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Air quality, climate and public health

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Size-Specific Particulate Matter Associated With Acute Lower Respiratory Infection Outpatient Visits in Children: A Counterfactual Analysis in Guangzhou, China

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The burden of lower respiratory infections is primarily evident in the developing countries. However, the association between size-specific particulate matter and acute lower respiratory infection (ALRI) outpatient visits in the developing countries has been less studied. We obtained data on ALRI outpatient visits ($N = 105{,}639$) from a tertiary hospital in Guangzhou, China between 2013 and 2019. Over-dispersed generalized additive Poisson models were employed to evaluate the excess risk (ER) associated with the size-specific particulate matter, such as inhalable particulate matter (PM_{10}), coarse particulate matter (PM_c), and fine particulate matter ($PM_{2.5}$). Counterfactual analyses were used to examine the potential percent reduction of ALRI outpatient visits if the levels of air pollution recommended by the WHO were followed. There were 35,310 pneumonia, 68,218 bronchiolitis, and 2,111 asthma outpatient visits included. Each 10 $\mu g/m^3$ increase of 3-day moving averages of particulate matter was associated with a significant ER (95% CI) of outpatient visits of pneumonia ($PM_{2.5}$: 3.71% [2.91, 4.52%]; PM_c: 9.19% [6.94, 11.49%]; PM_{10}: 4.36% [3.21, 5.52%]), bronchiolitis ($PM_{2.5}$: 3.21% [2.49, 3.93%]; PM_c: 9.13% [7.09, 11.21%]; PM_{10}: 3.12% [2.10, 4.15%]), and asthma ($PM_{2.5}$: 3.45% [1.18, 5.78%]; PM_c: 11.69% [4.45, 19.43%]; PM_{10}: 3.33% [0.26, 6.49%]). The association between particulate matter and pneumonia outpatient visits was more evident in men patients and in the cold seasons. Counterfactual analyses showed that $PM_{2.5}$ was associated with a larger potential decline of ALRI outpatient visits compared with PM_c and PM_{10} (pneumonia: 11.07%, 95% CI: [7.99, 14.30%]; bronchiolitis: 6.30% [4.17, 8.53%]; asthma: 8.14% [2.65, 14.33%]) if the air pollutants were diminished to the level of the reference guidelines. In conclusion, short-term exposures to $PM_{2.5}$, PM_c, and PM_{10} are associated with ALRI outpatient visits, and $PM_{2.5}$ is associated with the highest potential decline in outpatient visits if it could be reduced to the levels recommended by the WHO.

Keywords: particulate matter, lower respiratory infection, particle, China, children

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INTRODUCTION

Lower respiratory infections, such as pneumonia and bronchiolitis, are the sixth leading cause of death in all age groups, resulting in ∼2.4 million deaths worldwide in 2016 (1). The burden of lower respiratory infections is unevenly distributed across the world and is primarily born in the developing countries with socioeconomically disadvantaged communities, where proper nutrition, clean fuel, sanitation, and clean air are unavailable or inadequate (2, 3). China has experienced a staggering economic growth in the past 30 years, resulting in a steady increase in the life expectancy and improvement in the health outcomes in the country. From 1990 to 2019, the number of cases and mortalities of lower respiratory infections declined by 21.98 and 65.94%, respectively. In 2019, there were still 55.84 million cases, with 185,264.33 mortalities attributed to lower respiratory infections in China, making it the country's leading cause of mortality in children under-five (4).

Exposure to ambient particulate matter has been widely reported to be associated with lower respiratory infections (5–7). However, evidence on the association between size-specific particulate matter and lower respiratory infections, especially that from the developing countries where the level of air pollution is high, is relatively limited (8–10). Based on particle diameter, inhalable particulate matter (PM_{10}) can be divided into fine particles ($PM_{2.5}$) and coarse particles (PM_c). Most studies only focused on the health effects of $PM_{2.5}$, while the effects of PM_{10} and PM_c remain inconclusive.

The previous time-series studies that examined the association between the size-specific particulate matter and the risk of adverse health outcomes often reported the odds ratio or excess risk (ER) estimates per 1 or 10 $\mu g/m^3$ (11–13). However, these effect size estimates ignore the underlying statistical distributions of the air pollutants and may not be comparable across the size-specific particulate matter. In this study, we introduced the counterfactual analyses to effectively compare the potential reduction of acute lower respiratory infection (ALRI) hospitalizations (counterfactual outcomes) associated with the size-specific particulate matter (14). These counterfactual outcomes, which accounted for the statistical distributions of air pollutants, can be directly comparable for different particulate matter and, therefore, have more public health implications for policymakers.

In this current study, we investigate the association between the size-specific particulate matter and the outpatient visits of ALRI. Beyond these analyses, we further employed a counterfactual approach to investigate the potential percent reduction of ALRI outpatient visits if the levels of particulate matter were as low as those recommended by the WHO.

METHODS

Acute Lower Respiratory Infection Data

This study is a time-series analysis of ALRI outpatient visits from 2013 to 2019 in Guangzhou, China. Data on ALRI-related hospital outpatient visits were retrieved from the Guangdong Second Provincial General Hospital, which is located in the southwest of the city (**Figure 1**). This is one of the tertiary hospital in Guangzhou (15). According to the International Classification of Diseases, Tenth Revision (ICD-10), hospital outpatient visits with the primary diagnoses of pneumonia (J12-J18), bronchiolitis (J20-J21), and asthma (J45-J46) (16) were obtained between February 2013 and December 2019. We aggregated the three subtypes of ALRI into a series of daily time-series data (17–20).

Air Pollution and Meteorological Data

Daily concentrations of air pollution during the study period were obtained from 11 air monitoring stations in Guangzhou (**Figure 1**), such as PM_{10}, PM_c, $PM_{2.5}$, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3). Following a previous study (19), the PM_c concentrations were calculated by the subtracting $PM_{2.5}$ from PM_{10}, because PM_{10} consists of $PM_{2.5}$ and PM_c. Details on the measurement of air pollutants have been described previously (21). Approximately 1% of observation days had missing data for air pollutants, and a linear interpolation approach was used to fill in the missing data (the "na.approx" function in "zoo" package in R).

Daily meteorological data (mean temperature and relative humidity [RH]) were obtained from the National Weather Data Sharing System (http://data.cma.cn/). Because there is a potentially high correlation between different air pollutants and meteorological factors, we examined the Pearson correlation coefficients among these variables (22, 23).

Statistical Models

The ALRI data, daily air pollution concentrations, and meteorological data were linked by date. Following similar epidemiologic studies (11, 12), the association between particulate matter and hospital outpatient visits for ALRI was examined using a generalized additive over-dispersed Poisson model (GAM), where the property of over dispersion was tested using the approach proposed by Cameron and Trivedi (24) (**Supplementary Table 1**). In the model, public holidays (PH) and days of the week (DOW) were adjusted as categorical variables. Seasonal patterns, long-term trends, temperature, and RH were controlled through smoothing splines. Following the approaches used in the previous studies (25, 26), we selected six degrees of freedom (df) per year for temporal trends, a df of six for moving average temperature of the current day and the previous 3 days (Temp03), and RH.

Considering the delayed health effects of air pollutants, we examined the lag effects for different lag structures. We began with the same day (lag0) up to a 5-day lag (lag5) in the single-lag day models. We also considered the accumulated effects of multi-day lags (moving averages for the current day and the previous 1, 2, and 3 days [lag01, lag02, and lag03]).

Stratified Analyses

To evaluate the potential effect modifiers of the particulate matter–ALRI associations, we conducted the stratified analyses by sex (men vs. women), age group (age < 5 vs. age 5–14), and season (warm *vs* cold). The warm season was defined as the period from April to September, and the cold season was from

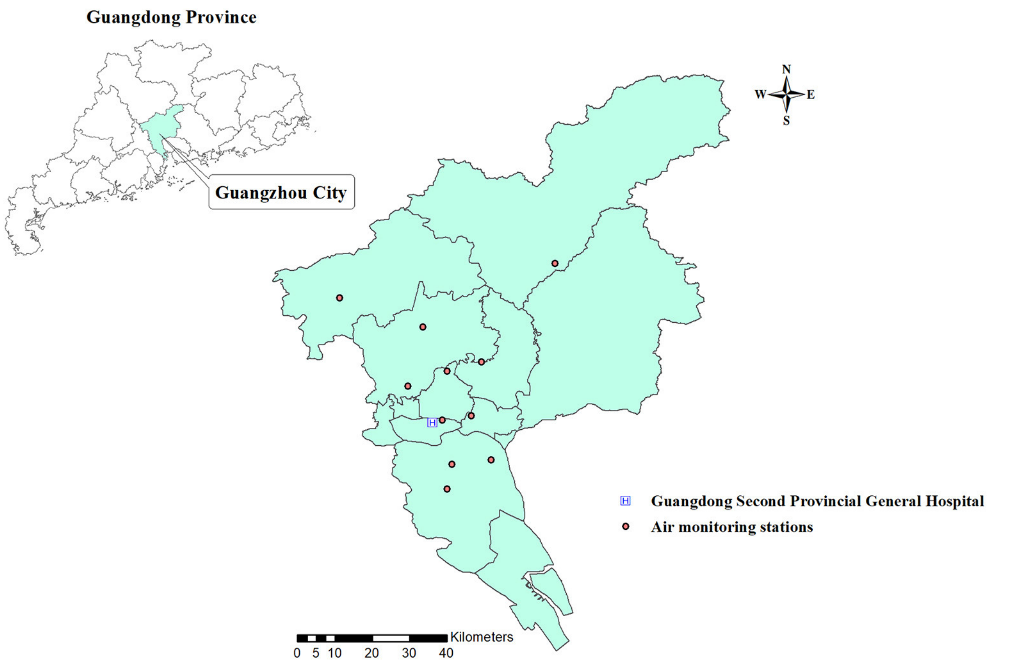

FIGURE 1 | Geographical distribution of the sample hospitals and air monitoring stations.

TABLE 1 | Summary statistics of acute lower respiratory infections outpatient visits, air pollutants, and meteorological variables.

	Mean	SD	Percentile				
			Min	25th	50th	75th	Max
Acute lower respiratory infections							
Pneumonia ($N = 35{,}310$)	12.5	9.1	0.0	6.0	11.0	16.0	73.0
Bronchiolitis ($N = 68{,}218$)	24.3	11.5	0.0	16.0	23.0	31.0	81.0
Asthma ($N = 2{,}111$)	0.8	1.4	0.0	0.0	0.0	1.0	12.0
Air pollution, $\mu g/m^3$							
PM_{10}	58.3	28.1	10.0	38.2	51.1	73.4	217.8
PM_c	21.0	9.9	0.8	14.7	18.8	25.3	77.7
$PM_{2.5}$	37.8	21.2	4.6	22.7	32.3	48.3	156.4
SO_2	13.6	8.5	2.8	8.6	11.9	16.5	166.4
NO_2	45.2	18.6	4.4	33.6	41.2	53.7	177.7
O_3	51.6	30.2	3.5	30.0	47.2	67.1	294.6
Meteorological variables							
Temperature, °C	22.8	5.9	1.7	19.0	25.0	27.5	32.8
Relative humidity, %	81.8	10.2	30.5	77.0	83.1	89.3	100.0

SD, standard deviation.

October to March. The 95% CI of the difference between the groups was calculated using the following formula:

$$Q_1 - Q_2 \pm 1.96\sqrt{(SE_1)^2 + (SE_2)^2}$$

where Q represents the estimated coefficient in each stratum, and SE is the corresponding standard error (27). The difference was considered statistically significant if the 95% CI did not include unity.

Counterfactual Analyses on the Burden of ALRI Attributable to Air Pollution

We estimated the burden of ALRI attributable to $PM_{2.5}$, PM_c, and PM_{10} by calculating the difference between the observed ALRI outpatient visits and the counterfactual visits predicted using well-recognized reference values of particulate matter recommended by the WHO (28) and our previously built generalized additive over-dispersed Poisson models. This difference between the observed and counterfactual ALRI outpatient visits represents the estimated burden of ALRI outpatient visits associated with the size-specific particulate matter. The counterfactual scenarios were set to be hypothetical values of $PM_{2.5}$ and PM_{10} set by the recently updated WHO Global Air Quality Guidelines (24 h mean: 15 $\mu g/m^3$ for $PM_{2.5}$ and 45 $\mu g/m^3$ for PM_{10}) (28). However, PM_c was not directly regulated by the WHO Air Quality Guidelines, the reference concentration for PM_c (30 $\mu g/m^3$) was defined as the difference between the standard concentrations of PM_{10} and $PM_{2.5}$ according to the previous studies (17, 20). The observed air pollution levels lower than the reference values were kept the same in the counterfactual scenario. The 95% CIs were constructed using 1,000 bootstrap replicates with a replacement for each model (29, 30).

Sensitivity Analyses

We applied a series of sensitivity studies to examine the accuracy of the main models. The main findings were assessed by changing the df in the smooth functions for temporal trends and meteorological factors. Additionally, we adjusted for the gaseous air pollutants (SO_2, NO_2, and O_3) in two-pollutant models. The models were regarded as robust if there were no significant changes after df-change or further adjustment for gaseous air pollutants.

In all statistical analyses, a $p \leq 0.05$ was considered statistically significant. All data cleaning, aggregation, and visualization, and statistical analyses were performed using the statistical computing environment R version 4.0.5 (31).

RESULTS

Figure 1 presents the geographical location of Guangzhou and the sample hospital, as well as the geographical distribution of the air monitoring stations in Guangzhou. A total of 105,639 pediatric outpatient visits were included in the study, with the following breakdown of cases: 35,310 pneumonia, 68,218 bronchiolitis, and 2,111 asthma. **Table 1** shows the summary statistics of ALRI subtypes, size-specific particulate matter (PM_{10}, PM_c, and $PM_{2.5}$), and gaseous pollutants (SO_2, NO_2, and O_3). The daily averages (SD) of pneumonia, bronchiolitis, and asthma cases were 12.5 (9.1), 24.3 (11.5), and 0.8 (1.4), respectively. The mean concentrations of PM_{10}, PM_c, and $PM_{2.5}$ in our study were 58.3, 21.0, and 37.8 $\mu g/m^3$. The mean (SD) of temperature and relative humidity was 22.8°C (5.9) and 81.8% (10.2%), respectively.

Figure 2 shows the correlation plot of the air pollutants and meteorological variables in our sample. All the Pearson's correlation coefficients were statistically significant except for the correlation between NO_2 and O_3. PM_{10} was significantly and strongly correlated with PM_c and $PM_{2.5}$ (Pearson's correlation coefficients: 0.81 and 0.93); NO_2 was moderately correlated with particulate matters (Pearson's correlation coefficients for PM_{10}, PM_c, and $PM_{2.5}$: 0.78, 0.66, and 0.70). Meteorological variables were negatively correlated with air pollutants except for the positive correlation between temperature and O_3.

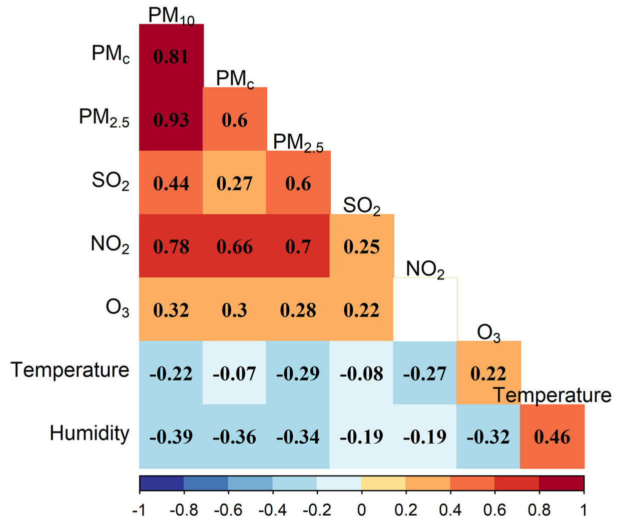

FIGURE 2 | Correlation plot of the air pollutants and meteorological variables.

Table 2 exhibits the ER of pneumonia, bronchiolitis, and asthma outpatient visits associated with per 10 $\mu g/m^3$ increase in $PM_{2.5}$, PM_c, and PM_{10} at lag03. The results revealed that size-specific particulate matter were significantly associated with pneumonia, bronchiolitis, and asthma, respectively, in single-pollutant models, where the ER of PM_c was the largest, followed by that of $PM_{2.5}$ and PM_{10}. The results were consistent and robust in two-pollutant models with further adjustment for SO_2, NO_2, and O_3, except for those asthma models controlling for NO_2. The corresponding exposure–response non-linear curves for the daily particulate matter and log relative risk are shown in **Supplementary Figure 1**.

Similar patterns of ER of ALRI outpatient visits associated with per 10 $\mu g/m^3$ increase in the size-specific particulate matter could be observed in **Figure 3**. Each 10 $\mu g/m^3$ increase in $PM_{2.5}$, PM_c, and PM_{10} was associated with the outpatient visits for pneumonia, bronchiolitis, and asthma on different lag days. In contrast, the effects of the size-specific particulate matter on asthma are less robust: the moving average lags of PM_c, and $PM_{2.5}$ were still significantly associated with the ALRI outpatient visits, but the effects of lag0 to lag5 of PM_c and $PM_{2.5}$ and different lags of PM_{10} were non-significant or at borderline significant. Sensitivity analyses using the different degrees of freedom for splines of temporal trends and temperature showed a generally consistent pattern (**Supplementary Table 2**).

Table 3 presents the estimated ER with 95% CI of pneumonia, bronchiolitis, and asthma stratified by sex, age group, and season,

TABLE 2 | Excess risk and 95% CIs of pneumonia, bronchiolitis, and asthma for each 10 μg/m^3 increase in $PM_{2.5}$, PM_c, and PM_{10} using single- and two-pollutants models at lag03.

Pollutants	Models	Pneumonia	Bronchiolitis	Asthma
PM_{10}				
	Single-pollutant model	**3.71 (2.91, 4.52)**	**3.21 (2.49, 3.93)**	**3.45 (1.18, 5.78)**
	Two-pollutant models			
	Control for SO_2	**3.81 (2.97, 4.66)**	**3.44 (2.69, 4.21)**	**3.46 (1.13, 5.85)**
	Control for NO_2	**2.47 (1.47, 3.47)**	**1.48 (0.58, 2.37)**	0.26 (−2.58, 3.19)
	Control for O_3	**4.06 (3.22, 4.91)**	**3.48 (2.72, 4.25)**	**3.72 (1.30, 6.20)**
PM_c				
	Single-pollutant model	**9.19 (6.94, 11.49)**	**9.13 (7.09, 11.21)**	**11.69 (4.45, 19.43)**
	Two-pollutant models			
	Control for SO_2	**9.32 (6.98, 11.72)**	**9.72 (7.58, 11.91)**	**11.70 (4.29, 19.63)**
	Control for NO_2	**5.58 (3.03, 8.19)**	**4.80 (2.45, 7.20)**	3.26 (−4.88, 12.09)
	Control for O_3	**9.52 (7.21, 11.87)**	**9.47 (7.37, 11.61)**	**12.09 (4.56, 20.17)**
$PM_{2.5}$				
	Single-pollutant model	**4.36 (3.21, 5.52)**	**3.12 (2.10, 4.15)**	**3.33 (0.26, 6.49)**
	Two-pollutant models			
	Control for SO_2	**4.61 (3.37, 5.87)**	**3.50 (2.39, 4.63)**	**3.45 (0.14, 6.87)**
	Control for NO_2	**2.30 (0.96, 3.65)**	0.39 (−0.78, 1.58)	−0.40 (−3.86, 3.18)
	Control for O_3	**4.85 (3.63, 6.09)**	**3.38 (2.29, 4.48)**	**3.54 (0.26, 6.91)**

The bold type represents the statistically significant ($p < 0.05$). The underline indicates the two-pollutant models are models that use $PM_{2.5}$, PM_c, or PM_{10} as the main air pollutant, with further adjustment for one of the gaseous pollutants (SO_2, NO_2, O_3).

