gaseous air pollutants (NO_2, SO_2, and O_3) as additional covariates. Third, we modeled composition-$PM_{2.5}$ by adjusting $PM_{2.5}$ mass in the single-pollutant model (Mostofsky et al., 2012). This approach helped eliminate confounding and irrelevant variations due to $PM_{2.5}$ mass. Furthermore, we examined the potential effect of varying the df for meteorological variables, ranging from 4 to 6. Additionally, we considered the moving average lag effect of temperature (temperature01–temperature04) to control for potential lagged confounding due to temperature.

All statistical analyses were performed by using R 4.3.2, and two-sided $P < 0.05$ was considered statistically significant.

3. Results

From January 1, 2014, to December 31, 2019, the mean daily concentrations of $PM_{2.5}$ mass, BC, Cl^-, NH_4^+, NO_3^-, and SO_4^{2-} were 34.8, 3.0, 1.3, 4.3, 5.5 and 8.7 μg/m^3, respectively (Table 1). The mean temperature and average relative humidity were 22.3 °C and 79.2 %, respectively. A total of 222 316 cases were reported throughout the year, with an average of 101.5 cases per day. Individuals aged 5–14 years old accounted for 40.0 % of the total ILI cases across all age groups. The average number of cases was 75.0 in the warm season and 128.1 in the cold season.

Spearman correlation coefficients among $PM_{2.5}$, $PM_{2.5}$ constituents, gaseous pollutants, and meteorological variables are shown in Table 2. A strong correlation was found between $PM_{2.5}$ and its constituents, as well as among individual $PM_{2.5}$ constituents themselves (Spearman correlation coefficients ranged from 0.77 to 0.97). $PM_{2.5}$ constituents (except for NO_3^- and O_3) were significantly and positively correlated with gaseous pollutants, such as NO_2, SO_2, and O_3. In addition, $PM_{2.5}$ composition was found to be negatively correlated with mean temperature and relative humidity.

Table 1
Descriptive statistics for meteorological data, $PM_{2.5}$, $PM_{2.5}$ constituents, gaseous pollutants and influenza-like illness cases in Guangzhou, 2014–2019.

Variable	Mean±SD	Percentile				
		Min	P_{25}	P_{50}	P_{75}	Max
Temperature (℃)	22.3 ± 6.0	3.5	17.8	23.6	27.4	31.4
Relative humidity (%)	79.2 ± 10.7	26.9	73.6	80.4	86.8	99.8
Air pollution (μg/m^3)						
$PM_{2.5}$	34.8 ± 17.1	6.1	22.2	31.0	44.2	132.6
NO_2	33.9 ± 10.7	9.3	26.5	31.2	39.4	81.6
SO_2	13.4 ± 5.5	5.1	9.6	12.2	15.9	40.2
O_3	94.9 ± 41.7	11.8	62.4	90.8	123.1	228.0
PM constituent (μg/m^3)						
BC	3.0 ± 1.1	1.0	2.3	2.8	3.6	8.1
Cl^-	1.3 ± 0.5	0.4	1.0	1.3	1.6	4.3
NH_4^+	4.3 ± 2.0	0.7	2.8	4.2	5.5	15.4
NO_3^-	5.5 ± 3.8	0.9	2.8	4.4	7.4	29.3
SO_4^{2-}	8.7 ± 3.3	1.8	6.2	8.2	10.6	32.4
Influenza cases and subgroups						
All cases	101.5 ± 246.3	0	7	24	77	2985
Male	55.3 ± 135.1	0	4	13	42	1627
Female	46.1 ± 111.5	0	3	11	34	1358
0–4 years old	35.6 ± 70.6	0	3	10	30	642
5–14 years old	40.6 ± 133.6	0	1	6	26	1735
15–24 years old	8.3 ± 25.9	0	0	1	5	329
25–59 years old	13.9 ± 30.4	0	1	3	11	249
60 years old and above	3.1 ± 5.7	0	0	1	3	50
Warm	75.0 ± 137.9	0	9	27	54	909
Cold	128.1 ± 318.0	0	5	19	108	2985