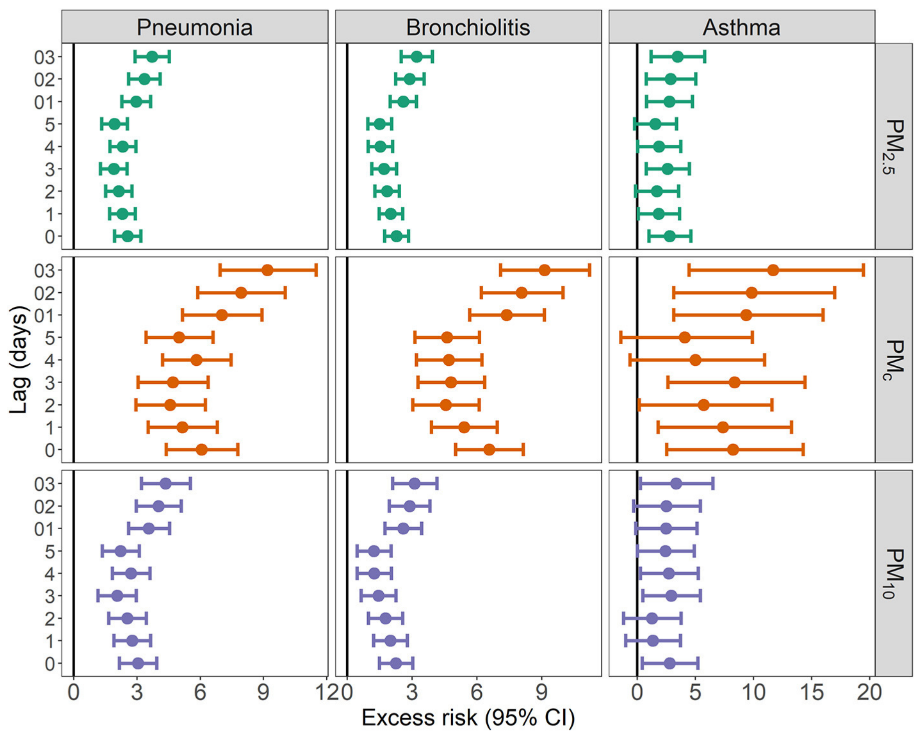

FIGURE 3 | Excess risk (95% CIs) of hospital outpatient visits associated with 10 μg/m^3 increase in PM_{10}, PM_c, and $PM_{2.5}$.

where the bold numbers indicate the significant differences across strata. We observed that each 10 μg/m^3 increase in PM_{10}, PM_c, and $PM_{2.5}$ was consistently associated with significantly different effects on pneumonia outpatient visits by sex and season groups. Similar differential effects were observed for the bronchiolitis associated with increases in PM_{10} and PM_c by different season

TABLE 3 | Excess risk and 95% CIs of pneumonia, bronchiolitis, and asthma for each 10 μg/m^3 increase in $PM_{2.5}$, PM_c, and PM_{10} stratified by gender, age group, and season.

Pollutants	Stratum	Pneumonia	Bronchiolitis	Asthma
PM_{10}				
	Gender			
	Male	**4.49 (3.54, 5.45)**	3.44 (2.68, 4.21)	4.46 (1.62, 7.39)
	Female	**2.68 (1.61, 3.75)**	2.76 (1.84, 3.69)	1.78 (−1.51, 5.18)
	Age			
	<5	3.50 (2.66, 4.34)	3.09 (2.36, 3.82)	1.78 (−0.97, 4.60)
	5–14	4.50 (2.71, 6.33)	3.70 (2.49, 4.92)	6.01 (2.39, 9.75)
	Season			
	Warm	**–0.06 (–1.24, 1.13)**	**2.13 (1.03, 3.23)**	6.53 (2.52, 10.69)
	Cold	**5.12 (4.00, 6.25)**	**3.76 (2.74, 4.79)**	1.76 (−1.00, 4.61)
PM_c				
	Gender			
	Male	**11.07 (8.36, 13.83)**	10.02 (7.82, 12.25)	15.65 (6.36, 25.74)
	Female	**6.70 (3.78, 9.71)**	7.57 (4.99, 10.21)	5.94 (-3.96, 16.87)
	Age			
	<5	8.69 (6.37, 11.06)	8.76 (6.69, 10.88)	6.96 (−1.69, 16.38)
	5–14	10.76 (5.65, 16.13)	10.75 (7.34, 14.27)	17.98 (6.46, 30.74)
	Season			
	Warm	**–0.93 (–4.33, 2.60)**	**3.77 (0.40, 7.26)**	22.14 (6.92, 39.53)
	Cold	**13.57 (10.46, 16.77)**	**11.92 (9.07, 14.84)**	9.39 (0.93, 18.56)
$PM_{2.5}$				
	Gender			
	Male	**5.31 (3.95, 6.69)**	3.48 (2.39, 4.58)	4.13 (0.30, 8.09)
	Female	**3.11 (1.58, 4.65)**	2.45 (1.14, 3.78)	1.92 (-2.54, 6.58)
	Age			
	<5	4.07 (2.87, 5.28)	2.88 (1.84, 3.93)	1.53 (−2.16, 5.35)
	5–14	5.59 (3.07, 8.17)	4.10 (2.39, 5.85)	6.13 (1.22, 11.28)
	Season			
	Warm	**0.08 (–1.49, 1.67)**	3.00 (1.56, 4.46)	**7.73 (2.62, 13.08)**
	Cold	**6.08 (4.42, 7.77)**	3.01 (1.51, 4.53)	**–0.30 (–4.05, 3.60)**

The bold type represents the statistically significant differences ($p < 0.05$).
Warm season: April to September; cold season: October to March.

strata, but not for $PM_{2.5}$. However, the differential effects across strata were much less significant for the asthma outpatient visits: it was only significantly different between the warm and cold seasons.

Table 4 shows the proportion reduction of ALRI (pneumonia, bronchiolitis, and asthma) outpatient visits attributable to $PM_{2.5}$, PM_c, and PM_{10} in Guangzhou from 2013 to 2019 using a counterfactual analysis framework (15 μg/m^3 for $PM_{2.5}$, 30 μg/m^3 for PM_c, and 45 μg/m^3 for PM_{10}). We found that $PM_{2.5}$ was associated with the largest decline in ALRI outpatient visits (pneumonia: 11.07%, 95% CI: [7.99, 14.30%]; bronchiolitis: 6.30% [4.17, 8.53%]; asthma: 8.14% [2.65, 14.33%]) if the levels of air pollution were reduced to the level of the reference guidelines.

DISCUSSION

In this study, we observed statistically significant ERs and a potential decline of ALRI (such as pneumonia, bronchiolitis, and asthma) outpatient visits associated with the size-specific particulate matter. The results were consistent in exposure assessment using different lags (lag 0–5 and moving averages of 1–3 days), two-pollutant models adjusting for SO_2, NO_2, and O_3, and various degrees of freedom. In counterfactual analyses that are of more public health significance, $PM_{2.5}$ was associated with the largest decline in the ALRI outpatient visits if the exposure was as low as the WHO reference guideline.

Consistent with a previous study (18), we observed dissimilar effect estimates associated with the size-specific particulate matter, and the largest ER was found to be that of PM_c, followed by that of $PM_{2.5}$ and PM_{10}. However, these results should be interpreted with caution as $PM_{2.5}$, PM_c, and PM_{10} have different means and standard deviations: the mean of PM_c in our sample (21.0 μg/m^3) was lower than the reference level (30 μg/m^3); the SD of PM_c (9.9 μg/m^3) was much smaller compared with that of $PM_{2.5}$ (21.2 μg/m^3) and PM_{10} (28.1 μg/m^3). Therefore, the ER of ALRI associated with PM_c

TABLE 4 | Counterfactual analysis on the percent of decline (95% confidence intervals) in acute lower respiratory infection outpatient visits if the level of $PM_{2.5}$, PM_c, and PM_{10} were reduced to the reference levels in Guangzhou from 2013 to 2019.

	Pneumonia	Bronchiolitis	Asthma
PM_{10}	**7.54% (5.80, 9.35%)**	**5.98% (4.57, 7.44%)**	**6.34% (0.47, 13.05%)**
PM_c	**1.33% (0.99, 1.67%)**	**1.46% (1.13, 1.81%)**	**1.78% (0.64, 3.07%)**
$PM_{2.5}$	**11.07% (7.99, 14.30%)**	**6.30% (4.17, 8.53%)**	**8.14% (2.65, 14.33%)**

The references of PM_{10}, $PM_{2.5}$, and PM_c concentration were 45 μg/m^3 for PM_{10}, 30 μg/m^3 for PM_c, and 15 μg/m^3 for $PM_{2.5}$, respectively.
The bold type represents the statistically significant ($p < 0.05$).

appeared to be the largest, which likely resulted from its smaller SD.

We found a larger effect of particulate matter–ALRI association among men than women, which is similar to the results of the sex-specific effects of particulate matter pollution reported previously (19). This may be due to the biological differences between men and women populations, such as hormones, sizes of airway diameters and lung sizes, and build, which will, in turn, result in the difference in the transport of pollutants and tissue deposition (17, 32). In addition, the observed associations between particulate matter and ALRI were stronger during the cold season, which is in line with the several previous studies (26, 33–35). There are several possible biological mechanisms, such as season-specific behavior, differences in $PM_{2.5}$ levels, constituent, and etiologic agents, which may be responsible for this seasonal difference.

The effects of particulate matter pollution on ALRI did not seem to be confounded by SO_2 and O_3. However, the associations between particulate matter pollution and ALRI decreased after adjusting for NO_2, in particular, the particulate matter-asthma associations became non-significant. It was difficult to ascertain their potential effects especially given the potential multicollinearity issue, possibly because NO_2 was highly correlated with particulate matter (**Figure 2**).

Given the limitation that the calculation of ER largely depends on the statistical distribution of the exposures, we further examined the potential proportion declination that would occur if exposure to size-specific particulate matter were reduced to the WHO recommended levels (15 μg/m^3 for $PM_{2.5}$, 30 μg/m^3 for PM_c, and 45 μg/m^3 for PM_{10}). Our counterfactual approach calculated the difference between the observed true number of hospitalizations and the estimated number of hospitalizations in counterfactual scenarios (the WHO recommended levels of air pollutants). Because the concentration of air pollutants for each person was input into the statistical models of the counterfactual analysis, this empirical approach is not subject to the underlying statistical distributions of the air pollutants. Our counterfactual analysis suggested that reducing $PM_{2.5}$ to the WHO reference was associated with the largest potential decline in ALRI outpatient visits, followed closely by the reduction of PM_{10}, while reducing PM_c to the WHO reference is associated with the lowest potential for a decline in ALRI outpatient visits, which is likely explained by the fact that the mean level of PM_c (21.0 μg/m^3) in our sample is lower than that of the WHO reference level (30 μg/m^3).

Our counterfactual analysis results have a more practical public health meaning than those of ER. The implication that reducing the level of $PM_{2.5}$ may be associated with the largest decline in ALRI outpatient visits is consistent with the previous studies reporting about the toxicity of smaller-sized particulate matter on lower respiratory infection hospitalizations (36–40). For example, Wang et al. specifically focused on the association between the size-specific particulate matter and childhood pneumonia, and they reported a graded impact of the size-specific particulate matter on the childhood pneumonia ($PM_1 > PM_{2.5} > PM_{10}$). Smaller-sized particulate matter is more likely to enter the smaller airways and cause severe health consequences.

Although the air quality has been substantially improved attributable to the effort of air quality management in China over the past decade (41, 42). The average level of particulate matter (especially $PM_{2.5}$ and PM_{10}) is still above the WHO recommended level. Northern Chinese cities with the high population densities can experience anomalously high levels of air pollution during the winter (43). Our results highlight the importance of focusing on the smaller-sized particulate matter due to its harmful effects on ALRI outpatient visits.

This study should be interpreted in view of several limitations. First, we used daily aggregated data to evaluate the short-term effect of particulate matter on health outcomes, but this aggregated nature of data could be subject to ecological bias. Second, a city-wide average concentrations of air pollution was used to represent the population exposure level, which could lead to exposure misclassification. Third, we included a relatively small number of asthma outpatient visits, which led to unstable point estimates and CIs for asthma. Fourth, since we used secondary data collected from the hospital administrative database, some important confounders (such as maternal smoking, prenatal care, and BMI) were not available to us. Lastly, we only used data from a single hospital, which limits the applicability of the results to the other regions of China.

Nonetheless, this study has several strengths. First, this is the first study to investigate the association between the size-specific particulate matter and subtypes of ALRI outpatient visits, while previous studies either reported the association between $PM_{2.5}$ and subtypes of ALRI outpatient visits or the association between the size-specific particulate matter and overall ALRI hospitalization without details on subtypes (5–7). Second, we used the counterfactual analyses to estimate the potential percent reduction in ALRI outpatient visits compared with the WHO-recommended levels. The results of counterfactual analyses have more substantial public health significance compared with ER, OR, and any other estimates associated with a fixed amount of increase in particulate matter (such as per 10 $\mu g/m^3$ increase in $PM_{2.5}$) (11–13).

CONCLUSIONS

In summary, this study suggests a larger potential percent of the reduction in ALRI outpatient visits if $PM_{2.5}$ could be lowered to the levels recommended by the WHO. The association between particulate matter and pneumonia outpatient visits was stronger among men patients and in the cold seasons. The results highlight the need for a consolidated effort to reduce the particulate matter pollution of smaller sizes and consequently improve the health outcomes of residents in China.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Ownership of the data does not belong to the individual. Requests to access these datasets should be directed to Chuming You, gd2hek@163.com.

AUTHOR CONTRIBUTIONS

ZL: conceptualization, investigation, visualization, writing—original draft, writing—reviewing, and editing. QM: investigation, visualization, and funding acquisition. QY and NC: investigation, writing—reviewing, and editing. CY: investigation, visualization, supervision, and project administration. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Greenhouse Gas Emissions and Health in the Countries of the European Union

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In the current era of globalization, a clean environment remains a crucial factor for the health of the population. Thus, improving air quality is a major focus of environmental policies, as it affects all aspects of nature, including humans. For these reasons, it is appropriate to take into account the health risks posed by greenhouse gas (GHG) emissions released into the atmosphere. With regard to global GHG emissions, there are concerns about the loss of protection of the ozone layer and it is very likely that climate change can be expected, which multiplies the environmental threat and has potentially serious global consequences. In this regard, it is important to pay increased attention to emissions that enter the atmosphere, which include countless toxic substances. The aim of this study was to examine the associations between selected GHG emissions and the health of the European Union (EU) population represented by disability-adjusted life years (DALYs). This aim was achieved using several analytical procedures (descriptive analysis, correlation analysis, cluster analysis, and panel regression analysis), which included five environmental variables (carbon dioxide (CO_2), methane (CH_4) in CO_2 equivalent, nitrous oxide (N_2O) in CO_2 equivalent, hydrofluorocarbons (HFC) in CO_2 equivalent, sulfur hexafluoride (SF_6) in CO_2 equivalent) and one health variable (DALYs). An emphasis was placed on the use of quantitative methods. The results showed that CO_2 emissions have a dominant position among selected GHG emissions. The revealed positive link between CO_2 and DALYs indicated that a decrease in CO_2 may be associated with a decrease in DALYs, but it is also true that this cannot be done without reducing emissions of other combustion products. In terms of CO_2, the least positive scores were observed in Luxembourg and Estonia. Germany had the lowest score of DALYs, representing the most positive health outcome in the EU. In terms of total GHG emissions, Ireland and Luxembourg were considered to be less positive countries compared to the other analyzed countries. Countries should focus on reducing GHG emissions in general, but from a health point of view, reducing CO_2 emissions seems to be the most beneficial.

Keywords: GHG, emissions, carbon dioxide, air quality, health, disability-adjusted life years, association, Europe

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INTRODUCTION

The world is dominated by ever-increasing production demands that leave traces in the environment. The other side of this coin is the degradation of the environment in connection with the production of greenhouse gas (GHG) emissions, climate change, loss of the protective ozone layer, global warming, which affect humanity, including its health (1, 2). According to a report published by the Intergovernmental Panel on Climate Change (3), humanity has been able to warm the planet over the past 50 years, while GHG emissions are considered a very serious aspect of human activity that contributes to this threatening state. These activities include the burning of fossil fuels, deforestation or intensive agriculture and others. Thus, it is important to pay increased attention to emissions that enter the atmosphere, which include countless toxic substances. In this sense, it is also possible to identify the world's biggest GHG emitters, and the fact remains that in 2015, the European Union (EU) ranked third behind China and the United States. The energy industry, agriculture, industrial processes, the use of products, and waste management were primarily responsible for this situation in the EU (4). These facts justify the importance of examining this problem in the EU. Reducing GHG emissions is a major environmental challenge of the 21st century and it is time to think about the current situation in different countries. An important message is the European Green Deal, a strategic plan to transform climate and environmental challenges into opportunities in order to build a modern, competitive and resource-efficient Europe. Striving to become the first climate-neutral continent also means a commitment to achieve zero net GHG emissions by 2050 (5).

It is the air that allows substances and chemicals to be transported around the world, while increasing air pollution and increasing GHG emissions almost always go hand in hand (6). Most GHGs have a long lifespan and are well-mixed in the ambient atmosphere. It is also true that emissions with the global warming potential can be harmful and degrade air quality, and their consequences can be reflected in global climate change affecting ecosystems and humanity (7, 8). It can be stated that GHG emission sources are all around. For instance, coal consumption in the energy sector is characterized by carbon dioxide (CO_2) and sulfur dioxide (SO_2) emissions. Rice cultivation, composting and livestock farming are dominant for methane (CH_4) emissions, while the use of synthetic fertilizers in the agricultural sector is the main source of nitrous oxide (N_2O) emissions (9–11). GHG and air pollutants share the same emission sources, and they come from the same natural and anthropogenic sources. In this regard, both air pollutants and CO_2 are all products of combustion. Thus, part of the link between CO_2 emissions and health should be explained by the air pollution that is emitted along with the CO_2 (1). Despite the interconnection, air pollutant and GHG emissions do not need to be synchronized and require harmonization through well-developed strategies (9).

Focusing on GHG emissions, the greatest consequences of global climate change with an impact on human health are represented by increased temperatures, the longer duration of temperatures and their intensity. The heat also causes the occurrence of new pollen allergens and the number of premature deaths due to overheating of the body. In addition, more frequent forest fires caused by drought increase the number of cases with severe burns. All these facts indicate that there is no doubt that climate change is a current and future risk factor for health (2). In the context of the main ide of this study, it can be assumed that tackling emissions can mean tackling climate, global warming, the environment at the same time, while public health co-benefits can also be expected (1, 12, 13). It is well-known that health effects due to climate change are a result of global emissions, but a national perspective is also important and the following findings provide a rationale.

In fact, GHG emissions reduce the health potential of a population, which can be seen in the losses expressed by disability-adjusted life years (DALYs) (14). A study conducted by Woodcock et al. (15) supported the idea that reducing CO_2 in London and Delhi through less use of motor vehicles and more use of lower-emission motor vehicles can lead to health benefits in terms of DALYs. Using a comparative method of health risk assessment in Malaysia, similar findings were revealed by Kwan et al. (16). This is in line with the fact that CO_2 is a substance that is harmful to health and a key substance in climate change, thus its global warming potential may also be reflected in the DALYs indicator (17, 18). Thus, it can be concluded that population health (measured as DALYs) is damaged by factors related to carbon emissions (19, 20). Using a panel regression analysis, Dong et al. (21) also supported the idea that carbon emissions have a long-term adverse effect on population health, while a 1% increase in carbon emissions could lead to a 0.298% higher number of outpatients and a 0.162% higher number of inpatients. On this basis, it seems that efforts to reduce carbon emissions could be beneficial from both an environmental and a health point of view, as highlighted by findings in the research from Belgium, in which a carbon tax has proved to be a tool for preventing DALYs, as well as for saving healthcare spending (22). At the same time, not only reducing carbon emissions, but also reducing nitrous oxide and methane emissions provides an opportunity to improve the environment and public health as such (23, 24). Accordingly, GHG emissions such as CO_2, CH_4 and N_2O are considered a health threat, even if the DALYs indicator is taken into account (25).

As pointed out, environmental aspects are related to a wide range of human lives, while GHG emissions are no exception. There is no doubt that GHG emissions could pose a greater or lesser threat to human health and the overall environment. Therefore, it is necessary to monitor emissions in individual countries, which simultaneously generate global emissions with a health effect in terms of climate change and global warming. International organizations emphasize the serious situation and call for active action to address it. The presented study provided a closer look at the links between GHG emissions and DALYs in the EU. The EU brings together countries that share the same goals, including health, but also economic and environmental ones (26, 27). In order to set effective strategies, it is important to know the situation in individual EU countries. The fact is that increased research attention has focused on climate change and its effects on public health, but no less important is the view of the link between GHG emissions and health. This issue has been overlooked and there is a lack of sufficient knowledge. The present study pointed to the trajectory of individual indicators and filled this gap in research, thus contributing to environmental and health issues from a unique point of view.

MATERIALS AND METHODS

Research Objective

The primary aim of this study was to examine the associations between selected GHG emissions and the health of the EU population represented by DALYs.

The research sample consisted of 27 EU countries, with the oldest data were from 2009 and the most recent from 2018 (annual data without any missing values). The period was chosen based on the assumption of certain changes in mortality in connection with the economic crisis in 2008, as pointed out by Laliotis et al. (28). The following countries were included in the analytical process: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden.

Research Data

The data can be considered relevant, as their sources are databases of international organizations such as Eurostat, which obtain data from national statistical offices. The relevance of the Global Burden of Disease (GBD) Study database is also evidenced by the very close connection with the Lancet journal (29).