Fig. 1 shows the RRs of ILI cases on different lag days for each IQR μg/m^3 increase in exposure to $PM_{2.5}$ and its constituents. In terms of a single-day lag, BC was significantly associated with ILI cases on lag0–lag4; NO_3^- was significantly associated with ILI cases on lag0–lag3; $PM_{2.5}$ and NH_4^+ were significantly associated with ILI cases on lag0–lag2; and SO_4^{2-} was significantly associated with ILI cases on lag0–lag1, whereas Cl^- had a significant effect on ILI cases on the lag0 only. The risks associated with $PM_{2.5}$ and its constituents tended to decrease with increasing lag days. Meanwhile, for multiday lag effects, $PM_{2.5}$, BC, NO_3^-, and NH_4^+ were significant for ILI cases on lag01–04 and SO_4^{2-} was significant for ILI cases on lag01–03. By contrast, the multiday lag effect of Cl^- on ILI was comparatively minor. $PM_{2.5}$ and NH_4^+ had the highest effect at the three-day moving average (lag02) with RRs of 1.091 (95 % CI: 1.054, 1.130) and 1.093 (95 % CI: 1.049, 1.138) for $PM_{2.5}$ and NH_4^+, respectively (Table S1). The highest RRs of BC, NO_3^-, and Cl^- were observed at the four-day moving average (lag03), with corresponding RRs of 1.111 (95 % CI: 1.074, 1.150) for BC, 1.103 (95 % CI: 1.061, 1.146) for NO_3^-, and 1.046 (95 % CI: 1.004, 1.090) for Cl^-. The strongest effects of SO_4^{2-} was observed at the two-day moving average (lag01) with RR of 1.098 (95 % CI: 1.058, 1.139). The observed trends remained consistent after adjusting the df for time trends to an average of 12 per year (Table S2), with the estimated effect sizes showing an overall increase compared to the model using 7 df per year. Notably, in the model with an average of 12 df per year for time trends, the multiday lag effects of Cl^-, SO_4^{2-}, $PM_{2.5}$, NH_4^+, BC, and NO_3^- were all significantly associated with ILI cases on lag01–lag04.

The stratified analyses of $PM_{2.5}$ and its constituents with the strongest effect on ILI are presented in Table 3. The estimated risks were generally similar between males and females. For example, with increasing IQR μg/m^3 exposure to BC, the RR was 1.100 (95 % CI: 1.061, 1.140) for males and 1.125 (95 % CI: 1.086, 1.166) for females. Compared with other individuals, people aged 15–24 years old were more susceptible to the effects of BC on ILI, whereas those aged 5–14 and 15–24 years old were more sensitive to Cl^- exposure.

Fig. 2 exhibits the seasonal differences in associations between the mass and constituents of $PM_{2.5}$ and ILI. In general, the effects of $PM_{2.5}$, BC, NH_4^+, NO_3^-, Cl^-, and SO_4^{2-} on ILI were stronger in the cold season than in the warm season. The effects on ILI in the 0–4, 15–24, and ≥ 60 year–old age groups were more obvious in the cold season than in the warm season.

The two-pollutant model showed that the addition of NO_2 and SO_2 reduced estimated effects. Specifically, the effects of Cl^-, NH_4^+, and SO_4^{2-} were no longer significant after the inclusion of these pollutants, with the exception of BC and NO_3^-. By contrast, the correlation of $PM_{2.5}$ and its constituents with ILI remained significant after adjusting for O_3. All $PM_{2.5}$ constituents, except BC and NO_3^-, had no statistically significant effects on health after adjusting for $PM_{2.5}$ mass. Sensitivity analyses, wherein the df of time and meteorological variables were modified or the lagged effects of temperature were taken into account, did not significantly change our main results (Table S3-S4).

4. Discussion

We investigated the short-term effects of the mass and constituents (BC, Cl^-, NH_4^+, NO_3^-, and SO_4^{2-}) of $PM_{2.5}$ on ILI in Guangzhou. Our results showed that exposure to the mass and constituents of $PM_{2.5}$ was associated with an increased incidence of ILI, with the association with BC being the most pronounced among associations with all constituents. Similar effects of $PM_{2.5}$ mass and constituents on ILI were observed between males and females. However, the effects of BC and Cl^- differed by age group, with the strongest effect of BC and Cl^- observed in the 15–24 year–old age group. Overall, the correlation between $PM_{2.5}$ mass

Table 2
Spearman correlation coefficients between $PM_{2.5}$, $PM_{2.5}$ constituents, gaseous pollutants and meteorological variables in Guangzhou, 2014–2019.

	$PM_{2.5}$	NO_2	SO_2	O_3	Tempera-ture	Relative humidity	BC	Cl^-	NH_4^+	NO_3^-	SO_4^{2-}
$PM_{2.5}$	1.00										
NO_2	0.69**	1.00									
SO_2	0.68**	0.41**	1.00								
O_3	0.34**	0.08**	0.25**	1.00							
Temperature	−0.34**	−0.38**	−0.11**	0.42**	1.00						
Relative humidity	−0.39**	0.01	−0.40**	−0.52**	0.15**	1.00					
BC	0.89**	0.79**	0.61**	0.32**	−0.17**	−0.15**	1.00				
Cl^-	0.85**	0.64**	0.57**	0.09**	−0.39**	−0.16**	0.79**	1.00			
NH_4	0.97**	0.68**	0.60**	0.20**	−0.47**	−0.33**	0.84**	0.86**	1.00		
NO_3	0.87**	0.77**	0.50**	−0.02	−0.66**	−0.20**	0.78**	0.85**	0.92**	1.00	
SO_4^{2-}	0.96**	0.59**	0.64**	0.42**	−0.24**	−0.42**	0.82**	0.77**	0.94**	0.77**	1.00