GHG Emissions

The analytical processes included five environmental indicators capturing GHG emissions, namely CO_2, CH_4 (in CO_2 equivalent), N_2O (in CO_2 equivalent), HFC (in CO_2 equivalent), and SF_6 (in CO_2 equivalent). The indicators representing GHG emissions were expressed in thousands of tons per 100,000 inhabitants. Data on GHG emissions as well as data on the average annual population in each country were collected from the Eurostat database (30) (Section: Environment and energy—Environment—Emissions of greenhouse gases and air pollutants—Air emissions accounts).

DALYs

The analyzes also included one indicator capturing health status, namely the DALYs indicator. This health indicator was expressed per 1,000 inhabitants of a particular country. The DALYs indicator expresses a measure of the gap in healthy years of life lived by a population as compared with a normative standard. In other words, DALYs are a time-based measure that adds together years of life lost due to premature mortality with the equivalent number of years of life lived with disability or illness. Thus, the DALYs indicator includes the years of life lost due to premature mortality (YLLs) and the years lived with a disability (YLDs) (31). Data on DALYs were obtained from the GBD database (32) [Section: IHME Data (TGBD Results Tool)], which can be considered as one of the largest databases for health-related indicators. Also, this indicator was expressed in terms of overall mortality (all diagnosis groups were included).

Statistical Approach

Several methods and procedures were used in the statistical processing, which was divided into three consecutive subsections, namely (i) Univariate View—Statistical Description, (ii) Bivariate View of Associations—Correlation Analysis and Regression Analysis, and (iii) Multivariate View of Associations—Cluster Analysis.

The main analytical calculations were performed using the programming language R v 4.0.3 (RStudio, Inc., Boston, MA, US), while Tableau v 2020.2 (Tableau Software, LLC, Seattle, WA, U.S.) was used secondarily.

Analysis With a Univariate View

For the purpose of providing a statistical description, the basic statistical characteristics were used, namely mean, median, standard deviation, skewness, kurtosis, minimum, maximum, first quartile and third quartile. These results can be found in the first subsection Univariate View—Statistical Description.

Analyzes With a Bivariate View

Subsequently, in the second subsection Bivariate View of Associations—Correlation Analysis and Regression Analysis, the non-parametric coefficient (Spearman's ρ) was used in the correlation analysis to assess the associations. In this subsection, the assumptions for the selection of panel regression models were also evaluated. The Breusch-Pagan test (33) was applied to assess the variability of the residues. The use of Wooldridge's test for unobserved individual effects (34) was aimed at assessing the significance of unobserved effects through the distribution of residues, while in the case of significant effects, it was recommended to apply a regression model that takes into account the internal data structure. Due to a certain probability within which it was possible to assume the occurrence of a serial correlation, the Baltagi and Li one-sided LM test was chosen to assess this specificity (35). The F test for the presence of individual effects (or time effects) was used to assess the significance of effects in the internal data structure in terms of countries and individual years. The Hausman test and the robust regression-based Hausman test (vcov: vcovHC) were useful in choosing a model with fixed (within) effects or a model with random effects. The application of Angrist and Newey's test (36) supported the choice between the mentioned models in terms of identifying the limitations of models with fixed effects. Two variants of regression models were presented in a robust version, namely a model with fixed effects, i.e., Oneway (individual) effect Within model (Arellano estimator), and a model with random effects, i.e., Oneway (individual) effect Random effect model: Swamy-Arora's transformation (White 2 estimator). The result of the regression analysis points to the associations between GHG emissions (independent variables) and health represented by DALYs (dependent variable). The regression result has a higher added value compared to the correlation result. However, even this association cannot be considered causal, as the causal links were not proven by the analyzes used in this study. Compared to the classical model (Ordinary Least Squares—pooling model), the panel models take into account the internal data structure (in this case the structure within countries). The study provided the results of a pooling model and two panel models to compare estimates, but the preference for one of them and for its result was given by the above-mentioned assumptions.

Analysis With a Multivariate View

The statistical processing also included cluster analysis, the results of which are presented in the subsection Multivariate View of Associations—Cluster Analysis. The indices in this analysis were recalculated in several steps. In the first step, the arithmetic average of the individual indicators was calculated for each country (the results of this step are given in **Supplementary Table 1**). The average for countries included all observed years (in all countries the number of years was identical: 2009–2018; $n = 10$). Subsequently, these average values were standardized from 0 to 1 (0 represented the least positive value and 1 the most positive value). The standardization was based on an Equation (1):

$$z_i = 1 - \frac{x_i - \min(x)}{\max(x) - \min(x)} \tag{1}$$

where x_i is the average of the reported values of the indicator for a specific country (for the observed period), *min(x)* is the lowest average value of the indicator (for the observed period) identified in the dataset containing all examined countries, *max(x)* is the highest average value of the indicator (for the observed period) identified in the dataset containing all examined countries.

In the subsequent step, the arithmetic average was calculated from the standardized values of individual GHG indicators for each country, thus creating a new variable—Greenhouse gases index. This index was developed for the purposes of this study and expresses a score ranging from 0 to 1, with 0 representing the least positive score in terms of all GHG emissions (a country with the highest average GHG production) and 1 representing the most positive score in terms of all GHG emissions (a country with the lowest average GHG production). The DALYs index was formed by only one variable, that is the standardized DALYs. This variable was created in the previous standardization step. The values adjusted in this way were the input to **Figure 2** and the cluster analysis (**Figure 3**). The cluster analysis included only two variables (Greenhouse gases index and DALYs index). The cluster analysis was performed using the Partitioning Around Medoids (PAM) algorithm (37) suitable for data in which the presence of outliers is expected, and using the algorithm of Manhattan distance. Simultaneously, a simpler cluster method, the k-means algorithm, was used. The optimal number of clusters was estimated using the silhouette method (38).

RESULTS

The results section provides three separate subsections according to the analysis and the purpose of the research. The first subsection, Univariate View—Statistical Description, offers a descriptive analysis, which was used for a more detailed presentation of selected indicators. The second subsection, Bivariate View of Associations—Correlation Analysis and Regression Analysis, presents the results of a correlation analysis that pointed to the associations between GHG emissions and DALYs in the EU. Several plots were also provided in this subsection. Furthermore, a regression analysis was also used to examine the significance of the associations between GHG emissions on DALYs, taking into account the internal structure of the data. In the third subsection, Multivariate View of Associations—Cluster Analysis, a cluster analysis identified homogenous clusters of EU countries in terms of assessing GHG emissions and DALYs. The other steps in this subsection were aimed at linking these environmental and health indicators in a more detailed specification of individual EU countries.

Univariate View—Statistical Description

This subsection presents the selected indicators in a more detailed univariate view. **Table 1** shows the basic descriptive measures, and it is clear that CO_2 (mean = 655.56 thousands of tons) dominated among the examined GHG emissions in EU countries, while the lowest mean value was found for SF_6 (mean = 0.82 thousands of tons). The values of skewness and kurtosis indicated some deviations from the normal distribution, but in most cases, there were small deviations. With a focus on the skewness measure, positive values were observed in all cases, indicating an increased presence of higher values and potential outliers in both GHG and DALYs indicators. A certain contamination of the normal distribution could also be detected by comparing the mean and median values. The values of minimum, maximum, first and third quartile also provided a closer look at the examined indicators. At this point, it should be noted that the dataset did not contain missing values and that all GHG emissions (except CO_2) are given in CO_2 equivalent.

In general, it can be stated that not only CO_2 but also CH_4 requires attention with the second highest mean value among all emissions. An increased attention should also be paid to emissions such as N_2O and HFC. On the contrary, the lowest mean value (in thousands of tons per 100,000 inhabitants) was found in SF_6. The production of each of these gases is relatively specific. For example, CO_2 is produced mainly by the combustion of fossil fuels, which seems to be easier to manage than N_2O, which is produced predominantly in agriculture. This idea underlines the fact that, in addition to assessing the global warming potential, the potential for reducing specific GHG emissions should be taken into account.

When focusing on CO_2, some deviations from other GHG emissions were evident. The level (in thousands of tons per 100,000 inhabitants) of other GHG emissions was much lower than the level of CO_2 (e.g., SF_6). Thus, the significant amount of CO_2 emissions means that there is a lot of space to reduce its production. There were several countries showing clear evidence that this is possible (**Supplementary Table 1** provides values for comparison between countries). The sample included countries where CO_2 emissions ranged from very high level (Luxembourg) to very low level (Sweden). When assessing GHG emissions, it is also necessary to take into account their negative effects, which are not proportional, as some GHGs can affect global warming

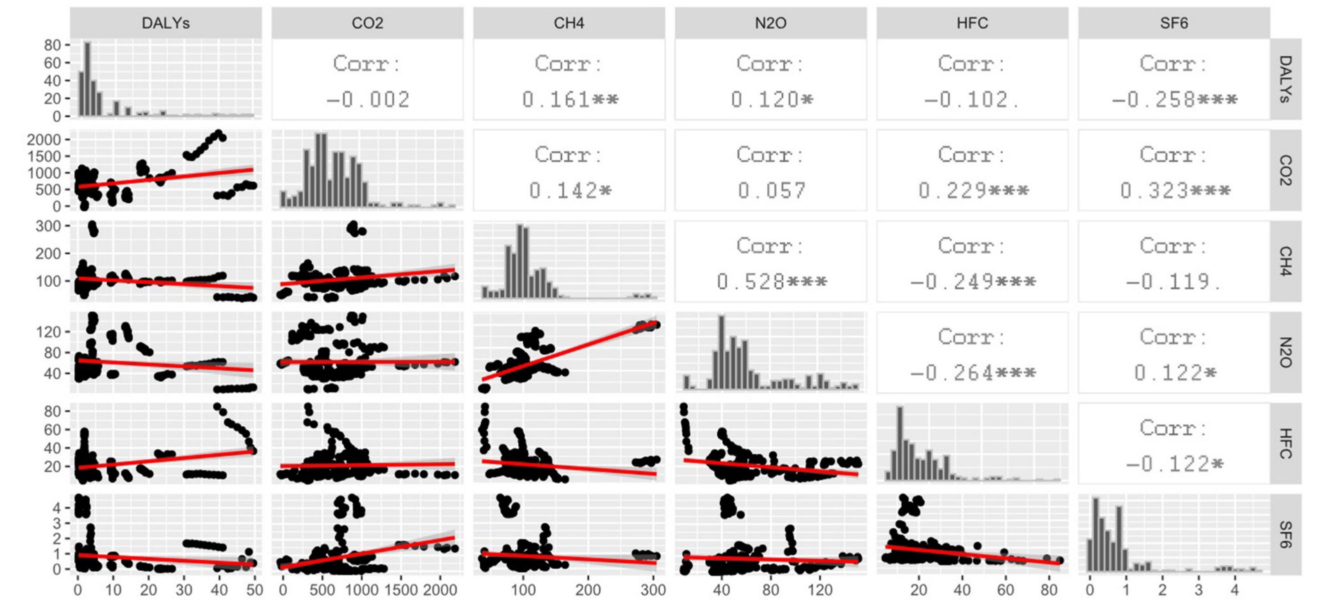

FIGURE 1 | Correlation analysis of GHG indicators (in thousands of tons per 100,000 inhabitants) and DALYs (in years per 1,000 inhabitants) without classification of EU countries, and plots of individual indicators. Sig: 0.1; *0.05; **0.01; ***0.001.

more than others. Some gases occur less in the atmosphere, but they capture heat several times more effectively than CO_2. In this study, the global warming potential of individual greenhouse gases was expressed in terms of CO_2, as the CO_2 equivalent was used for other emissions. The analysis also included one health indicator, based on the results of which it can be stated that the EU population lived on average 7.45 healthy life years less than they could (calculated per 1,000 inhabitants).

Bivariate View of Associations—Correlation Analysis and Regression Analysis

This subsection points out the associations between the analyzed indicators in a bivariate view.

Figure 1 completes the information on GHG and DALYs indicators. Thus, it clarifies their structure as well as the associations between them in order to better understand the issue. Density plots are shown in a diagonal line, scatter plots are below the diagonal line, and correlation coefficients are above the diagonal line (Spearman's ρ). Regarding the associations between individual GHG emissions and DALYs, a significant correlation was found for CH_4, N_2O and SF_6. In these cases, a significance could be confirmed at the level of $\alpha < 0.05$. However, it is necessary to distinguish between positive and negative correlation coefficients. A negative correlation was found between SF_6 and DALYs ($\rho = -0.258$). It is also useful to focus on the associations between the individual GHG indicators, within which it was possible to find the highest rate of correlation between N_2O and CH_4 ($\rho = 0.528$). Furthermore, it was possible to point out a positive correlation between SF_6 and CO_2 ($\rho = 0.323$), as well as a negative correlation between HCF and N_2O ($\rho = -0.264$).

Table 2 shows the correlations between GHG emissions and DALYs in terms of individual EU countries. In other words, the table shows the associations in which the inputs were individual GHG emissions and DALYs for each country in individual years ($N = 10$). A significant positive correlation coefficient indicated that in the years when a country showed a higher value of DALYs, it was also possible to observe a higher value of a certain GHG emission and vice versa. On the other hand, a significant negative coefficient indicated that in the years when a higher value of DALYs was measured, it was possible to observe a lower value of a certain GHG emission and vice versa. Across EU countries, significant positive correlations were found mainly for CO_2 and CH_4, while the highest number of negative correlations was found for HCF. **Supplementary Table 1** provides the average values of the examined indicators in individual EU countries, as well as the inclusion of countries in the cluster.

Table 3 provides an evaluation of the assumptions for selecting appropriate regression models. The results of the test to verify the constancy of residue variability (Breusch Pagan) indicated the presence of significant heteroscedasticity in almost all cases, while this contamination was not confirmed only for N_2O. The serial correlation was verified using Wooldridge's test for unobserved individual effects and the Baltagi-Li one-sided LM test. Based on the results, it was possible to confirm the significance in all cases at the level of $\alpha < 0.05$. Therefore, the choice of robust estimation methods was considered appropriate. The results of the F test applied within the data structure from the point of view of countries showed a significance in all of the analyzed cases at the level of $\alpha < 0.001$. On the contrary, the

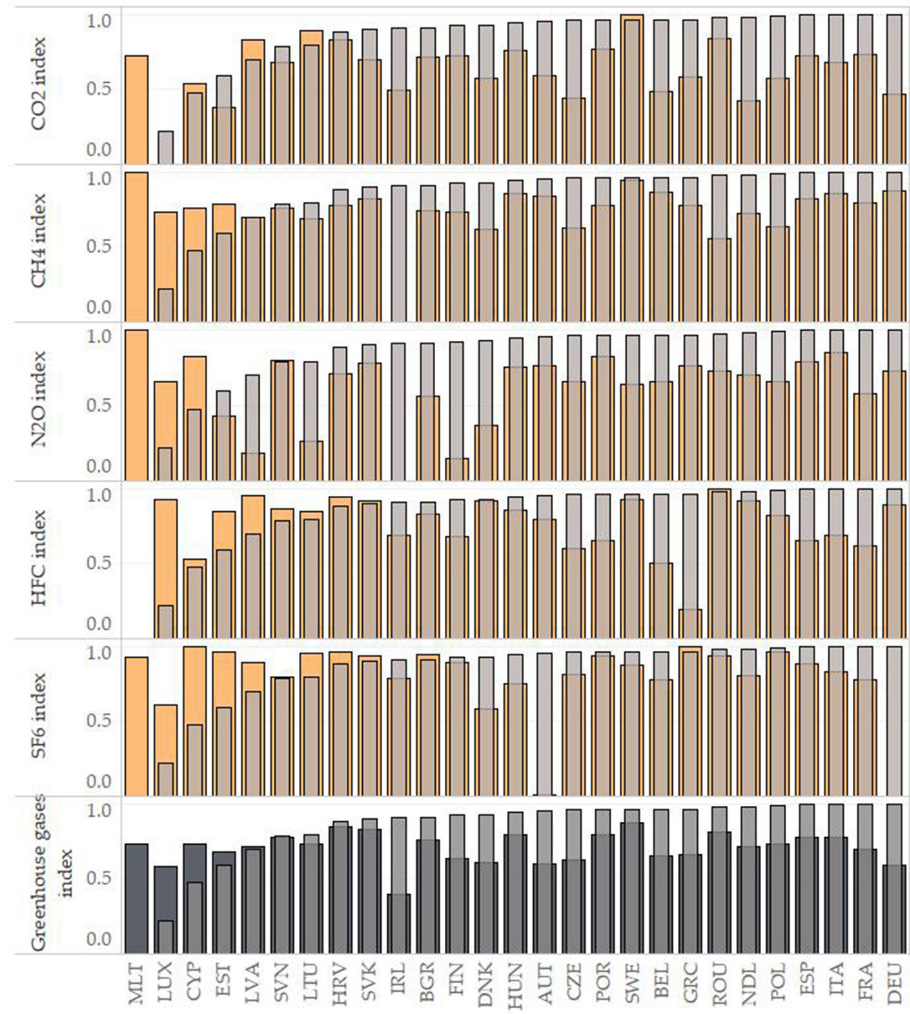

FIGURE 2 | Scores of DALYs index and GHG indices in individual EU countries. Note: The lower the column the less positive the assessment. The countries are ranked from the lowest to the highest DALYs index. The DALY index is shown in each partial graph by a transparent gray color, the individual GHG indices by a yellow color and the Greenhouse gases index by a dark opaque gray. AUT, Austria; BEL, Belgium; BGR, Bulgaria; CYP, Cyprus; CZE, Czech Republic; DEU, Germany; DNK, Denmark; ESP, Spain; EST, Estonia; FIN, Finland; FRA, France; GRC, Greece; HRV, Croatia; HUN, Hungary; IRL, Ireland; ITA, Italy; LTU, Lithuania; LUX, Luxembourg; LVA, Latvia; MLT, Malta; NDL, Netherlands; POL, Poland; POR, Portugal; ROU, Romania; SVK, Slovakia; SVN, Slovenia; SWE, Sweden.

TABLE 1 | Descriptive analysis of GHG emissions (in thousands of tons per 100,000 inhabitants) and DALYs (in years per 1,000 inhabitants).

Statistics	CO_2	CH_4	N_2O	HFC	SF_6	DALYs
n	270	270	270	270	270	270
Mean	655.56	103.99	61.86	20.99	0.82	7.45
Median	605.22	96.8	52.57	17.04	0.51	2.58
Std. Dev.	357.4	43.51	32.05	12.89	1.01	11.01
Skewness	1.12	2.66	1.12	1.86	2.38	2.25
Kurtosis	2.9	9.44	0.53	4.62	5.13	4.46
Minimum	−35.27	36.66	8.92	4.55	0.02	0.24
Maximum	2186.22	304.96	151.18	84.93	4.67	49.53
Quartile I	423.24	81.89	39.71	11.83	0.22	1.37
Quartile III	877.62	116.27	69.71	26.48	0.86	9.31

n, frequency of observations; Std. Dev., standard deviation; Quartile I, first quartile (25th percentile); Quartile III, third quartile (75th percentile).

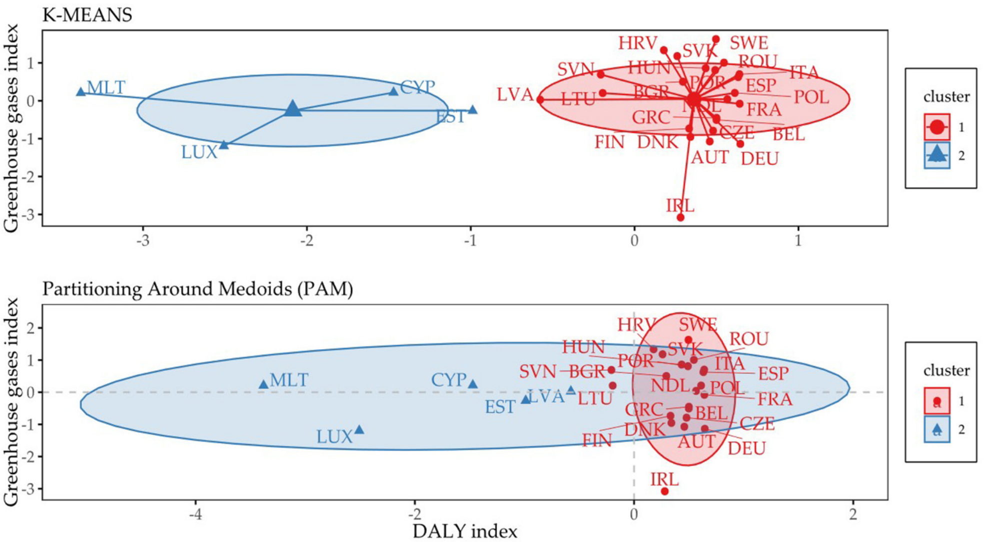

FIGURE 3 | Cluster maps: Country positions based on the DALYs index score and the Greenhouse gases index score. AUT, Austria; BEL, Belgium; BGR, Bulgaria; CYP, Cyprus; CZE, Czech Republic; DEU, Germany; DNK, Denmark; ESP, Spain; EST, Estonia; FIN, Finland; FRA, France; GRC, Greece; HRV, Croatia; HUN, Hungary; IRL, Ireland; ITA, Italy; LTU, Lithuania; LUX, Luxembourg; LVA, Latvia; MLT, Malta; NDL, Netherlands; POL, Poland; POR, Portugal; ROU, Romania; SVK, Slovakia; SVN, Slovenia; SWE, Sweden.

results of the F test applied within the data structure from the point of view of years were not significant in any of the analyzed cases. Based on these results, only the effect resulting from the country structure was taken into account in the regression models. The preference of a fixed effects model or a random effects model was supported by the results of the tests in the last three rows of the table. If the results of the Hausman test and its robust version [Hausman (vcovHC)] showed a significance, a fixed effects model was preferred, otherwise a random effects model was considered more appropriate. In general, the result of Angrist and Newey's test with a *p*-value of <0.05 indicates significant limitations of the model with fixed effects. In **Table 3**, it was possible to observe certain limitations in the model containing CO_2 as an independent variable. Based on this fact, it was appropriate to take into account the results of both models (random and fixed) when assessing the association between CO_2 emissions and DALYs. Apart from this exception, the recommendations for model preference in the other analyzed cases were clear.