Note: ** $p < 0.001$

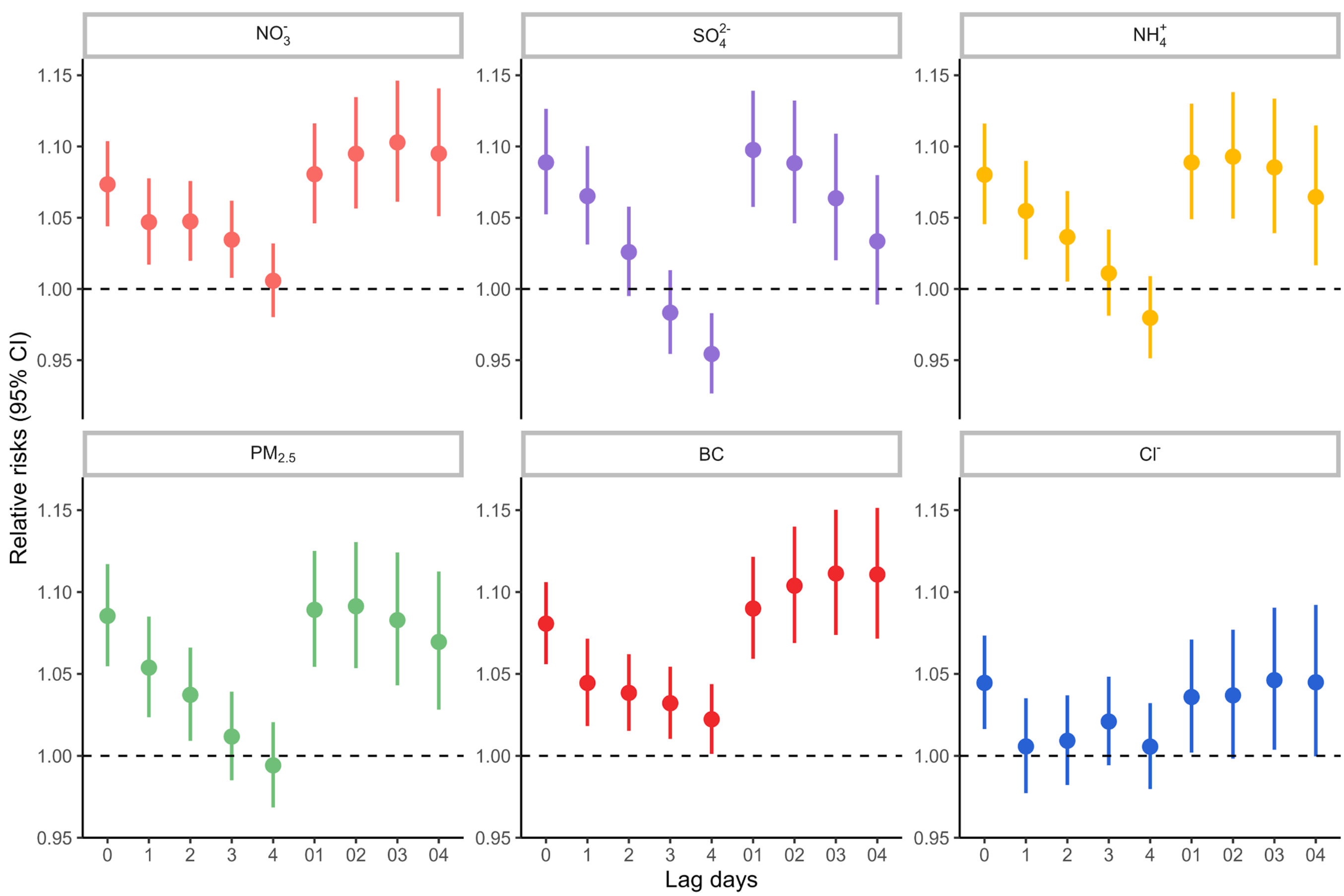

Fig. 1. Relative risk (95 % CI) of ILI cases at different exposure days for every IQR μg/m^3 increase in exposure to $PM_{2.5}$ and its constituents. The x-axis represents $PM_{2.5}$ and its constituents measurements at several single-lag (lag0 to lag4) and moving-average (lag01 to lag04) days before illness onset. For instance, lag0 corresponds to the current day concentration, lag1 corresponds to the concentration of the day before illness onset; lag01 corresponds to the two-day moving averages of current and previous day concentrations of air pollutants.

and constituents and ILI was more pronounced during the cold season than during the warm season. These results contribute to a deep understanding of the full picture of the health effects of $PM_{2.5}$ and its constituents on ILI.

We observed that $PM_{2.5}$ mass and constituents were significantly associated with ILI onset, suggesting that combustion-related and secondary particles are the main cause of the acute negative effects of exposure to PM pollution. No study has specifically reported an association between $PM_{2.5}$ constituents and ILI. However, existing environmental epidemiology studies have provided evidence of the deleterious effects of $PM_{2.5}$ constituents on respiratory mortality and diseases (Zhang et al., 2020a). A case-crossover study involving 32 cities in China found that increases in per IQR of EC (odd ratios [OR]: 1.015 [95 % CI: 1.001–1.031]) and in OC (OR: 1.028 [95 % CI: 1.006–1.050]) per IQR were positively associated with respiratory mortality with a three-day lag (Zhou et al., 2022). Similarly, a study in Korea discovered associations between $PM_{2.5}$ constituents and respiratory mortality (Kim et al., 2022). Lin et al. indicated that $PM_{2.5}$ constituents were associated with the onset of asthma (Wang et al., 2022) and acute respiratory distress syndrome (Lin et al., 2018).

Among all $PM_{2.5}$ constituents, BC exhibited the largest magnitude of effect on ILI. BC is a product of the incomplete combustion of biomass and fossil fuels, with most emissions originating from industrial and transportation sources. The effects of BC on the respiratory system have

Table 3
Relative risk (95 % CI) of ILI cases among subgroups stratified by gender and age, associated with per IQR μg/m^3 increase in exposure to $PM_{2.5}$ (lag02), BC (lag03), Cl^- (lag03), NH_4^+ (lag02), NO_3^- (lag03) and SO_4^{2-} (lag01).

Subgroup	$PM_{2.5}$	BC	Cl^-	NH_4^+	NO_3^-	SO_4^{2-}
Gender						
Male	1.081 (1.042, 1.121)	1.100 (1.061, 1.140)	1.037 (0.993, 1.083)	1.083 (1.038, 1.130)	1.089 (1.046, 1.134)	1.094 (1.053, 1.137)
Female	1.104 (1.065, 1.145)	1.125 (1.086, 1.166)	1.057 (1.013, 1.104)	1.105 (1.059, 1.152)	1.119 (1.075, 1.165)	1.102 (1.060, 1.145)
Age (years)						
0–4	1.092 (1.050, 1.134)	1.084 (1.044, 1.126)	0.991 (0.948, 1.037)	1.124 (1.076, 1.174)	1.113 (1.067, 1.161)	1.109 (1.066, 1.155)
5–14	1.081 (1.037, 1.127)	1.115 (1.071, 1.161)	1.082 (1.029, 1.137)	1.069 (1.017, 1.123)	1.072 (1.024, 1.122)	1.106 (1.057, 1.157)
15–24	1.154 (1.087, 1.225)	1.199 (1.131, 1.270)	1.122 (1.049, 1.200)	1.117 (1.043, 1.196)	1.199 (1.122, 1.281)	1.085 (1.022, 1.153)
25–59	1.129 (1.079, 1.182)	1.131 (1.081, 1.182)	1.076 (1.022, 1.133)	1.145 (1.088, 1.205)	1.163 (1.106, 1.224)	1.119 (1.069, 1.172)
≥ 60	1.108 (1.032, 1.190)	1.129 (1.055, 1.207)	1.056 (0.975, 1.144)	1.111 (1.025, 1.204)	1.167 (1.079, 1.262)	1.080 (1.004, 1.162)