Table 4 shows the results of the regression models. Despite the not entirely clear recommendation of the model preference for CO_2, it was possible to observe a significant positive coefficient in both models (fixed and random). A significant association was also found for N_2O, which also showed a positive β coefficient. Accordingly, a decrease in CO_2 and N_2O emissions was associated with a decrease in DALYs in EU countries and vice versa. In the case of CH_4, the fixed (within) effects model was recommended, the result of which did not prove to be significant. The significant associations with DALYs could not be confirmed even in the analyzed cases of HFC or SF_6. The significance of the associations between GHG emissions and DALYs was assessed on the basis of β coefficients, but the determination coefficients (R^2) also provided useful information in assessing the associations. The highest values were found for CO_2.

Multivariate View of Associations—Cluster Analysis

This subsection points to the associations between the analyzed indicators in a multivariate view. **Figure 2** shows the GHG emission indices and the DALYs index in individual EU countries. The indices ranged from 0 to 1 (standardized score), where 0 was the least positive score and 1 was the most positive score in terms of GHG emissions as well as DALYs. The calculation of GHG indices (CO_2 index, CH_4 index, N_2O index, HCF index, SF_6 index, DALYs index) was performed using the arithmetic average of the values of individual indicators for the observed period in each EU country and subsequent standardization. The Greenhouse gases index represented the average of individual indices of GHG emissions.

Based on the results in **Figure 2**, Malta (MLT) could be considered as an outlying country due to the acquired slightly asymmetric values. This country showed the least positive score of the DALYs index but, in several cases, a very positive score of the GHG emission indices. Among the EU countries, Germany showed the most positive score of the DALYs index, followed by France, Italy and Spain. In terms of total GHG emissions in countries (Greenhouse gases index), the least positive score was identified in Ireland, followed by countries such as Luxembourg, Germany and Austria. On the other hand, countries such as Sweden, Croatia and Slovakia could

TABLE 2 | Correlation coefficients between GHG emissions and DALYs by EU country.

ID	CO_2	CH_4	N_2O	HFC	SF_6
AUT	0.750**	0.995†	0.611*	−0.935†	−0.486
BEL	0.894†	0.988†	0.919†	−0.966†	0.479
BGR	−0.375	0.142	−0.388	−0.175	−0.640*
CYP	0.811***	0.177	0.777***	0.094	0.017
CZE	0.562*	0.893†	−0.711**	−0.984†	0.839***
DEU	0.811***	0.967†	0.499	−0.183	−0.923†
DNK	0.881†	0.980†	0.556*	0.974†	−0.453
ESP	0.834***	0.800***	−0.164	0.723**	0.496
EST	−0.657**	0.768***	−0.935†	−0.975†	−0.970†
FIN	0.117	0.980†	0.809***	0.786***	−0.017
FRA	0.922†	0.991†	0.778***	0.069	0.956†
GRC	0.278	0.106	0.412	−0.425	0.170
HRV	0.564*	0.006	0.769***	−0.933†	0.662**
HUN	0.552*	0.801***	−0.905†	−0.640**	−0.651**
IRL	0.748**	−0.875†	−0.509	−0.630*	0.061
ITA	0.945†	0.947†	0.944†	−0.958†	0.425
LTU	−0.863***	0.710**	−0.506	−0.773***	−0.498
LUX	0.952†	0.953†	0.978†	−0.709**	−0.987†
LVA	−0.248	−0.895†	−0.937†	−0.962†	−0.925†
MLT	0.934†	−0.191	0.929†	−0.974†	0.590*
NDL	0.820***	0.959†	0.661**	0.906†	0.569*
POL	−0.238	0.903†	−0.545	−0.148	−0.849***
POR	−0.393	0.604*	0.255	−0.939†	0.881†
ROU	0.648**	0.812***	−0.256	−0.663**	−0.237***
SVK	0.576*	0.689**	0.752**	−0.895†	0.780***
SVN	−0.758**	0.958†	0.539	−0.861***	0.535
SWE	0.893†	0.992†	0.815***	0.879†	0.808***

*Sig: *0.1; **0.05; ***0.01; †0.001. Negative correlations are highlighted in red and positive correlations are highlighted in green. A richer color indicates a stronger correlation. Non-significant correlations are not highlighted.*

ID, country identifier; AUT, Austria; BEL, Belgium; BGR, Bulgaria; CYP, Cyprus; CZE, Czech Republic; DEU, Germany; DNK, Denmark; ESP, Spain; EST, Estonia; FIN, Finland; FRA, France; GRC, Greece; HRV, Croatia; HUN, Hungary; IRL, Ireland; ITA, Italy; LTU, Lithuania; LUX, Luxembourg; LVA, Latvia; MLT, Malta; NDL, Netherlands; POL, Poland; POR, Portugal; ROU, Romania; SVK, Slovakia; SVN, Slovenia; SWE, Sweden.

TABLE 3 | Assumptions of regression models with GHG emissions as independent variables and DALYs as a dependent variable.

Assumptions	CO_2	CH_4	N_2O	HFC	SF_6
Breusch Pagan	98.24†	5.77**	1.18	73.14†	13.89†
Wooldridge	3.06***	1.47	2.82***	2.68***	1.88*
Baltagi Li LM	9.19†	12.94†	11.79†	13.31†	11.29†
F Test Country	214.73†	842.65†	592.10†	70.59†	222.84†
F Test Year	0.18	0.11	0.01	0.79	0.01
Hausman	33.00†	4.91**	1.79	59.95†	0.96
Hausman (vcovHC)	33.11†	22.49†	2.12	2.29	0.38
Angrist and Newey	115.95**	85.65	86.96	68.47	31.88
Model	R/F	F	R	R	R

*Sig: *0.1; **0.05; ***0.01; †0.001; R, random effects model; F, fixed (within) effects model.*

be considered positive. With a focus on the indicator with a dominant position among selected GHG emissions, CO_2, the least positive scores were found in Luxembourg and Estonia. Based on the results of the regression analysis, these countries have great opportunities to improve the environment as well as the health of their population.

Figure 3 provides maps of individual countries included in the created clusters based on the linking of the acquired DALYs

TABLE 4 | Regression analysis results: associations between GHG emissions (independent variables) and DALYs (dependent variable).

DALYs—dependent variable		CO_2	CH_4	N_2O	HFC	SF_6
Pooling	β (SE)	10.41 (9.97)	−0.70 (0.55)	−0.38 (0.50)	0.36 (0.34)	−0.01 (0.01)
	β (SE)	578.04† (70.9)	109.17† (10.13)	64.68† (6.77)	18.34† (2.58)	0.91† (0.25)
	R^2	0.1	0.03	0.02	0.09	0.01
Within	β (SE)	49.71† (12.51)	1.05 (0.67)	0.46 (0.28)	−2.16 (1.35)	0.01 (0.03)
	R^2	0.32	0.05	0.01	0.2	0.002
Random	β (SE)	35.07† (6.19)	0.82*** (0.26)	0.31** (0.15)	−0.52 (0.38)	0.002 (0.01)
	α (SE)	394.35† (71.99)	97.85† (8.76)	59.56† (6.40)	24.84† (2.94)	0.81† (0.22)
	R^2	0.24	0.03	0.006	0.03	<0.001

*Sig: *0.1; **0.05; ***0.01; †0.001.*

index and the Greenhouse gases index (based on Equation 1). Two clustering methods were used, the k-means algorithm, the output of which is shown in the upper graph, and the PAM algorithm, the output of which is shown in the lower graph. Malta, Luxembourg, Cyprus, Estonia and possibly Latvia (cluster 2) could be considered as countries with different values obtained in the assessed dimensions compared to the countries in the first cluster. The PAM map can be interpreted in such a way that the closer the country is to the right side of the graph (x-axis), the more positive the DALYs index obtained. Simultaneously, the higher the country (y-axis), the more positive the score in total emissions (Greenhouse gases index). Thus, the link can be seen in such a way that the closer the country is to the upper right corner, the more positive the country's position in terms of the DALYs index and the Greenhouse gases index. Accordingly, Sweden was the country with the most positive assessment.

The k-means map presented in **Figure 3** shows ellipses that were formed based on the Euclidean distance, and the PAM map shows ellipses that were formed using the distance based on the distribution of t. In general, it can be stated that a country outside an ellipse in the PAM map is a country with different scores compared to other countries in an ellipse. On this basis, it was possible to assess Ireland in a negative sense in terms of GHG emissions.

DISCUSSION

Humanity does not realize that GHG have existed in the atmosphere for a very long time. It is possible to speak of several years, decades or several thousand years. These gases affect the entire planet, regardless of which country produced them. Several studies declare an explicit link between health and environmental degradation, while evidence suggests that many diseases as well as premature deaths can be attributed to poor air quality and GHG emissions (12, 13, 39). In this already serious situation, it is desirable for each country to behave responsibly and to adopt emission reduction programs (40, 41). These facts were the motivation for examining the associations between GHG emissions and the health of the EU population represented by DALYs. First of all, the results identified the true state of GHG emissions in the EU, and a more detailed insight was provided using the descriptive analysis. The highest mean value was observed for CO_2 and the lowest mean value was observed for SF_6. This study supported the well-known fact that CO_2 is considered to be one of the largest contributors to poor atmospheric quality among GHG emissions, and this finding was also confirmed by other authors (7, 17, 18, 25). It should be noted that CO_2 accounts for up to 82% of world emissions, while CH_4 accounts for 11%, N_2O for 5%, HFC for 2% and SF_6 for <0.2% (4). For DALYs in the EU, the results indicated a mean value of 7.45, which can be seen as an average of 7.45 years of life lost due to premature mortality, together with years lived with disability or illness. On the other hand, a median value was 2.58 years, which indicated deviations in EU countries.

In terms of comparing the observed DALYs and GHG emissions in individual countries, Germany was considered to be a country with the most positive score of DALYs, although this country acquired the third least positive score of total GHG emissions. On the other hand, Malta was considered to be a country with the least positive score of DALYs, but this country was characterized by the most positive score of emissions. These findings are consistent with other evidence (4), and the authors of this study call for further research to clarify which factor better explains these results. The least positive score of total GHG emissions was found in Ireland, while this country also showed a less positive score of DALYs from all EU countries. Only nine countries achieved worse DALYs than Ireland.

The associations between GHG emissions and DALYs within the EU as a whole were assessed using Spearman's ρ, and the significant correlations were confirmed for CH_4, N_2O a SF_6. In individual EU countries, significant positive correlations with DALYs were found mainly for CO_2 and CH_4, while the highest number of negative correlations was found for HCF. In the regression analysis, the significant and positive associations with DALYs were found for both CO_2 and N_2O. This finding indicates that a decrease in CO_2 and N_2O emissions may be associated with a reduction in DALYs, which can be considered desirable from an environmental and health point of view. In this way, it is possible to increase the level of population health, however, it should be noted that this cannot be done without reducing emissions of other combustion products, which were not the subject of this study (1). This finding can be explained by their global warming potential and climate change leading to heat stress (2). The significant associations with DALYs were not confirmed for CH_4, HFC or SF_6. This finding does not necessarily mean that CH_4, HFC and SF_6 are not associated with health, as these emissions also contribute significantly to climate change, ozone depletion and global warming.

The findings of this study are in line with the findings of several authors who identify CO_2 emissions as a health damaging factor in general (21), but also in terms of DALYs (17, 19, 20). Thus, it is possible to agree that CO_2 emissions are significantly associated with public health (21) which emphasizes the need to implement effective measures to improve health, but also to improve the environment. One such measure seems to be a carbon tax as an effective tool for achieving health benefits in terms of DALYs as well as economic benefits (22). Another opportunity could be to increase the price of emission allowances and reduce the maximum number of emission allowances. In addition, there is no doubt that measures to reduce the use of motor vehicles in cities also play an important role, as this step can lead to a reduction in DALYs (15, 16). However, as pointed out in this study, not only CO_2 is associated with health, the results showed a significant association between N_2O and DALYs, which is in line with the idea of Montagu et al. (23), who saw low emissions of nitrous oxides as a win for health and the environment. It should also be noted that although this research did not support another association, other authors identified a reduction in CH_4 emissions as an opportunity to improve air quality and public health as such (24). For these reasons, environmental policy and decision-making should apply a comprehensive approach to GHG emissions (42–44), as public health co-benefits can also be expected when reducing them (1, 12, 13).

Based on the findings revealed by the cluster analysis in combination with the results in **Supplementary Table 1**, countries such as Malta, Luxembourg, Cyprus, Estonia and possibly Latvia were considered to be lagging behind other EU countries, especially in terms of DALYs. These countries have great potential for improving health. Special attention should also be paid to Ireland, where the least positive score of total GHG emissions was observed. As the significant association between CO_2 and DALYs was identified, countries with the least positive CO_2 score also have great potential for improving health. By reducing CO_2 emissions, countries such as Luxembourg, Estonia, but also Ireland can expect health benefits in terms of DALYs. On the other hand, this cannot be done without reducing emissions of other combustion products (1).

Policy Implications

The results of our analyzes represent valuable findings for health and environmental policy makers, as well as support the creation of a platform for the development of strategic plans focused on reducing GHG emissions in the future. The health effects due to climate change are a result of global emissions, but the global success of reducing emissions cannot be achieved without active action in individual countries. However, it is first necessary to know the situation in countries, and this view in the EU was offered by this study. It is organizations such as the EU or the Organization for Economic Co-operation and Development (OECD) that require emissions control in their Member States, and it is therefore essential that policy-makers have up-to-date assessments of environmental emissions and public health in countries (14). None of the ambitious strategic objectives of reducing emission at international level can be achieved without evidence-based actions performed in individual countries. In any case, the results of the analyzes provided by this study are a good basis for successful measures. Policy makers have a unique position in the adoption and support of evidence-based measures with an effort to improve the health of the population, as well as the environment. Cooperation between researchers and policy makers in the field of environment and health could have great potential (45). Green and ecological mechanisms to reduce carbon footprint and improve energy efficiency should be developed in many dimensions of the country's life (46, 47). It would also be an effective way to take action at the population level, while programs aimed at educating people about protecting the environment and reducing emission from the consumer world play an important role. In many countries, environmental health is currently becoming a research and political domain rather than educational. This also justifies the importance of improving environmental literacy, which is considerably underestimated in many countries. Environmental literacy is that it comprises an awareness of and concern about the environment and its associated problems, as well as the knowledge, skills, and motivations to work toward solutions of current problems and the prevention of new ones (48).

Strengths

The study enriches the current state of knowledge by clarifying the associations between GHG emissions and public health represented by DALYs. The analyzes respected the internal structure of the data. An emphasis was placed on the use of quantitative methods. The results of this study offer a fundamental and much-needed pillar for further research on this issue at the national and international levels. The study also showed the real situation in individual EU countries and provided a comparison of these countries. The findings are of great importance for the development of evidence-based plans in terms of improving the environment and the health of the population.

Limitations

Potential limitations may include the endogeneity problem that may occur in regression analysis. Given this potential limitation, the results should be accepted with some caution. Another potential limitation can include the fact that the GHG indices entering the analytical procedures were not adjusted (they were not weighted) in any way, either according to the intensity of occurrence, or to their health effects. A certain limitation is also the fact that the health indicator (DALYs) presents the outcome for the total population (regardless of age, gender, etc.) and all diagnoses. With a focus on the correlation analysis, it is necessary to be careful in interpretations, as the revealed correlations were supported on a very small sample. Regarding the limitations of the regression model, it should be noted that the model used in this study did not examine causality as such, and therefore the results cannot be interpreted as causal links. All results can only be seen in terms of associations, while a consideration of causal links can be misleading. In addition, the model did not include control variables for better investigation of the revealed associations. Last but not least, the specific nature of environmental and health policies in countries needs to be emphasized. Each country takes a different approach to reducing GHG emissions, and ignoring this fact can be seen as a limitation. However, by using techniques respecting the specificity of the data structure (panel regression analysis), this shortcoming could be adequately recorded, captured and incorporated into computational processes. A similar limitation can be identified in the health indicator. There may be differences in the prevalence of individual diseases between countries. A certain disease may occur in one country more than in another. However, the mechanism for calculating the DALYs indicator reduced these differences. Also, the application of panel models captured possible specifics of countries and incorporated them into computational processes. In the case of this study, it can be assumed that the difference in GHG emissions and DALYs due to the specifics of countries did not skew the main results.

Future Directions

From a computational perspective, future research activities should focus mainly on assessing the causal links between environmental indicators and DALYs. In the future, it will also be appropriate to include economic variables that allow for the approximation of countries' industries and a more accurate identification of emission sources. From this perspective, future research ambitions could also focus on the spatial panel regression method. Also, the DALYs indicator could be decomposed according to age groups, gender or specific diagnoses. An ambition for future research could also be the expansion of a sample of countries, e.g., involvement of other continents or other international communities, such as OECD countries.

CONCLUSION

The study focuses on the proclaimed issue of the environment and human health in EU countries. The primary aim of this study was to examine the associations between selected GHG emissions and the health of the EU population represented by DALYs. Based on the results, it was possible to conclude that there is a certain link between GHG emissions and DALYs, while a dominant result was identified for CO_2, which can be considered as a health risk factor. The study also calls for a more comprehensive analysis of the associations between emissions and population health and emphasizes the need for a multidisciplinary examination of the issue. The results of the study showed valuable findings that are important for EU countries and their leaders. In fact, the exact determination of the effects of individual GHG emissions on the deterioration of health is also problematic. This problem is also based on the global perspective of emissions released into the atmosphere. Therefore, the results of this study should not be seen as a clear link between national GHG emissions and national DALYs, and the global effects of emissions and climate change should be taken into account in public policy-making. Nevertheless, the study reveals possible hidden phenomena in the EU.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: Eurostat. Eurostat database. Greenhouse gas emissions by source sector. http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=env_air_gge&lang=en. Global Burden of Disease Study. Results. 2019. Institute for Health Metrics and Evaluation: Seattle, United States. http://ghdx.healthdata.org/gbd-results-tool.

AUTHOR CONTRIBUTIONS

BG: conceptualization, investigation, writing—review and editing, visualization, supervision, project administration, and funding acquisition. MR: conceptualization, methodology, formal analysis, data curation, and writing—original draft preparation. VI: conceptualization, investigation, resources, writing—original draft preparation, writing—review and editing, and visualization. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.756652/full#supplementary-material

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Ambient Air Pollution and Hospitalizations for Ischemic Stroke: A Time Series Analysis Using a Distributed Lag Nonlinear Model in Chongqing, China

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Short-term exposure to air pollution has been associated with ischemic stroke (IS) hospitalizations, but the evidence of its effects on IS in low- and middle-income countries is limited and inconsistent. We aimed to quantitatively estimate the association between air pollution and hospitalizations for IS in Chongqing, China. This time series study included 2,299 inpatients with IS from three hospitals in Chongqing from January 2015 to December 2016. Generalized linear regression models combined with a distributed lag nonlinear model (DLNM) were used to investigate the impact of air pollution on IS hospitalizations. Stratification analysis was further implemented by sex, age, and season. The maximum lag-specific and cumulative percentage changes of IS were 1.2% (95% CI: 0.4–2.1%, lag 3 day) and 3.6% (95% CI: 0.5–6.7%, lag 05 day) for each 10 $\mu g/m^3$ increase in $PM_{2.5}$; 1.0% (95% CI: 0.3–1.7%, lag 3 day) and 2.9% (95% CI: 0.6–5.2%, lag 05 day) for each 10 $\mu g/m^3$ increase in PM_{10}; 4.8% (95% CI: 0.1–9.7%, lag 4 day) for each 10 $\mu g/m^3$ increase in SO_2; 2.5% (95% CI: 0.3–4.7%, lag 3 day) and 8.2% (95% CI: 0.9–16.0%, lag 05 day) for each 10 $\mu g/m^3$ increase in NO_2; 0.7% (95% CI: 0.0–1.5%, lag 6 day) for each 10 $\mu g/m^3$ increase in O_3. No effect modifications were detected for sex, age, and season. Our findings suggest that short-term exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3 contributes to more IS hospitalizations, which warrant the government to take effective actions in addressing air pollution issues.