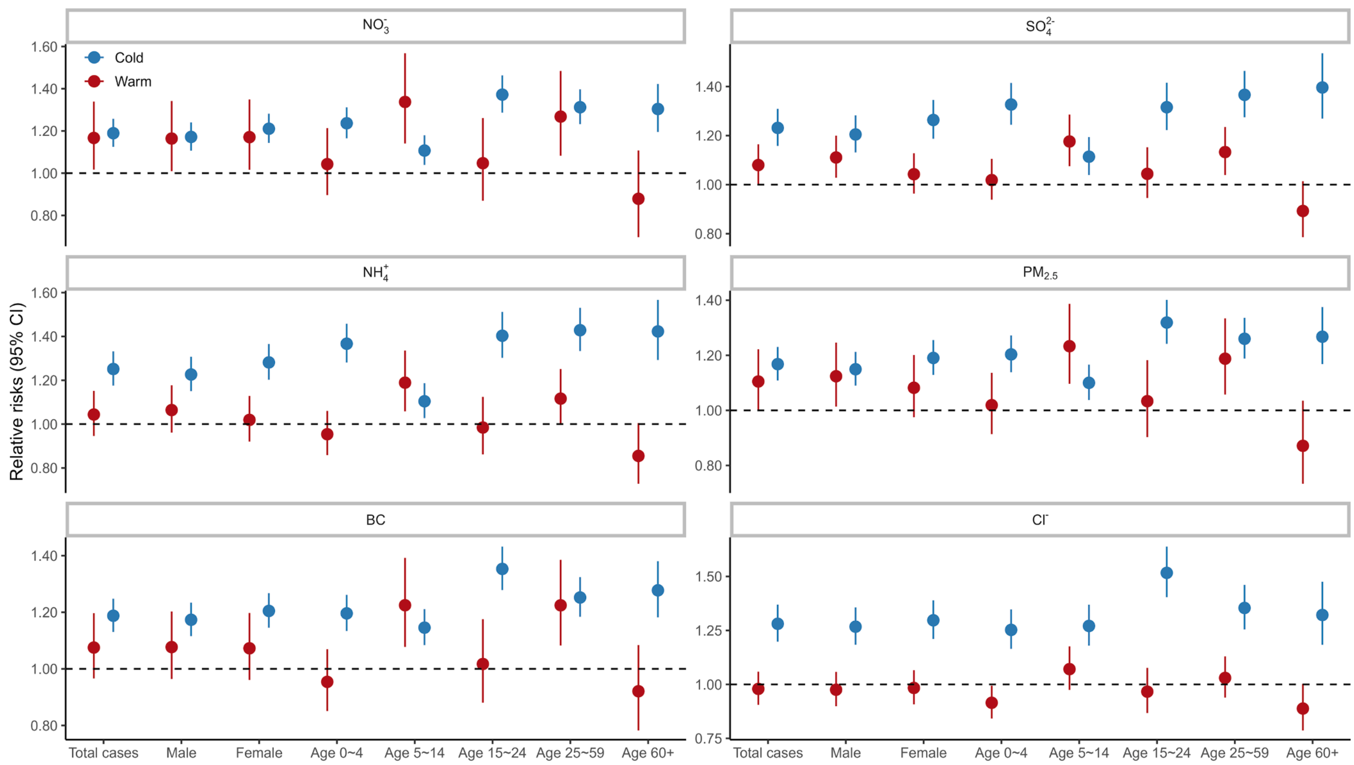

Fig. 2. Season-specific relative risk (95 % CI) of ILI cases by IQR μg/m^3 increase in exposure to Cl^- (lag03), SO_4^{2-} (lag01), $PM_{2.5}$ (lag02), NH_4^+ (lag02), BC (lag03), and NO_3^- (lag03).

been well documented in prior research. For example, a study in Brazil indicated that exposure to BC considerably increased the risk of acute respiratory illnesses in children under the age of 12 years, with a RR of 1.07 (95 % CI: 1.03–1.11) (Nascimento et al., 2020). Additionally, a systematic analysis demonstrated a strong association between BC exposure and childhood asthma, with an RR of 1.08 (95 % CI: 1.03–1.14) (Khreis et al., 2017). In our sensitivity analyses, consistent results were found from the model adjusting for $PM_{2.5}$ mass, indicating that the effects of BC on ILI were not attributable to $PM_{2.5}$ alone. BC can produce toxicity through mechanisms, such as oxidative stress, cell signaling and activation, and mediator release, thereby triggering inflammatory processes in the respiratory and cardiovascular systems (Paunescu et al., 2019; Meldrum et al., 2017). These changes may increase the susceptibility of the respiratory system to virus infections, potentially leading to ILI. In Guangzhou, liquid fuels used in transportation are the primary source of BC (Zhang et al., 2020b). The results of this study therefore provide a strong case for further limiting emissions from pollution sources, particularly from transportation-related air pollutants.

Water-soluble inorganic ions comprise the primary constituents of $PM_{2.5}$, accounting for 20 %–77 % of $PM_{2.5}$ mass (Huang et al., 2014; Huy et al., 2020). Among these constituents, NH_4^+, NO_3^-, and SO_4^{2-} constitute the majority of the water-soluble inorganic ions of $PM_{2.5}$, accounting for approximately 90 % of the total ions (Zhang et al., 2021, 2018). Our findings are consistent with the results of prior studies, indicating the detrimental effects of water-soluble inorganic ions on respiratory health. For instance, a study in Taiwan demonstrated that for each 1 μg/m^3 increase in NO_3^-, the estimated RR for emergency room visits due to asthma was 1.006 (95 % CI: 1.003–1.008) at a lag of one day (Hwang et al., 2017). Nitta et al. found positive associations between per IQR increase in NH_4^+, NO_3^-, SO_4^{2-}, and respiratory mortality (Ueda et al., 2016). Another study in New York State reported that NH_4^+, NO_3^-, SO_4^{2-} were positively associated with respiratory hospitalizations (Jones et al., 2015).

Potential mechanisms for the toxic effects of the water-soluble inorganic ions of $PM_{2.5}$ include inducing reactive oxygen species generation and mitochondrial proliferation in lung epithelial cells; these phenomena can lead to cell damage through oxidative stress (Zou et al., 2016). Animal testing has provided valuable insights into the harmful effects of the three primary $PM_{2.5}$ constituents on the respiratory system

(Zhang et al., 2021). Its findings demonstrated that in the mouse lung, exposure to NO_3^- resulted in the considerable destruction of alveoli, thickening of small airway walls, and infiltration of inflammatory cells, all of which reduced respiratory capacity. The effect of SO_4^{2-} exposure on the respiratory system was considerably weaker than that of NO_3^- exposure, whereas the effect of NH_4^+ exposure on respiratory function did not show statistical significance. Similar to the aforementioned findings, the present study found that among the three main water-soluble inorganic ions of $PM_{2.5}$, NO_3^- had the most pronounced effect on ILI. However, after adjusting for the total mass of $PM_{2.5}$, the statistical significance of their effects on ILI diminished. Further research is necessary to validate their connection with ILI.

In this study, stratified analyses showed that the estimated effects of $PM_{2.5}$ mass and constituents on ILI were similar between males and females; this result is consistent with the findings of previous studies (Lu et al., 2022; Bachwenkizi et al., 2021; Hwang et al., 2017). However, other studies found that $PM_{2.5}$ constituents had a greater effect on men than on women (Zhou et al., 2022; Wang et al., 2022). Our age-stratified analysis revealed that the effects of $PM_{2.5}$ and its constituents on ILI were most pronounced in the 15–24 year–old age group, and individuals aged 5–14 and 15–24 years old appeared to be more sensitive to BC and Cl^- than individuals of other ages. These findings are consistent with previous results showing that the ILI risk associated with exposure to PM pollutants was higher among the 15–24 year–old group than among other age groups (Huang et al., 2016; Lu et al., 2022). One possible explanation for these findings is that individuals in these age groups may be exposed to high doses of air pollution during their daily commuting activities to work or school (Zuurbier et al., 2010). Conversely, compared with young individuals, adults and older adults may be more inclined to self-administer medications unless their condition becomes severe or uncontrollable. This situation may lead to an underestimation of ILI incidence in ILI surveillance statistics for 25–59 and $\geq$ 60 year–old age groups. Mainland China recommends prioritizing influenza vaccination for children aged 6 months to 5 years and older adults aged 60 years or older. Studies have shown that influenza vaccination coverage is higher in these age groups than in other age groups (Wang et al., 2018). Influenza vaccination may offer protection against influenza infection in these populations.