Keywords: air pollution, short-term, ischemic stroke, hospitalizations, DLNM

INTRODUCTION

Stroke is a predominant public health concern in the world and the leading cause of death in China, which caused 6.2 million deaths and 132 million disability-adjusted life years globally in 2017 (1, 2). In China, ischemic stroke (IS) is the main subtype of stroke, accounting for 80% of all stroke events (3). Moreover, the incidence of IS has increased sustainedly in China in recent years (4), which has generated a huge burden on healthcare costs and the economy. Therefore, identification of modifiable risk factors for IS has substantial public health implications.

Many factors have been confirmed to be related to IS, including smoking, lacking of physical exercise, hypertension, obesity, and atrial fibrillation (5). In addition, increasing epidemiological evidence has shown a striking relationship between air pollution exposure and IS (6, 7). A study conducted in nine US counties demonstrated the short-term effects of PM_{10}, CO, SO_2, and NO_2 on hospitalizations for IS (8). Another study by Tian, Y. et al. observed a significant increase in hospitalizations for IS with transient increases of $PM_{2.5}$, SO_2, NO_2, O_3, and CO in China (9). However, most of these studies were conducted in high-income countries, and the scientific evidence that generated in low- or middle-income countries was scarce, especially in China (10). Recently, data from the National Epidemiological Survey of Stroke in China showed that the estimated mortality-to-incidence ratio (MIR) of stroke is the highest in the southwest and the lowest along the eastern and southern coasts; the proportion of registered medical doctors per 1,000 of the population is the highest in northern and eastern China and the lowest in the southwest (4). Furthermore, the geographical regions with high correlation between IS mortality and $PM_{2.5}$ gradually moved from western and northern China to the southwest during 1990–2015. Therefore, it was of great importance to explore the associations between air pollution and IS in the southwest.

Chongqing is a major heavy industrialized city located in Southwest China. Heavy industry and valley basin structure contributed to some of the worst air pollution in comparison with China's other cities. Thus, it is more meaningful to study the associations between the ambient air pollution and the occurrence of IS in Chongqing.

In this study, we conducted a time series analysis to investigate the associations between short-term exposure to air pollution and daily IS hospitalizations in Chongqing, China.

MATERIALS AND METHODS

Study Area and Health Data Collection

Chongqing is a major heavy industrialized city and one of the four municipalities in China. It is an urban city with an area of 5472.68 km^2 and a population of greater than 8.6 million in 2017 (11).

Data on daily hospital admissions for IS in this study were retrieved from 3 tertiary-level comprehensive hospitals (The Second Affiliated Hospital of Chongqing Medical University, University-Town Hospital of Chongqing Medical University, and The Southeast Hospital) with approximately 3,500, 1,500, and 1,200 inpatient beds, respectively. The medical information was recorded on Platform of Medical Data Science Academy of Chongqing Medical University, and it included the patients' age, sex, diagnosis, dates of admission, and discharge. We identified admissions for IS (International Classification of Diseases (ICD)-10 code I63) from January 1, 2015 to December 31, 2016 according to the 10th revision of ICD-10 codes.

Environmental Data

Data on air pollution, including levels of $PM_{2.5}$, PM $<$ 10 μm in aerodynamic diameter (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3) between January 1, 2015 and December 31, 2016, were obtained from the China Air Quality Online Monitoring and Analysis Platform. There were 17 fixed monitoring stations that measure concentrations of air pollution in Chongqing. In the Chinese air quality online monitoring system, PM_{10} and $PM_{2.5}$ were monitored by continuous automatic β-ray monitoring method, SO_2 and O_3 by ultraviolet fluorescence, and NO_2 by chemiluminescence. These measurements were completed in adherence to the China National Quality Control (GB3095-2012) protocol. We derived 24-h mean concentrations of these pollutants in Chongqing to represent each individual's daily exposure levels except for ozone (by averaging 8-h maximum values). Weather conditions including daily mean temperature and mean relative humidity were sourced from the National Meteorological Information Center of China. All the monitoring stations and hospitals were located in urban areas (**Figure 1**).

Statistical Analysis

Spearman's correlation coefficient was applied to explore the correlation between air pollutants and meteorological factors. For the time series analysis, we used generalized linear model combined with a distributed lag non-linear model (DLNM) to investigate both non-linear and delayed effects of air pollutants on daily hospitalizations for IS. As daily IS hospital admissions data being quantitative data, belonging to small probability events, and conforming to Poisson distribution, there a Poisson regression models allowing for overdispersion was used. The model is as follows:

$$\begin{aligned} Log\,(Yt) = {} & \alpha + cb\left(Xt,\ lag\right) + cb\left(Mean\ Temt, lag\right) \\ & + ns\left(RHt, df = 3\right) + ns\left(Timet, df = 7{*}years\right) \\ & + factor\,(DOW) + factor(holiday) \end{aligned}$$

where t is day of observation, Yt refers to the number of IS hospital admissions, $cb\left(Xt, lag\right)$ and $cb\left(Mean\ Temt, lag\right)$ indicate the matrix of air pollution and mean temperature by applying the DLNM, Xt and $Mean\ Temt$ represent pollutant concentrations and mean temperature at day t, $ns\left(RHt, df = 3\right)$ are natural cubic spline with 3 degrees of freedom for daily relative humidity, $ns\left(Timet, df = 7{*}year\right)$ is 7 degrees of freedom per year, to control long-term trend and seasonality (12, 13), DOW is the day of the week, and holiday is the variable for the holiday effect. We adopt a linear and a natural cubic spline ($df = 3$) function to fit the exposure–response relationship and the lag–response relationship, respectively (13). Also, the parameter of lag–response relationship between mean temperature and IS was equal to air pollutants. Furthermore, the non-linear relationship between air pollution and IS was explored by a natural cubic spline function ($df = 3$) when the cumulative effect appears to be strongest.

Previous studies had shown that the lagged effect of air pollutants was usually short. In this study, single-day lags (from lag 0 day to lag 7 day) combined with cumulative lags (from lag 01 day to lag 07 day) were applied to evaluate the lagged effects of air pollutants. We initially performed single-pollutant model to assess the association between air pollution and IS

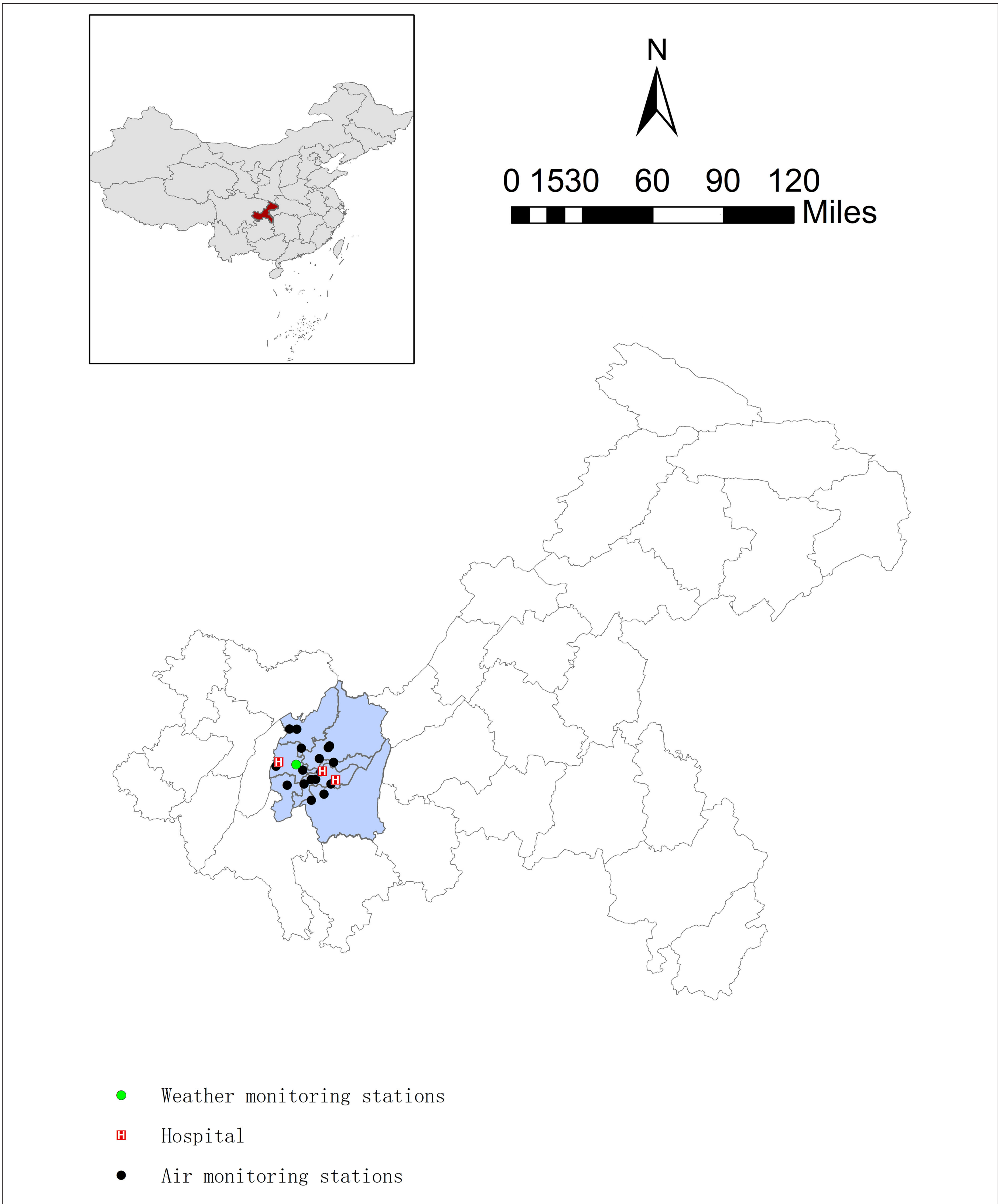

FIGURE 1 | Spatial distributions of air quality monitoring stations, weather monitoring stations, and addresses of hospitals in Chongqing, China.

TABLE 1 | Distribution of daily IS admissions, air pollutants, and meteorological factors in Chongqing, China (January 2015–December 2016).

Variables	Mean±SD	Min	P10	P25	P50	P75	P90	P95	P99	Max
Cardiovascular and cerebrovascular disease	20.48 ± 9.49	2.0	9.0	13.0	19.0	26.0	34.0	38.0	47.0	57.0
IS	3.15 ± 2.00	0.0	1.0	2.0	3.0	4.0	6.0	7.0	9.0	13.0
Gender										
Male	1.35 ± 1.23	0.0	0.0	0.0	1.0	2.0	3.0	4.0	5.0	7.0
Female	1.80 ± 1.45	0.0	0.0	1.0	2.0	3.0	4.0	5.0	6.0	7.0
Age										
<75	1.07 ± 1.08	0.0	0.0	0.0	1.0	2.0	3.0	3.0	4.0	6.0
≥75	2.07 ± 1.55	0.0	0.0	1.0	2.0	3.0	4.0	5.0	6.0	10.0
Season										
Warm	3.06 ± 1.95	0.0	1.0	2.0	3.0	4.0	6.0	7.0	8.0	13.0
Cold	3.23 ± 2.04	0.0	1.0	2.0	3.0	5.0	6.0	7.0	9.0	10.0
$PM_{2.5}$ ($\mu g/m^3$)	54.41 ± 30.72	10.0	25.0	34.0	46.0	66.0	93.0	114.0	164.1	212.0
PM_{10} ($\mu g/m^3$)	81.75 ± 40.68	13.0	41.0	54.0	74.0	98.0	131.0	164.5	228.8	293.0
SO_2 ($\mu g/m^3$)	14.55 ± 6.59	4.0	7.0	10.0	13.0	18.0	23.0	27.0	36.4	42.0
CO (mg/m^3)	1.04 ± 0.28	0.4	0.7	0.9	1.0	1.2	1.4	1.5	1.8	3.4
NO_2 ($\mu g/m^3$)	45.05 ± 12.69	16.0	30.0	36.0	44.0	53.0	62.0	69.0	79.0	96.0
O_3 ($\mu g/m^3$)	68.11 ± 45.38	4.0	15.0	29.0	60.0	101.0	135.0	150.5	184.3	223.0
Temperature (°C)	19.60 ± 7.47	1.2	9.6	13.0	20.1	25.2	29.4	31.4	34.3	36.2
Relative humidity (%)	75.36 ± 10.93	43.0	60.3	68.0	76.0	84.0	90.0	92.0	94.6	96.3

$PM_{2.5}$, particles with aerodynamic diameter < 2.5 μm; PM_{10}, particles with aerodynamic diameter < 10 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone; IS, ischemic stroke.

hospitalizations, and then, the significant air pollutants were included in subsequent analysis.

We conducted stratification analysis to explore the potential effect modification by age (< 75, ≥ 75 years), sex (male, female), and season [cold season, warm season). The risk estimates were expressed in terms of the percentage changes (excess risk, ER (%)] in IS hospitalizations per 10 $\mu g/m^3$ increment of air pollutants (except that CO was per 1 mg/m^3) and their respective 95% confidence intervals (CIs). We further evaluated the statistical significance of the differences as $(\hat{Q}1 - \hat{Q}2)/\sqrt{SE1^2 + SE2^2}$, such that the $\hat{Q}1$ and $\hat{Q}2$ represent the estimates for the two subgroups, and SE1 and SE2 represent their respective standard errors.

Sensitivity analysis was also performed to identify the robustness of the results by (a) fitting two-pollutant models. Correlation coefficient $r > 0.60$ between air pollutants was not included in multipollutant model to avoid collinearity; (b) changing the degrees of freedom in the natural cubic spline function of time (6–8 *df*) and meteorological variables (4–6 *df*). All analyses were conducted through "dlnm" and "splines" packages in R software (version 3.6.3). *p*-Value less than 0.05 was considered as statistically significant.

RESULTS

Basic characteristics of patients with IS, meteorological factors, and air pollution are displayed in **Table 1**. There was a total of 14,969 hospital admissions for cardiovascular and cerebrovascular diseases from 3 hospitals during January 1, 2015 to December 31, 2016. Overall, 2,299 patients with IS formed the basis of this study, with a daily average of 3 cases. 57.1% were men and 65.9% were patients aged ≥75 years. The mean 24-h $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and 8-h maximum O_3 concentrations were 54.41 $\mu g/m^3$, 81.75 $\mu g/m^3$, 14.55 $\mu g/m^3$, 1.04 mg/m^3, 45.05 $\mu g/m^3$, and 68.11 $\mu g/m^3$, respectively.

The Spearman's correlation coefficients between air pollutants and meteorological factors are listed in **Table 2**. $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO were positively and moderately or strongly correlated. O_3 exposure was negatively and weakly associated with $PM_{2.5}$, SO_2, and CO, whereas the correlation coefficient with PM_{10} and NO_2 was not statistically significant. Temperature was positively associated with O_3, and negatively associated with other air pollutants, whereas relative humidity was positively associated with CO, and negatively associated with other air pollutants.

Figure 2 shows that exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3 was significantly associated with IS. In single-day lag structures, exposures to $PM_{2.5}$ (lag 2 day–lag 4 day), PM_{10} (lag 2 day–lag 5 day), SO_2 (lag 4 day), NO_2 (lag 2 day, lag 3 day), and O_3 (lag 6 day) were associated with increased IS cases. The maximum lag-specific percentage changes for each 10 $\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3 were 1.2% (95% CI: 0.4–2.1%, lag 3 day), 1.0% (95% CI: 0.3–1.7%, lag 3 day), 4.8% (95% CI: 0.1–9.7%, lag 4 day), 2.5% (95% CI: 0.3–4,7%, lag 3 day), and 0.7% (95% CI: 0.0–1.5%, lag 6 day), respectively. In cumulative lag structures, the unfavorable effects of $PM_{2.5}$, PM_{10}, and NO_2 occurred to lag 04 day–lag 06 day, lag 04 day–lag 06 day, and lag 04 day–lag 05 day, and the corresponding maximum percentage

TABLE 2 | Spearman's correlation coefficients between air pollutants and meteorological factors.

Variables	$PM_{2.5}$	PM_{10}	SO_2	CO	NO_2	O_3	Temperature	Relative humidity
$PM_{2.5}$	1.00							
PM_{10}	0.95**	1.00						
SO_2	0.61**	0.68**	1.00					
CO	0.60**	0.56**	0.56**	1.00				
NO_2	0.71**	0.74**	0.61**	0.53**	1.00			
O_3	−0.09*	0.04	−0.15**	−0.44**	−0.04	1.00		
Temperature	−0.26**	−0.15**	−0.35**	−0.41**	−0.23**	0.73**	1.00	
Relative humidity	−0.12**	−0.29**	−0.39**	0.23**	−0.14**	−0.65**	−0.38**	1.00

*$PM_{2.5}$, particles with aerodynamic diameter < 2.5 μm; PM_{10}, particles with aerodynamic diameter < 10 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone; * p <0.05; ** p <0.01.*

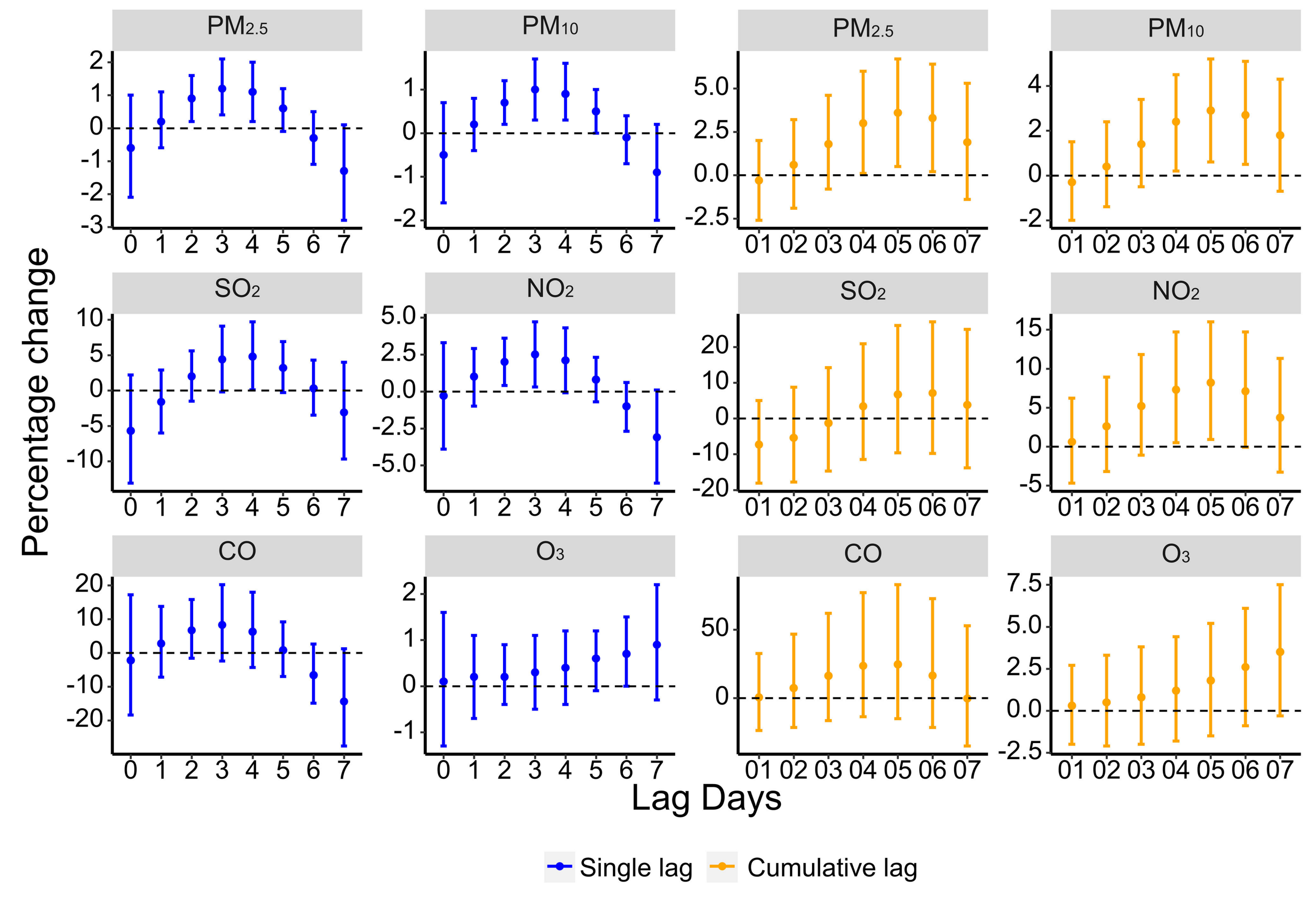

FIGURE 2 | Percentage changes [excess risk, ER (%)] of IS cases for each pollutant at various lags.

changes were 3.6% (95% CI: 0.5–6.7%, lag 05 day), 2.9% (95% CI: 0.6–5.2%, lag 05 day), 8.2% (95% CI: 0.9–16.0%, lag 05 day) (**Supplementary Table S1**), whereas no association between CO and IS had been detected.

The exposure–response curves for $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 with hospitalizations for IS are displayed in **Figure 3**. The exposure–response curve for NO_2, SO_2, and O_3 showed thresholds for their associations with hospitalizations for IS: 50–75 μg/m^3 for NO_2, 20–30 μg/m^3 for SO_2, and 100–150 μg/m^3 for O_3. The exposure–response relationship for $PM_{2.5}$, PM_{10}, and CO was almost linear.

Stratified and sensitivity analyses were performed on the basis of reaching the maximum effect of $PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3 in the cumulative lag structure. The associations

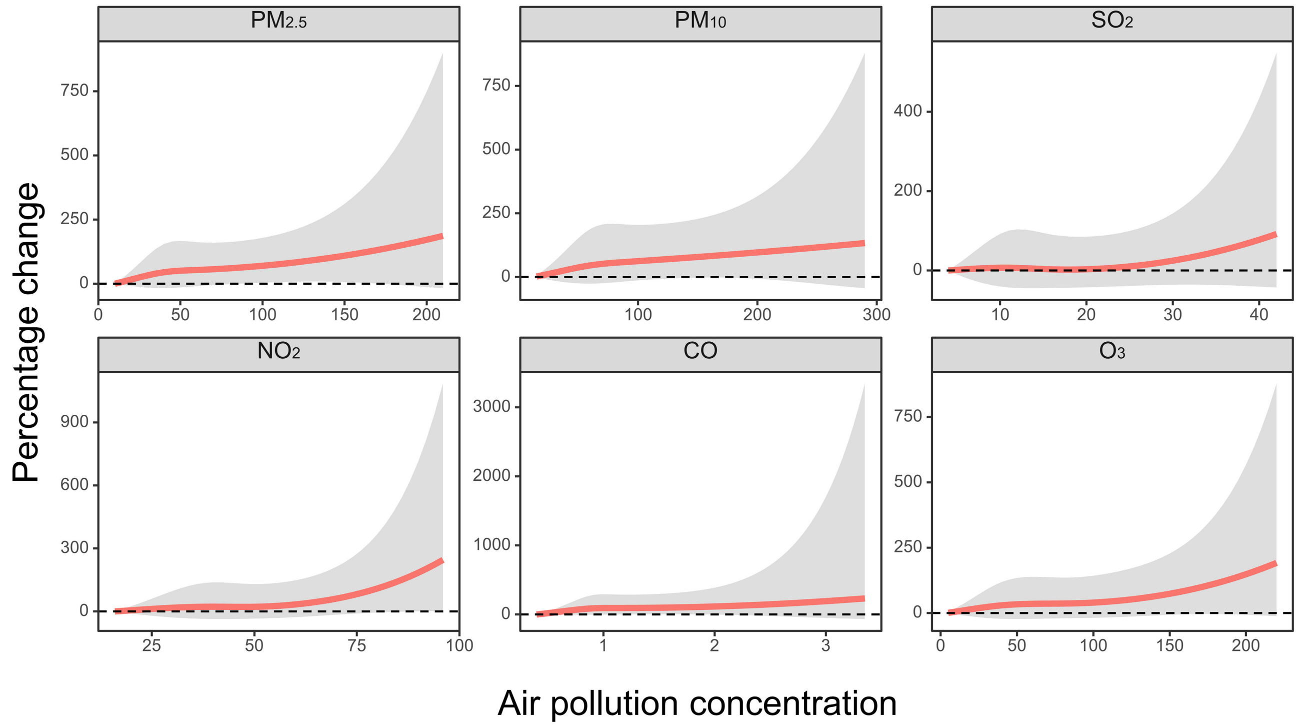

FIGURE 3 | The concentration–response relationship curves between $PM_{2.5}$ (lag 05 day), PM_{10} (lag 05 day), SO_2 (lag 06 day), NO_2 (lag 05 day), and O_3 (lag 07 day) and IS hospitalizations. *X*-axis: each air pollution concentrations; *y*-axis: the percentage changes [excess risk, ER (%)] of air pollution on IS.

TABLE 3 | Percentage changes [excess risk, ER (%)] for IS hospitalizations with per 10 $\mu g/m^3$ increase of exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3 stratified by age, sex, and season.

Variables	$PM_{2.5}$		PM_{10}		SO_2		NO_2		O_3	
	ER% (95%CI)	p–value	ER% (95%CI)	p– value	ER% (95%CI)	p– value	ER% (95%CI)	p– value	ER% (95%CI)	p– value
Male	22.8 (−15.4–78.0)		3.3 (0.0–6.7)		−1.8 (−23.5–26.2)		12.6 (1.8–24.6)		−2.2 (−6.7–2.7)	
Female	9.1 (−20.6–49.9)	0.636	3.0 (0.2–5.8)	0.891	21.5 (−2.4–51.2)	0.210	7.6 (−1.5–17.4)	0.502	2.1 (−2.0–6.5)	0.184
<75	25.1 (−16.1–86.5)		4.3 (0.9–7.9)		9.8 (−15.9–43.4)		10.9 (−0.6–23.7)		−1.7 (−6.7–3.6)	
≥75	8.5 (−19.1–45.6)	0.576	2.5 (−0.1–5.1)	0.398	11.1 (−9.3–36.0)	0.947	9.0 (0.5–18.2)	0.805	1.2 (−2.6–5.1)	0.383
Warm	5.8 (−1.8–14.0)		3.4 (−1.5–8.5)		−1.7 (−28.4–35.0)		9.6 (−3.2–24.1)		1.1 (−3.7–6.2)	
Cold	3.8 (0.1–7.7)	0.651	3.5 (0.7–6.4)	0.964	21.9 (0.7–47.7)	0.255	15.2 (4.9–26.4)	0.530	3.6 (−3.3–10.9)	0.579

$PM_{2.5}$, particles with aerodynamic diameter < 2.5 µm; PM_{10}, particles with aerodynamic diameter < 10 µm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; O_3, ozone; CI, confidence intervals.

between air pollutant exposures and the hospitalizations for IS were evaluated in subgroups based on sex, age, and season (**Table 3**). For $PM_{2.5}$, PM_{10}, SO_2, and NO_2, the effects were still significant in cold season subgroup. In addition, both sex and the younger received adverse effects when exposed to PM_{10}, whereas NO_2 seems to be more susceptible to men and the elder. Although the percentage changes were somewhat different and some of them were insignificant, we did not find any significant effect modification across sex, age, and season (all p for effect modification > 0.05).

Table 4 provides the results of the two-pollutant model, and further adjustment for other pollutant exposures did not materially change the associations between $PM_{2.5}$, PM_{10}, SO_2, NO_2, andO_3 exposures and IS. Results of the sensitivity analysis (**Supplementary Table S2**) indicated that the effect estimates of the association between air pollution and IS hospitalizations were not substantially affected with the use of alternative *df* value for time (6–8 per year), temperature (3–6), and relative humidity (3–6), although some of the associations became insignificant for temperature ($df = 6$).

DISCUSSION

There is growing interest in the associations between ambient air pollution and risk of IS, but data on the associations in low-

TABLE 4 | Percentage changes [excess risk, ER (%)] of IS for each pollutant in two-pollutant model.

		ER% (95%CI)	*p*- value
$PM_{2.5}$	NULL	3.6 (0.5–6.7)	
	O_3	2.7 (−0.5–6.1)	0.715
PM_{10}	NULL	2.9 (0.6–5.2)	
	CO	2.7 (0.0–5.4)	0.907
	O_3	2.3 (−0.2–4.8)	0.759
SO_2	NULL	7.1 (−9.8–27.0)	
	CO	3.4 (−13.5–23.7)	0.787
	O_3	0.6 (−16.2–20.7)	0.626
NO_2	NULL	8.2 (0.9–16.0)	
	CO	7.0 (−1.2–15.8)	0.838
	O_3	6.8 (−1.0–15.1)	0.789
O_3	NULL	3.5 (−0.3–7.5)	
	$PM_{2.5}$	2.6 (−1.4–6.9)	0.778
	PM_{10}	2.2 (−2.0–6.6)	0.672
	SO_2	3.4 (−0.6–7.6)	0.971
	NO_2	3.0 (−1.1–7.3)	0.888
	CO	3.3 (−0.5–7.3)	0.970

$PM_{2.5}$, particles with aerodynamic diameter < 2.5 μm; PM_{10}, particles with Aerodynamic diameter < 10 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; O_3, ozone; CI, confidence intervals.

or middle-income cities are still limited, especially in Southwest China. Chongqing is mainly associated with heavy industry with a valley basin structure, which has a great impact on ambient air pollution. Therefore, we conducted this time series study combining with DLNM to evaluate the short-term effects of ambient air pollutants on hospitalizations for IS in Chongqing. The data obtained in this analysis indicated that short-term exposure to $PM_{2.5}$, PM_{10}, NO_2, O_3, and SO_2 was significantly associated with increased hospitalizations for IS. Age, sex, and season did not appear to significantly modify the associations between short-term exposure to air pollution and IS onset. The sensitivity analysis showed a robustness of the pollutant model results.

In single-pollutant models, we found that each 10 $\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3 was associated with a 1.2, 1.0, 4.8, 2.5, and 0.7% increase in IS hospitalizations, respectively, which were similar to several previous studies (14–16). For example, Hu's study conducted in Yancheng city has shown that IS hospitalizations increased 1.06% (95% CI: 0.21–1.91%) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ (14). Another multicity study reported that per 10 $\mu g/m^3$ evaluation of NO_2 was associated with 2.6% change in hospitalizations for IS (15). Wellenius *et al.* investigated the association of air pollution with hospitalizations for IS in nine US cities, with a cohort restricted to patients aged above 65 years. They observed that an elevation of IQR in PM_{10} (22.96 $\mu g/m^3$), SO_2 (6.69 $\mu g/m^3$), and NO_2 (11.93 $\mu g/m^3$) concentrations was associated with 1.03, 1.35, and 2.94% increases in hospitalizations for IS, respectively (8). Another study conducted in Guangzhou indicated that each IQR increase of $PM_{2.5}$ (41 $\mu g/m^3$), O_3 (99 $\mu g/m^3$), SO_2 (15 $\mu g/m^3$), and NO_2 (44 $\mu g/m^3$) corresponded to an RR value of 1.0272, 1.0173, 1.0344, 1.0423, respectively (17). In addition, a nationwide time series analysis in China indicated that each increase of 10 $\mu g/m^3$ in $PM_{2.5}$, SO_2, and NO_2 was associated with a 0.34, 1.37, and 1.82% increase in hospitalizations for IS (9). Their studies suggest that the major components of air pollutants vary significantly from region to region, which does affect the occurrence of IS in different cities.

In China, the evidence of the effect of CO exposure on IS risk is still controversial. A study conducted in Taiwan found that CO was significantly and positively associated with IS hospitalizations in the single-pollutant model, but it became insignificant in the multipollutant model (18). However, research from Hong Kong observed a negative association between ambient CO concentrations and stroke hospitalizations (19). In addition, several other studies in China found no association between CO and IS risk (15, 20), which was consistent with our results. The inconsistency of the results on the associations between CO and IS might be attributable to variations in air pollution levels, outcome definitions, weather conditions, population susceptibility, and sociodemographic characteristics across studies.

The identification of potentially susceptible subpopulations has significant implications for public health. Some studies did not identify any effect modification by sex and age between air pollution and IS (21–23), which were in line with our study. In addition, this study found no effect modification by season, whereas the adverse effects of $PM_{2.5}$, PM_{10}, NO_2, and SO_2 remained significant in cold season. This may be attributable to a high number of foggy days during cold season in Chongqing. During our study period, the mean AQI in Chongqing (80.75) was higher than a less foggy city, such as Guangzhou (68.79), which was similar to Chongqing in population and land area (24).

The biological mechanism of air pollution-induced IS has not been fully investigated. Several possible mechanisms have been proposed to be related to the inflammation (25), oxidative stress (26), abnormal lipid metabolism (7, 27), and autonomic dysfunction (7). For example, $PM_{2.5}$ can trigger the release of pro-inflammatory mediators causing systemic inflammation, which impaired blood–brain barrier (BBB) stability and induces to the generation of ROS and oxidative stress (28). Inhalation of SO_2 can affect heart rate variability, increase oxidation, and exacerbate blood clotting and thrombosis formation (29). In addition, a study showed that exposure to O_3 and particulate pollutants increased endothelin 1, leading to vascular endothelial dysfunction and subsequent brain damage (30).

Our study has some potential limitations. First, small sample sizes might lead to lower statistical power; therefore, subsequent studies with large sample sizes would be expected. Second, city-level concentration of air pollution rather than individual exposure was utilized as the exposure concentration, which might underestimate the effect of air pollution. Third, we selected only 3 hospitals in one single city, so the generalization of the results requires caution. Finally, although we adjusted for several confounders such as seasonality, day of week, public holiday, and weather conditions, there might exist some other confounding factors.

CONCLUSIONS

This study suggests that short-term exposure to $PM_{2.5}$, PM_{10}, NO_2, O_3, and SO_2 was associated with increased hospitalizations for IS in Chongqing, China. Our study provides new evidence on the association between air pollution and IS. Further studies are warranted to help government effectively reduce the burden of air pollution.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Chongqing Medical University in Chongqing, China. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HC wrote the manuscript and analyzed the data. PL and YD collected and inputted the data. JF, YX, ML, ZC, KP, and LZ reviewed the results and provided guidelines for presentation and interpretation. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.762597/full#supplementary-material

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Effect of Cold Spells and Their Different Definitions on Mortality in Shenzhen, China

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A high premium has been put on researching the effects of cold spells because of their adverse influence on people's daily lives and health. The study aimed to find the most appropriate definition of the cold spell in Shenzhen and quantify the impact of cold spells on mortality. Based on the daily mortality data in Shenzhen from 2013 to 2017 and the meteorological and pollutant data from the same period, we quantified the effect of cold spells using eight different definitions in the framework of a distributed lag non-linear model with a quasi-Poisson distribution. In Shenzhen, low temperatures increase the risk of death more significantly than high temperatures (using the optimal temperature as the cut-off value). Comparing the quasi-Akaike information criterion value, attribution fraction (b-AF), and attribution number (b-AN) for all causes of deaths and non-accidental deaths, the optimal definition of the cold spell was defined as the threshold was 3rd percentile of the daily average temperature and duration for 3 or more consecutive days (all causes: b-AF = 2.31% [1.01–3.50%], b-AN = 650; non-accidental: b-AF = 1.92% [0.57–3.17%], b-AN = 471). For cardiovascular deaths, the best definition was the temperature threshold as the 3rd percentile of the daily average temperature with a duration of 4 consecutive days (cardiovascular: b-AF = 1.37% [0.05–2.51%], b-AN = 142). Based on the best definition in the model, mortality risk increased in cold spells, with a statistically significant lag effect occurring as early as the 4th day and the effect of a single day lasting for 6 days. The maximum cumulative effect occurred on the 14th day (all-cause: RR = 1.54 [95% CI, 1.20–1.98]; non-accidental: RR = 1.43 [95% CI, 1.11–1.84]; cardiovascular: RR = 1.58 [95% CI, 1.00–2.48]). The elderly and females were more susceptible to cold spells. Cold spells and their definitions were associated with an increased risk of death. The findings of this research provide information for establishing an early warning system, developing preventive measures, and protecting susceptible populations.

Keywords: temperature, cold spell, characteristics, mortality, vulnerable populations

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INTRODUCTION

Extreme atmospheric events have increased in frequency, intensity, and severity during the last several decades as a result of global climate change (1, 2). Because of the impact of severe temperature occurrences on people's everyday lives and health, a premium has been placed on describing and investigating their effects. Numerous studies have demonstrated that extra-temperature factors significantly impact mortality and morbidity (3, 4). The effect relationship is U- or inverse J-shaped, and there is a threshold effect at which the fatality risk increases at above or below the optimal temperature (5–7). However, the optimum temperature and its associated health effects vary across cities, countries, and areas (8–10). Particularly concerning is the fact that even during periods of global warming, extreme cold temperatures continue to increase, with a stronger tendency for cold spell occurrences (11, 12).

The cold spell is a distinctive type of extreme atmospheric event that manifests as anomalous low-temperatures over consecutive days (13, 14). The detrimental effects of heatwaves have been extensively researched, little knowledge exists about the impacts of cold spells on mortality in temperate regions. Exposure to a cold spell increases the risk of premature morbidity and mortality, especially for patients with cardiovascular and respiratory diseases, and for older adults (15–17).

Currently, there is no standard definition of a cold spell. In Chinese meteorology, the definition of a cold spell consists of three scenarios. After the transit of cold air in an area, (i) the minimum temperature drops by more than 8°C within 24 h; (ii) the temperature drops by more than 10°C within 48 h; (iii) the temperature drops by more than 12°C continuously within 72 h, with the minimum temperature below 4°C simultaneously (http://www.cma.gov.cn). These definitions are based on absolute temperatures and do not take regional variances into account. As a result, the majority of studies described cold spells using the percentile threshold approach, which considers two indications: the temperature threshold and the duration of the temperature below the thresholds (15, 18). This method provides an objective and representative assessment of the effect of a cold spell. Although this conforms to the generally recognized definition of a cold spell, there are minor variations in the definition of cold spells among researchers. Zhou et al. utilized the 5th percentile of daily mean temperatures as an indication of exposure with a duration of at least 5 consecutive days between December and March in China (19). In the Czech Republic, a cold spell was defined as at least 2 consecutive days with average daily temperatures below the 10th percentile of the mean annual cycle (20). This discrepancy in definitions might be due to regional variation.

The effect of the cold spell on human health has been examined extensively in developed countries. However, few studies have been performed in developing countries. Investigating the association between cold spells and human health is critical for developing countries, which lag behind developed countries in their capacity to manage severe climatic events. In addition, China is a vast territory with diverse temperatures, economic growth, and lifestyles. Using the definition in extant research does not adequately represent the effect of the cold spell in China (21–23). Hence, the definitions and impacts of cold spells varied according to the locations and demographic groups examined in the studies. It becomes essential to explore the optimal definition of cold spell, to analyze its influences, and to create suitable preventive measures in a given location.

In the present study, we aimed to determine the most appropriate definition of a cold spell in Shenzhen by evaluating eight different definitions. Then, using the most accurate definition, the effect of cold spells on mortality was investigated. Finally, a subgroup analysis was conducted to identify the vulnerable populations.

MATERIALS AND METHODS

Study Area

Shenzhen is a developed coastal city in southeastern China, lying between 113°46′∼114°37′ E and 22°27′∼22°52′N, next to Hong Kong. The city has a subtropical monsoon climate with year-round southeast winds and extended periods of sunlight. Each year, the rainy season lasts from April until September. In other months, the weather is dry and warm. Compared to other central and northern China cities, Shenzhen has better air quality as China's first special economic zone. As of December 2017, the resident population was 12.53 million.

Data Sources

Daily meteorological data for Shenzhen were acquired from the Shenzhen Meteorological Service Center from 2013 to 2017, including daily temperature (°C) and relative humidity (%). Air pollution data, including daily average concentrations of ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), inhalable particles with aerodynamic diameter <10 mm (PM10), inhalable particles with aerodynamic diameter <2.5 mm (PM2.5), and sulfur dioxide (SO_2), were measured by seven national monitoring stations in Shenzhen. Extreme cold, cold, mild cold, mild heat, heat, and extreme heat were classified according to specific percentile (1st, 5th, 25th, 75th, and 95th). Daily mortality data were provided by the Shenzhen Center for Disease Control and Prevention (CDC). The cause of death was coded and classified by the Classification of Diseases 10th version (ICD-10) as follows: all-causes (ICD-10: A00-U99); non-accidental (ICD-10: A00-R99); cardiovascular diseases (ICD-10: I00-I99) and respiratory disease (J00-J99); accidental (ICD-10: V01-X59). Daily non-accidental and cardiovascular mortality were stratified by sex (female and male) and age (<65 and ≥65 years).

Definition of the Cold Spell

According to studies on the health impacts of cold spells, the temperature intensity and duration need to be considered in the definition. We estimated the short-term influence of cold spells on mortality in Shenzhen considering eight types of cold spells with distinct definitions. The optimal definitions were determined by the quasi-Akaike information criterion (QAIC) (24), attribution risk fraction, and attribution risk number (25).

Using daily average temperature as an exposure metric for cold conditions, which accurately captures exposure throughout the day and night, policymakers may easily comprehend the data (26). The eight different definitions of cold spells are defined as the threshold (3rd and the 5th percentile of temperatures) for at least 2, 3, 4, and 5 consecutive days in Shenzhen.