The seasonal patterns of associations between $PM_{2.5}$ and its constituents with ILI demonstrated stronger effects during the cold season than during the warm season. These findings align with previous research results. For example, a study in Beijing revealed that associations among NO_3^-, SO_4^{2-}, and respiratory mortality were more obvious in the cold season than in the warm season (Li et al., 2015). Similarly, Zhang et al. reported an increased risk of nonaccidental mortality related to SO_4^{2-} and NH_4^+ during the cold season (Zhou et al., 2022). Several factors could potentially contribute to seasonal differences in the effects of $PM_{2.5}$ and its constituents on ILI. First, the sources and constituents of PM may vary by season, leading to substantial differences in the most harmful constituents during different times of the year (Bell et al., 2008). Second, seasonal variations in weather patterns can affect PM concentrations. For example, low winter temperatures can accelerate the transformation of air pollutants from gases into particles, whereas low wind speeds can slow the spread of air pollutants (Dai et al., 2013). Furthermore, the health consequences of air pollution may be influenced by the daily routines and vulnerability of individuals across different seasons (Chen et al., 2013). However, other studies reported contradictory findings. A study in London found high associations between BC and adult respiratory admissions during the warm period of the year (Samoli et al., 2016). Similarly, two other studies reported that $PM_{2.5}$ constituents had stronger effects on respiratory outcomes in warm seasons than in other seasons (Hwang et al., 2017; Jones et al., 2015). The heterogeneity of seasonal differences in the effects of $PM_{2.5}$ and its constituents can be attributed to variations in climatic conditions, socioeconomic characteristics, and proportions of susceptible populations. The specific causes require further research.

In this study, we evaluated the relationship between $PM_{2.5}$ and its constituents and ILI in Guangzhou by using a time-series design, which helps provide insight into the health effects of $PM_{2.5}$ on ILI. However, this work has several limitations. First, exposure misclassification is unavoidable because data were derived from monitoring stations rather than individual exposure data. Future studies should incorporate personal monitoring or advanced modeling to improve exposure estimates. Second, the use of an ecological design precluded considering potential confounders at the individual level or investigating individual-level relationships. Studies with detailed individual data are needed to address this limitation. Third, ILI surveillance data may have been inadequate, and findings may not accurately represent the entire population. Combining surveillance data with comprehensive sources, such as electronic health records, could enhance accuracy. Fourth, this study was conducted only in Guangzhou. Therefore, generalization to other regions or populations may be limited. The findings of this study may offer valuable insights for other cities with similar climatic conditions, demographic characteristics, healthcare systems, and pollutant compositions and exposure patterns. However, in regions with substantially different climates or pollutant source structures, these results may need to be adjusted or independently validated. Future multiregional studies are needed to verify the generalizability of the findings of this work.

5. Conclusions

Our study provides suggestive evidence of the harmful effects of $PM_{2.5}$ constituents on ILI cases, with BC emerging as the most influential among components. In addition, individuals aged 5–14 and 15–24 years appeared to be more sensitive to BC and Cl^- exposure than other individuals. This finding is reinforced by the stronger associations observed during the cold season than during the warm season. These results emphasize the importance of developing public health policies to prevent pollution by $PM_{2.5}$ constituents. However, further research is needed to confirm causality.

Abbreviations

PM: particulate matter; ILI: influenza-like illness; DALYs: disability-adjusted life-years; BC: black carbon, Cl^-: chlorine, NH_4^+: ammonia, NO_3^-: nitrate, SO_4^{2-}: sulfate; NO_2: nitrogen dioxide, SO_2: sulfur dioxide, O_3: ozone; CI: confidence interval; RR: relative risk; IQR: interquartile range

Ethics approval and consent to participate

The ethics approval was waived by the ethics committee of Guangzhou CDC after consultation according to the law on the prevention and control of infectious diseases. Because cases should truthfully provide relevant information in the prevention of infectious disease, and the analytical data sets were constructed anonymously.

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CRediT authorship contribution statement

Jianyun Lu: Resources, Data curation. **Xiaowei Ma:** Resources, Data curation. **Weidong Fan:** Writing – review & editing, Visualization, Software, Methodology. **Jing Wei:** Resources, Data curation. **Xianbo Wu:** Validation, Supervision, Resources, Project administration. **Keyi Wu:** Writing – original draft, Software, Methodology, Conceptualization. **Yining Huang:** Writing – review & editing. **Fei Zou:** Validation, Supervision, Resources, Project administration. **Zhiwei Huang:** Writing

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Consent for publication

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2024.117540.

Data availability

The data that has been used is confidential.

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