Statistical Analysis

Examining the Effect of Temperature

A cross-basis function represents the non-linear exposure-outcome relationship of the delay in the distributed lag non-linear model (DLNM) (27). Previous studies showed that death has a significant non-linear relationship with the daily mean temperature. Considering that the number of daily deaths is over-dispersion, a quasi-Poisson regression model was used. The model is described as:

$$\begin{aligned} log\left[E\left(Y_t\right)\right] = \alpha + \beta Temp_{t,l} + NS(RH_t, 2) + NS(Time, 7) \\ + \gamma HOL + \varepsilon DOW \end{aligned} \quad (1)$$

where t is the observation day; $E(Y_t)$ denotes the expected count of death on day t; α is the intercept; and $Temp_{t,l}$ is the matrix obtained by applying the temperature with the number of lag days l and the coefficient β in DLNM. We use a 4 *df* natural cubic spline function to estimate the lag effect. According to previous studies and to fully capture the total impact of temperature exposure in this region, the lag is 14 days. *NS* in the model is the natural cubic spline function; RH_t represents the relative humidity on day t with the degrees of freedom (2 *df*); *Time* is included to control long-term temporal trend (7 *df* per year); Day of Week (*DOW*, serial number from 1 to 7) is a multi-categorical variable that indicates day t as a day from Monday to Sunday to control for the confounding effects of the day of the week; Holiday (*HOL*, $HOL = 1$ when it is a public holiday) is a binary variable that denotes a legal holiday in China to control the confounding effect. ε and γ are the coefficients. The choices of the degrees of freedom were optimized with QAIC.

Examining the Effect of the Cold Spell

Data from November to March of each year were included from the time-series change-point analyses to prevent any potential bias due to heat effects and the lag effects of a cold spell on daily death. To investigate the impact of a cold spell on different lags and its cumulative effect on mortality, a DLNM with a quasi-Poisson distribution was constructed. The model using eight different definitions of cold spells is:

$$\begin{aligned} log\left[E\left(Y_t\right)\right] = \alpha + \beta_1 CS_{t,l} + NS(Temp_t, 2) + NS(RH_t, 2) \\ + NS(Time, 7) + \gamma HOL + \varepsilon DOW \end{aligned} \quad (2)$$

where CS_t refers to the dummy variable that indicates the cold spell on day t (0: days without cold spell; 1: days with cold spell); $\beta_1 CS_{t,l}$ is the cross-basis object to estimate the effect of cold spells; β_1 is vectors of the regression coefficients of the cold spell, with a linear function of exposure-response dimension, and the lag effect of the cold spell is a natural cubic spline function of 4 *df*; the maximum lag of the cold spell is set as 14 days.

Compared with RR, attribution fraction and number can better quantify the disease burden caused by a cold spell, which is more instructive for developing public health interventions. Under the DLNM framework, the attributable risk fraction and number are calculated from a backward perspective. The 95% empirical confidence intervals (eCI) were estimated from the related 2.5 and 97.5 percentiles of the resultant distribution through Monte Carlo simulation. Additionally, stratified analyses were also conducted by age group (<65 or ≥65 years) and sex (female and male).

We tested for statistically significant differences in effect estimates between the categories of the potential effect modifiers (e.g., between males and females) by calculating the 95% confidence intervals (95% CI):

$$\left(\hat{Q}_1 - \hat{Q}_2\right) \pm 1.96\sqrt{\widehat{SE}_1^2 + \widehat{SE}_2^2} \quad (3)$$

where $\hat{Q}_1$ and $\hat{Q}_2$ are the estimates for the two categories, and $\widehat{SE}_1$ and $\widehat{SE}_2$ are their respective standard errors (28, 29).

Sensitivity Analysis

We evaluated the robustness of the study results by varying the *df* of time (6 and 8 per year), varying the *df* of cold spells (3 and 5), varying the *df* of average daily temperature and relative humidity (3 and 4), and adding air pollution to the model. All statistical analyses were performed in R software (version 3.5.2) using the dlnm package (30).

RESULTS

Characteristic Causes of Death

Table 1 displays the number of total deaths from 2013 to 2017 in Shenzhen. The number of deaths was slightly increased year by year, of which a large proportion of deaths causes were non-accidental. The daily mortality from non-accidental and cardiovascular disease, stratified by sex and age, is summarized in **Supplementary Table S1**. There were 65,325 all-causes of deaths, 56,034 non-accidental deaths, and 23,030 cardiovascular deaths in the whole study. In non-accidental deaths, 61.90% were males and 54.79% were in the elderly. For cardiovascular deaths, 61.60% were males, and 64.10% were in the elderly. The average daily number of non-accidental deaths was 30.72. Among them, the number of deaths in the <65 age groups was 16.83, significantly more than that in the ≥65 age groups.

Impact of Temperature and Mortality

Figure 1 shows the cumulative exposure-response effect of temperature on total deaths, non-accidental deaths, and deaths from cardiovascular diseases. The curves for all three exposure effects were U-shaped, where the lowest adverse effect temperature was 25.5°C for the all-causes of deaths, 26°C for the non-accidental deaths, and 25.8°C for the cardiovascular deaths. Both below and above optimal temperature increase the risk of death, and the effect is statistically significant. The

TABLE 1 | Summary statistics for mortality in Shenzhen, 2013–2017.

Causes of death	Period					
	All	2013	2014	2015	2016	2017
All causes	65,325	11,936	12,847	12,998	14,476	13,068
Non-accidental	56,034	10,161	10,920	11,206	12,328	11,419
Cardiovascular	23,030	4,654	4,628	4,602	4,733	4,413
Respiratory	4,197	626	658	727	1,137	1,049
Other[a]	29,433	5,507	5,634	5,877	6,458	5,957
Accidental	5,400	1,035	1,136	991	1,301	937
Other[b]	3,891	740	791	801	847	712

[a] *"Other" meant other causes of death that do not include cardiovascular cause and respiratory cause in the non-accidental death category.*
[b] *"Other" meant other causes of death that do not include non-accidental cause and accidental cause in the all causes death category.*

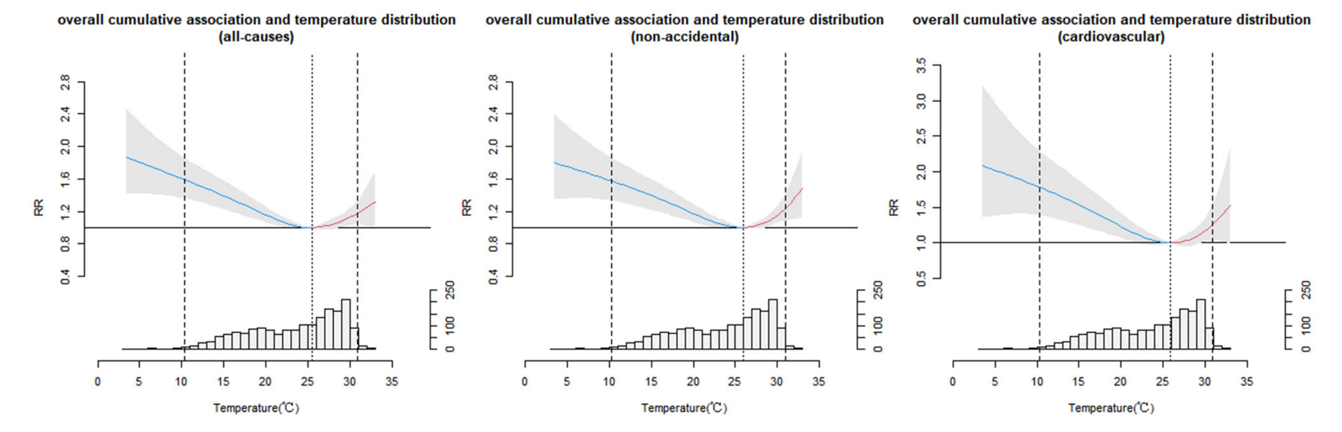

FIGURE 1 | Overall cumulative exposure-response relationship between temperature distribution and mortality in Shenzhen, 2013–2017.

low-temperature effect was more significant than the high-temperature effect for all three outcomes (using the optimal temperature as the reference value). The complete results are listed in **Supplementary Table S2**.

Impact of Cold Spell and Mortality

The total number of days that a cold spell event occurred during the study period varied with the definition of a cold spell (**Table 2**). For example, under the lenient criteria, when the threshold was below the 5th percentile of the daily average temperature with a duration of ≥2 days, the total number of days was 83 days. The total number of days only was 12 days under the stringent definition, when the threshold was set as the temperature below the 3rd percentile of the daily average temperature last for ≥5 consecutive days.

Because of different definitions of cold spells, even the QAIC values, attributable risk fraction, and attributable risk number calculated by the same model are not equal (**Table 2**). For all causes of deaths and non-accidental deaths, the optimal definition of a cold spell was the temperature threshold at the 3rd percentile of the daily average temperature with a duration of 3 consecutive days. With that definition, the QAIC value is minimum, while both b-AF and b-AN achieve their maximum values (all-cause: b-AF = 2.31% [1.01–3.50%], b-AN = 650; non-accidental: b-AF = 1.92% [0.57–3.17%], b-AN = 471). For cardiovascular deaths, the optimal definition was the temperature threshold at the 3rd percentile of the daily average temperature, with a duration of 4 consecutive days. Under the optimal definition, the QAIC values were the lowest, while the b-AF value and b-AN value were the highest, and all of them were statistically significant (cardiovascular: b-AF = 1.37% [0.05–2.51%], b-AN = 142).

Subsequent analysis was performed based on the best definition and optimal model. The cumulative lag effect of cold spells with the optimal definition is displayed in **Table 3**. Mortality risk increased with the cold spell in all three outcomes, with a statistically significant lag effect occurring as early as the 4th day and the effect of a single day lasting up to a total of 6 days. Moreover, the maximum cumulative effect occurred on the 14th day (all-cause: RR = 1.54 [95% CI, 1.20–1.98]; non-accidental: RR = 1.43 [95% CI, 1.11–1.84]; cardiovascular: RR = 1.58 [95% CI, 1.00–2.48]).

Impact of Cold Spells Stratified by Sex and Age

Stratification analyses were conducted according to sex and age in non-accidental and cardiovascular deaths. The cumulative

TABLE 2 | The QAIC value, attributable risk fraction, and attributable risk number calculated in the model under the eight different definitions of the cold spell.

Percentile	No. of consecutive days	Cold spell days	All-causes			Non-accidental			Cardiovascular		
			QAIC	b-AF (%)	b-AN (*n*)	QAIC	b-AF (%)	b-AN (*n*)	QAIC	b-AF (%)	b-AN (*n*)
≤3rd	≥2	49	5105.86	2.09 (0.65–3.49)	591	4894.57	1.64 (0.09–3.07)	405	4215.01	1.74 (−0.63 to 3.88)	181
	≥3	41	5104.09	2.31 (1.01–3.50)	650	4892.65	1.92 (0.57–3.17)	471	4214.82	1.66 (−0.51 to 3.58)	173
	≥4	20	5113.84	1.02 (0.15–1.78)	287	4895.01	1.06 (0.19–1.83)	260	4206.87	1.37 (0.05–2.51)	142
	≥5	12	5107.16	0.92 (0.40–1.37)	258	4891.13	0.88 (0.34–1.34)	215	4211.29	0.83 (−0.04 to 1.53)	86
≤5th	≥2	83	5104.29	2.28 (0.13–4.26)	644	4890.76	2.12 (−0.06 to 4.13)	521	4259.48	0.87 (−1.45 to 2.95)	91
	≥3	71	5105.75	2.28 (0.44–4.04)	643	4894.66	1.94 (0.04–3.65)	476	4216.70	1.09 (−2.03 to 3.83)	114
	≥4	44	5114.95	1.36 (−0.22 to 2.73)	383	4895.99	1.44 (−0.16 to 2.86)	354	4216.25	0.66 (−2.09 to 2.91)	69
	≥5	28	5115.85	0.81 (−0.20 to 1.72)	229	4897.32	0.85 (−0.23 to 1.79)	208	4214.88	0.18 (−1.75 to 1.68)	18

QAIC, quasi-Akaike information criterion; b-AF, attributable risk fraction; b-AN, attributable risk number.

TABLE 3 | Summary of cumulative relative risk of the cold spell on mortality at lag 0–14 days under the best definition.

Group	Cumulative relative risk (RR, 95% CI)[a]				
	Lag 0	Lag 0–3	Lag 0–7	Lag 0–10	Lag 0–14
All-causes	1.00 (0.96–1.05)	1.08 (0.96–1.21)	1.25 (1.07–1.46)*	1.36 (1.11–1.65)*	1.54 (1.20–1.98)*
Non-accidental	1.00 (0.95–1.05)	1.06 (0.94–1.19)	1.20 (1.02–1.41)*	1.29 (1.05–1.57)*	1.43 (1.11–1.84)*
Females	1.02 (0.95–1.10)	1.10 (0.92–1.32)	1.24 (0.97–1.58)	1.39 (1.02–1.88)*	1.55 (1.05–2.27)*
Males	0.99 (0.93–1.05)	1.03 (0.90–1.20)	1.18 (0.97–1.44)	1.23 (0.96–1.57)*	1.36 (1.00–1.86)*
<65 years	1.01 (0.95–1.32)	1.09 (0.92–1.29)	1.23 (0.98–1.54)	1.32 (1.00–1.76)*	1.46 (1.02–2.10)*
≥65 years	0.99 (0.93–1.06)	1.04 (0.89–1.21)	1.18 (0.96–1.46)*	1.26 (0.97–1.64)*	1.40 (1.01–1.96)*
Cardiovascular	1.03 (0.94–1.14)	1.22 (0.98–1.51)	1.48 (1.13–1.95)*	1.52 (1.07–2.16)*	1.58 (1.00–2.48)*
Females	1.08 (0.93–1.25)	1.36 (0.97–1.90)	1.81 (1.18–2.77)*	2.11 (1.22–3.66)*	2.35 (1.16–4.76)*
Males	1.00 (0.89–1.14)	1.13 (0.86–1.48)	1.30 (0.92–1.83)	1.21 (0.77–1.89)[†]	1.19 (0.67–2.12)[†]
<65 years	1.16 (0.99–1.36)	1.48 (1.04–2.11)*	1.49 (0.96–2.33)	1.41 (0.78–2.53)	1.27 (0.59–2.73)
≥65 years	0.97 (0.87–1.09)	1.09 (0.84–1.42)	1.46 (1.05–2.03)*	1.55 (1.02–2.37)*	1.72 (1.00–2.95)*

[a] *The results of cumulative relative risk at lag 0–14 days were performed under the best definition in model.*
**Statistically significant results at the 5% level (P < 0.05).*
[†] *Z-test for the difference between the two relative risks of subgroup analysis results at the 5% level (P < 0.05).*

lag effect and single-day effect of the cold spell on non-accidental death and cardiovascular death for each subgroup are presented in **Table 3** and **Figure 2**, respectively. The single-day effect of the cold spell on non-accidental deaths in older people occurred on lag 5 and lasted for 3 days, with a significant cumulative effect occurring on day 14 (non-accidental: elderly: RR = 1.40 [95% CI, 1.01–1.96]). For cardiovascular deaths, the cold spell showed a more significant risk influence in females than males. The lag effect starting from lag 3 lasted for about 6 days, with the maximum cumulative RR value on the 14th day (cardiovascular: female: RR = 2.35 [95% CI, 1.16–4.76]). The effect of the cold spell on cardiovascular deaths in the elderly appeared at lag 4 and lasted for about 5 days, with the maximum cumulative RR value on the 14th day (cardiovascular: elderly: RR = 1.72 [95% CI, 1.00–2.95]).

The non-accidental deaths subgroups did not differ significantly on attribution risk fraction and attribution risk number, and the male group value was not statistically significant (**Table 4**). The attributable risk fraction of cardiovascular deaths was highest for women and older people (cardiovascular: female: b-AF = 2.56% [95% eCI, 0.50–4.18%], b-AN = 104; elderly: b-AF = 1.70% [95% eCI, 0.05–3.06%], b-AN = 115).

Sensitivity Analysis

The result showed that the model was robust, and there was no change in the conclusions by changing the temperature *df* (3–4), relative humidity *df* (3–4), cold spell *df* (3–5), time *df* (6–8), and pollutant variables (SO_2, NO_2, CO, O_3, and PM2.5) (**Supplementary Figures S2–S6**).

DISCUSSION

The eight definitions of a cold spell proposed in our study encompass all combinations of two temperature thresholds (3rd and 5th percentiles) and four types of duration (2, 3, 4, and 5 days). Compared to QAIC criterion and the

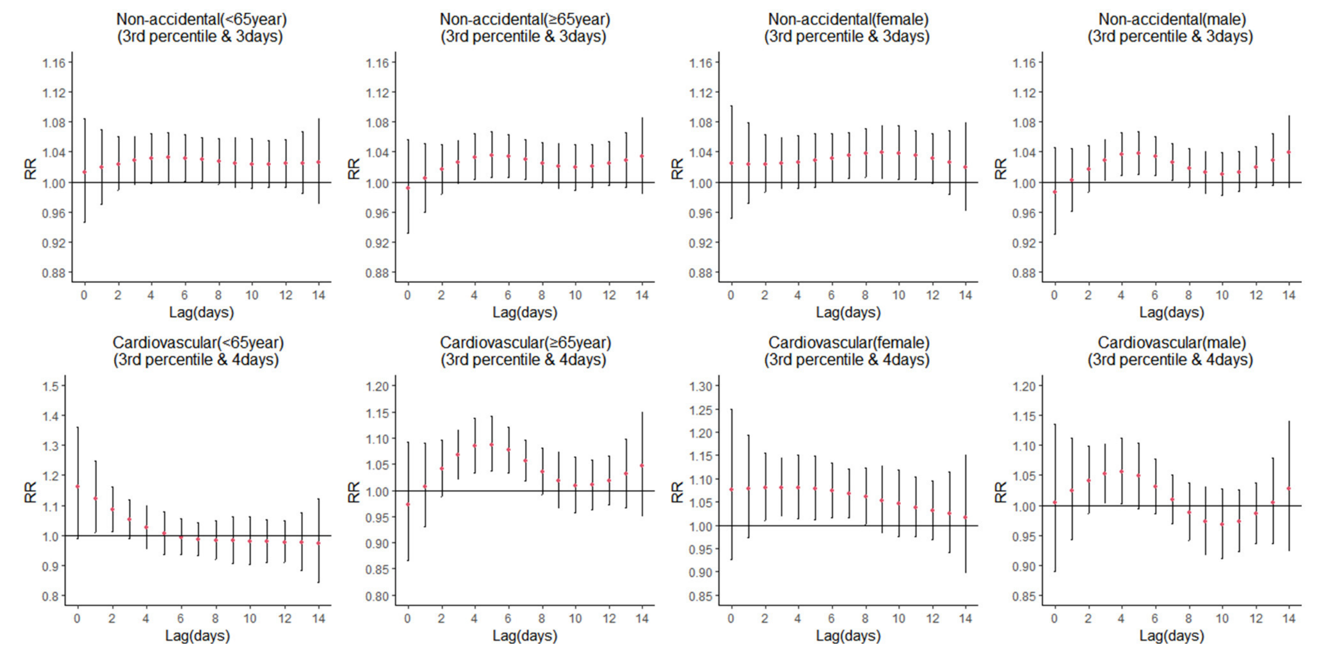

FIGURE 2 | Lag-effects of the cold spell on mortality (non-accidental and cardiovascular) stratified by sex and age.

TABLE 4 | The attributable fraction and number of non-accidental and cardiovascular mortality stratified by sex and age.

Group	b-AF (%)	b-AN (*n*)
Non-accidental		
Females	2.39 (0.29–4.23)	225
Males	1.65 (−0.05–3.15)	249
<65 years	1.95 (0.03–3.61)	211
≥65 years	1.91 (0.05–3.55)	262
Cardiovascular		
Females	2.56 (0.50–4.18)	104
Males	0.57 (−1.26–2.06)	36
<65 years	0.88 (−1.46–2.62)	32
≥65 years	1.70 (0.05–3.06)	115

b-AF, attributable risk fraction; b-AN, attributable risk number.

attribution risk fraction under eight definitions, in Shenzhen, the optimal definitions for all-cause deaths and non-accidental deaths were determined to be least 3 or more consecutive days in which the daily average temperature less than the threshold was at the 3rd percentile of daily mean temperatures. For cardiovascular deaths, the definition was at least 3 or more consecutive days in which the daily average temperature less than the threshold was at the 4th percentile of daily mean temperatures. Using the best definition, we have estimated the effect of local cold spells on all causes of death, non-accidental deaths, and cardiovascular deaths in Shenzhen and identified susceptible persons. This is the first study in the Shenzhen region to examine the most appropriate definition of a cold spell and the relationship between cold spells and mortality for different outcomes.

We have observed that temperature had an influence on mortality (**Figure 1**). Extreme cold, cold, mild cold, heat, and extreme heat had significant risk effects on the three outcomes, and the impacts of cold temperature were more significant than those of the heat (**Supplementary Table S2**). This relationship was agreed with previous results that indicated that the temperature decreases as the mortality increases (9, 31). The results confirm that cold spells increase the risk of all-cause, non-accident, and cardiovascular mortality, irrespective of which of the eight definitions are used. However, the optimal definition of a cold spell was different for the three outcomes (**Supplementary Figure S1**). This could also be an explanation for the different sensitivities of different death causes to low temperature (32). Among the selected optimal definitions, the lag effect of cold waves on all causes of death, non-accidental death, and cardiovascular death manifested first and lasted the longest, which has important implications for constructing an optimal early warning system. Meanwhile, there is a significant public health benefit in determining the optimal definition for an early warning system to prevent even more fatalities. According to the optimal definition, the cold spell increased the risk of all-cause and non-accidental death by 54 and 43%, respectively, and increased the risk of cardiovascular disease mortality by 58% in the cumulative lag of 14 days. Exposure to low temperatures may increase the risk of acute death events in residents with cardiovascular disease by increasing blood pressure, platelet counts, blood cholesterol, and fibrinogen levels, as well as promoting inflammatory responses, exacerbating the symptoms of cardiovascular diseases (33, 34). In winter, low temperature is an established risk factor for mortality of cardiovascular disease, as numerous previous studies had found (32, 35–38).

Sex and age were modifiers of the relationship between cold spells and mortality. Our present research discovered that during cold spells, older individuals had a greater risk of non-accidental and cardiovascular death than younger adults (**Table 3**). This is consistent with the findings of several studies that the risk of death in low-temperature situations is significantly greater in the elderly than in younger adults (12, 36). Because organs gradually decline with age and thermal regulation systems weaken with increasing age, and the higher incidence of chronic diseases such as respiratory, congestive heart failure and cardiovascular diseases in the elderly, along with their activity limitations, they are more susceptible to cold spell events (39). At present, China is facing severe challenges related to the aging of its population. These findings have important public health and policy implications in the current context of climate change and cold extremes. Compared with the non-cold spell period, Females had a substantial 135% increased risk of death for non-accidental causes and a significant 72% increased risk of death for cardiovascular causes on lag 14 days during the cold spell period. Furthermore, females had significantly higher cumulative lag effects of cold spells than males in non-accidental and cardiovascular deaths and had more prolonged lag effects, in line with some previous studies (40–42). This difference may be attributed to different physiology in males and females, which varies considerably (43). Men, on average, have a higher tolerance for extreme temperatures and a greater capacity to control their body temperature than women do (44). Meanwhile, females in China have a longer life expectancy than men, resulting in a larger proportion of females than males among the elderly (41). Hence, the elderly and the females need to pay special attention during cold spells.

Our study has critical public health and policy implications for Shenzhen. First, despite its low latitude, Shenzhen is more sensitive to the effects of cold spells. Previous studies have confirmed this finding, with southern regions being more susceptible to cold wave impacts than other locations (45–47). This may be because populations in warmer regions lack physiological acclimation and behavioral adaptation, making them more susceptible to cold impacts. Simultaneously, many locations lack appropriate heating systems and medical services to deal with cold periods. Second, early warning systems for cold spells play a critical role in mitigating cold-weather health hazards. A necessary precondition for designing an early warning system is a clear definition of a cold spell. Through comparing eight different definitions, we were able to determine which definition was most beneficial to prevent which cause of death. The results of our study highlight the real impact of cold spells, and the government should strengthen the development of relevant specific policies and formulate intervention programs in Shenzhen. For instance, central home heating should be provided to the cities in the south of China in winter. Prior to the onset of the cold period, the government and local communities should strengthen cold spell-related health education and awareness. Hence, maintaining an accurate and timely warning system and monitoring atmospheric parameters are essential for early warning and protecting susceptible populations. Finally, we identified populations sensitive to cold spells, emphasizing the critical nature of risk awareness and personal preventive actions. It is recommended that older adults in the southern region, especially females, avoid outside activity during cold spells. In addition, during the cold spells, we should offer more professional medical services and health education to older adults.

Nevertheless, this study has a number of limitations. First, data collection was only over a short period, 5 years. Second, the distributed lag non-linear model has been widely studied and successfully employed for investigating the effects of temperature on mortality. However, the model is more sensitive to the choice of the lag day, exhibiting a strong dependence (48). There have been studies showing that air pollutant concentrations can influence the effect of temperature on daily death rates (49–51). However, our observations did not find any significant results. Our findings do not establish a causative link between cold spells and mortality but only report associations (52). Last, the meteorological data were obtained from fixed monitoring stations, which are not a good representation of individual actual exposure levels, leading to the individual estimation errors and affecting the cold spell death effects.

CONCLUSIONS

This study aimed to investigate the impact of cold spells, which were found to be a significant risk factor for mortality in Shenzhen. The definition of a cold spell as the threshold at the 3rd percentile of mean temperature, and duration at least 3 consecutive days, was the most appropriate for all-cause deaths and non-accidental death. For cardiovascular deaths, the optimal definition was the threshold at the 3rd percentile of mean temperature, and duration was at least 4 consecutive days. Under this definition, both older adults and women were susceptible. These findings provide a clear basis and scientific information for developing an early warning system and establishing preventive measures to reduce the health risks of the cold spell.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CM and FK contributed to conception and design of the study. CM and YX analyzed the data. CM wrote the manuscript. PY and JC supervised and guided the writing of the manuscript.

PY, JP, SH, YD, GL, SY, and YF conceptualized and designed the study. All authors reviewed and approved the final manuscript and contributed to the study.

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SUPPLEMENTARY MATERIAL

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Effects and Interaction of Meteorological Parameters on Influenza Incidence During 2010–2019 in Lanzhou, China

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Background: Influenza is a seasonal infectious disease, and meteorological parameters critically influence the incidence of influenza. However, the meteorological parameters linked to influenza occurrence in semi-arid areas are not studied in detail. This study aimed to clarify the impact of meteorological parameters on influenza incidence during 2010–2019 in Lanzhou. The results are expected to facilitate the optimization of influenza-related public health policies by the local healthcare departments.

Methods: Descriptive data related to influenza incidence and meteorology during 2010–2019 in Lanzhou were analyzed. The exposure-response relationship between the risk of influenza occurrence and meteorological parameters was explored according to the distributed lag no-linear model (DLNM) with Poisson distribution. The response surface model and stratified model were used to estimate the interactive effect between relative humidity (RH) and other meteorological parameters on influenza incidence.

Results: A total of 6701 cases of influenza were reported during 2010–2019. DLNM results showed that the risk of influenza would gradually increase as the weekly mean average ambient temperature (AT), RH, and absolute humidity (AH) decrease at lag 3 weeks when they were lower than 12.16°C, 51.38%, and 5.24 g/m^3, respectively. The low Tem (at 5th percentile, P_5) had the greatest effect on influenza incidence; the greatest estimated relative risk (RR) was 4.54 (95%CI: 3.19–6.46) at cumulative lag 2 weeks. The largest estimates of RRs for low RH (P_5) and AH (P_5) were 4.81 (95%CI: 3.82–6.05) and 4.17 (95%CI: 3.30–5.28) at cumulative lag 3 weeks, respectively. An increase in AT by 1°C led to an estimates of percent change (95%CI) of 3.12% (−4.75% to −1.46%) decrease in the weekly influenza case counts in a low RH environment. In addition, RH showed significant interaction with AT and AP on influenza incidence but not with wind speed.

Conclusion: This study indicated that low AT, low humidity (RH and AH), and high air pressure (AP) increased the risk of influenza. Moreover, the interactive effect of low RH with low AT and high AP can aggravate the incidence of influenza.

Keywords: influenza, meteorology, distributed lag non-linear model, interaction, seasonally

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INTRODUCTION

Influenza is an acute respiratory disease caused by the influenza virus, which belongs to category C infectious diseases in China. The influenza virus easily mutates and spreads mainly through aerosol droplets and contact (1, 2). Therefore, influenza infections can transform into outbreaks or epidemics. According to the World Health Organization, approximately 290,000–650,000 patients died due to respiratory tract infection, and 3–5 million people develop serious related diseases each year (3). Considering that the influenza virus is highly infectious and can cause severe morbidity, the burden of influenza cannot be neglected. Although China has established an influenza surveillance network, the latest research suggests that an average of 88,100 people die each year due to influenza-related respiratory diseases across the country (4, 5). It is essential to comprehend the epidemiological characteristics of influenza to reduce the burden of this disease. Because of global warming, the influence of meteorological parameters on the spread and incidence of influenza has become more critical. Seasonal changes in the incidence of respiratory diseases especially influenza reveal that the peak time of their occurrence is during winter and spring (6–9). The onset of influenza is sensitive to the climate, particularly temperature and humidity, giving rise to influenza seasonality in temperate regions. Low temperature significantly increases the incidence of influenza (10, 11). A study suggested that low humidity contributed to the spread of influenza in Shenyang, China (12). However, the relationship between influenza incidence and meteorological parameters such as air pressure (AP) and wind has yet to be clarified. Furthermore, it is difficult to hold a certain factor responsible for the occurrence of the disease because the effects of meteorological parameters are comprehensive and interdependent.

Lanzhou, located in northwestern China, experiences low precipitation, strong evaporation, and relatively lower temperature and is considered a typical arid city with a temperate semi-arid climate (13). The association between meteorological parameters and influenza incidence in semi-arid areas has rarely been reported. Therefore, this study was conducted to analyze the association between meteorological parameters and influenza in Lanzhou and to evaluate the interactions of RH with other meteorological parameters during 2010–2019. The results are expected to assist in the prevention and control of influenza infections, thereby reducing the burden of influenza in the future.

MATERIALS AND METHODS

Data Collection

Data related to influenza cases were obtained from the Lanzhou Center for Disease Control and Prevention (CDC) legally reported infectious disease database from January 01, 2010 to December 31, 2019. The descriptive data included gender, age, diagnosis date, etc. Meteorological data were obtained from the daily report of Lanzhou Meteorological Bureau, including daily average ambient temperature (AT), RH, AP, Sunshine hours (SH), and wind speed (WS). Several demographic studies (14–17) have reported a significant relationship between the spread of influenza and absolute humidity (AH); therefore, this parameter was also included in the analysis.

Calculation of AH

AH is the weight of water content per unit volume of gas, usually expressed as vapor pressure (VP) in g/m^3. The ideal gas law (1) was combined with the Clausius–Clapeyron relationship (18) to calculate the saturated VP Es(T) (mb) from daily temperature (2) and then included the relative humidity (RH) (3) to derive the AH (19, 20) as shown below:

$$\rho v = 1000 \times \frac{v}{G_v T} \tag{1}$$

$$E_S(T) = E_S(T_0) \times EXP\left[\frac{L}{G_v}\left(\frac{1}{T_0} - \frac{1}{T}\right)\right] \tag{2}$$

$$VP = 100 \times E_s(T) \times \frac{RH}{100} \tag{3}$$

Where G_v is the gas constant of water vapor [461.53 J/(kg·K)]; v is the VP; T is the daily AT (K); $E_S(T)$ is the saturated VP; T_0 is the reference temperature (273.15 K); L is the standard latent heat of evaporation for 1 kg of water (2,257 kJ/kg).

Case Definition

The influenza case was defined as a person with a sudden onset of fever (≥38°C), chills, cough and/ or sore throat, a generalized feeling of weakness and pain in the muscles, together with varying degrees of soreness in the head and abdomen. Influenza cases should meet the standard diagnostic criteria for influenza (WS 285-2008) from the National Health Commission of the People's Republic of China. All these influenza cases were diagnosed and confirmed by a positive pathogenic test of the influenza virus. Once diagnosed, each case must be reported to the National Information System for Disease Control and Prevention immediately and we thus obtained the daily incidence data of influenza from this reporting system.

Statistical Analysis

Considering the over-dispersion of the daily incidence of influenza, a weekly time-series database of influenza incidence and meteorological parameters was established for the period of 2010–2019 in Lanzhou. First, a descriptive analysis was performed on the collected data. Then, the Spearman correlation analysis was used to explore the correlation between meteorological parameters and weekly influenza case counts. The distributed lag non-linear model (DLNM) with Poisson distribution was applied to explore the effects of meteorological parameters on influenza incidence, which included weekly mean average AT, RH, AP, WS, AH, and weekly cumulative SH. Next, the response surface model and stratified model were used to indicate the interaction effects between RH and other meteorological parameters (AT, AP, and WS) on influenza incidence. Finally, a sensitivity analysis was performed by changing the degree of freedom of the penalized smoothing spline function from 3 to 8 for Tem and humidity (AH and RH) and either controlling or not controlling the autocorrelation.

The DLNM model was established for each variable including AT, AH, RH, AP, SH, and WS, while controlling for long-term trend and seasonality by using a time-stratified method (employing simple indicator variables) (21, 22). Considering the delayed impact of infection and morbidity (23), the maximum lag period was determined to be 3 weeks to estimate the cumulative effect (relative risk, RR) of the meteorological parameters on influenza incidence. By using the median level of each meteorological parameter as a reference, the cumulative RR and 95% confidence interval (CI) were calculated to determine the extreme effects of low and high levels in the 5th and 95th percentiles (P_5 and P_{95}) in the model. For example, the effect of low RH on influenza incidence was analyzed by comparing the 5th percentile with the median level. The main model (24) was as follows:

$$\log\left[E(Y_i)\right] = \alpha + cb(X_{i,l}) + \sum ns(Z_{i,t}, df) + strata + \log\left(Y_{i-1}\right) \quad (4)$$

Where i is the week of the observation; Y_i is the observed weekly case counts in Lanzhou during week *i*; $E(Y_i)$ is the expected number of influenza case counts during week *i*; α is the intercept; *cb*() represents the two-dimensional model used to fit the non-linearity and lag weeks of meteorological parameters by using cross-basis function; $X_{i,l}$ represents the meteorological parameters during week *i*, indicates the weekly mean AT ($AT_{i,l}$), mean RH ($RH_{i,l}$), mean AH ($AH_{i,l}$), mean AP ($AP_{i,l}$), mean WS ($WS_{i,l}$), and SH ($SH_{i,l}$), respectively. $Z_{i,t}$ refers to other meteorological parameters except for $X_{i,l}$; the strata variable represents an indicator to control the long-term trend and seasonality for the combination of year and month; $\log(Y_{i-1})$ represents the number of influenza cases in the previous week to control the autocorrelation; the degree of freedom (*df*) of the natural spline smoothing function in the formula was selected according to the Akaike's information criteria. Concerning the collinearity, two variables having a high correlation (Spearman correlation coefficient >0.7) were not included in the same model.

Considering the characteristics of the temperate semi-arid climate in Lanzhou, the response surface model and stratified model (25) were established to fit the interaction effect of RH with other meteorological parameters on influenza incidence through three-dimensional maps. In the stratified model, the 5th and 95th percentiles were used as tangents for the RH to be divided into two-categorical variables, which were divided into two levels: "low" and "high." Low-RH referred to the case when RH was less than the 5th percentile, and High-RH referred to the case when the RH was higher than the 95th percentile. The model is shown in Equations (5) and (6):

$$\log\left[E(Y_i)\right] = \alpha + tp(RH, X_i) + ns\left(weather\right) + strata + \log\left(Y_{i-1}\right) \quad (5)$$

$$\log\left[E\left(Y_i\right)\right] = \beta_1 X_i + \beta_2 RH_b + \beta_3 X_i : RH_b + ns(weather) + strata + \log\left(Y_{i-1}\right) \quad (6)$$

Where *tp*() represents the response surface function; X_i represents the meteorological parameters (AT, SH, and WS) that interact with RH; *weather* represents other meteorological parameters except X_i; RH_b represents two-categorical variables of RH; β_3 is the interaction effect of RH with other meteorological parameters on influenza case counts; other variables are the same as those in foregoing model.

All analyses were conducted by using the "mgcv" and "dlnm" packages in R4.0.0 in this study. Results were considered statistically significant when $P < 0.05$.

RESULTS

Descriptive Data Related to Weekly Influenza Case Counts and Meteorological Data

During the study period (2010–2019), a total of 6,701 cases of influenza were reported in Lanzhou, of which 3,905 were in males and 3,374 were in females (sex ratio 1.13). Among the patients, 53.93% were children under the age of 14 years. **Table 1** shows the summary statistics of the meteorological variables. The mean values of AT, RH, AH, AP, SH, and WS were respectively 11.12°C, 51.21%, 6.01 g/m^3, 848.01 hPa, 43.42 h, and 1.15 m/s. **Table 2** shows the correlation between influenza case counts and meteorological parameters. All meteorological parameters including AT, RH, WS, AH, and SH were negatively correlated with influenza incidence ($P < 0.05$), while AP was positively correlated with influenza incidence. The correlation of AT and AH with influence incidence was stronger ($r_{AT} = -0.53$ and $r_{AH} = -0.55$, respectively) than that of others. The time-series distribution of weekly meteorological parameters and influenza case counts from 2010 to 2019 demonstrated a clear seasonal pattern (**Figure 1**).

Lag Effect of Meteorological Parameters on Influenza Incidence

The correlation between meteorological parameters and weekly influenza case counts was estimated by the cumulative RR

TABLE 1 | Basic information related to influenza case counts and meteorological parameters in Lanzhou, China during 2010–2019.

Variable	Mean	S.D.	Min	Percentiles			Max
				25	50	75	
AT (°C)	11.12	9.88	−8.84	1.72	12.76	19.93	29.86
AP (hPa)	848.01	4.38	838.47	844.31	848.38	851.40	858.26
RH (%)	51.21	12.28	18.39	42.92	52.04	60.43	87.00
WS (m/s)	1.15	0.22	0.56	0.99	1.14	1.30	1.76
AH (g/m^3)	6.01	3.62	1.24	2.51	5.26	8.96	14.40
SH (h)	43.42	14.45	1.30	32.70	43.30	53.95	83.20
Cases (counts)	12.79	25.07	0.00	2.00	5.00	12.00	311.00

S.D., standard deviation; Min, minimum; Max, maximum. AT, RH, AH, AP, WS, and SH represent, respectively, weekly mean average ambient temperature, mean relative humidity, mean absolute humidity, mean air pressure, mean wind speed, and weekly cumulative sunshine hours, respectively. "Cases" represents weekly influenza case counts.

after a lag of 3 weeks from the DLNM model (**Figure 2**). After controlling for the long-term trend and seasonality, the median of each meteorological parameter was taken as reference, and an approximately "L"-shaped correlation was observed between AT, RH, and AH and the risk of influenza.

TABLE 2 | Spearman correlation between influenza case counts and meteorological parameters in Lanzhou, China during 2010–2019.

Variable	Cases	AT	RH	WS	AH	AP	SH
Cases	1.00						
AT	−0.53*	1.00					
RH	−0.21*	0.03	1.00				
WS	−0.24*	0.41*	−0.41*	1.00			
AH	−0.55*	0.92*	0.41*	0.23*	1.00		
AP	0.38*	−0.79*	0.16*	−0.52*	0.16*	1.00	
SH	−0.20*	0.47*	−0.59*	0.46*	0.20*	−0.44*	1.00

""Represents $P < 0.05$. AT, RH, AH, AP, WS, and SH represent, respectively, weekly mean average ambient temperature, mean relative humidity, mean absolute humidity, mean air pressure, mean wind speed, and weekly cumulative sunshine hours, respectively. "Cases" represents weekly influenza case counts.*

The risk of influenza gradually increased as the AT, RH, and AH decreased, when they were lower than 12.16°C, 51.38%, and 5.24 g/m^3, respectively. A "J"-shaped correlation was observed between AP and the risk of influenza. When AP was higher than 853.47 hPa, the risk of influenza rapidly increased as the AP increased. Medium WS increased the risk of influenza. Sensitivity analysis displayed steady results which were insensitive to the specifications of the parameters (**Supplementary Figures 1**, **2**).

Based on the above results, we analyzed the lag effect of various meteorological parameters on the onset of influenza at different lag days under extreme conditions fitted by the DLNM model, such in cold (<-4.64°C, P_5 of AT) and hot (>24.49°C, P_{95} of AT) conditions (**Figure 3**). With various lag weeks, a significant effect of cold and hot weathers was observed on influenza incidence during 1–3 lag weeks. Low AT (P_5) exhibited the largest estimated effect at lag 2 weeks, and the cumulative RR was 4.54 (95%CI: 3.19–6.46). Significant effects of dry RH and dry AH were observed during 0–3 lag weeks. Dry RH (P_5) and dry AH (P_5) exhibited the largest estimated effect at lag 3 weeks, and the cumulative RRs were 4.81 (95%CI: 3.82–6.05) and 4.17 (95%CI: 3.30–5.28), respectively. The relative wet effect [RH (P_{95}) and dry AH (P_{95})] reduced the risk of influenza. The extreme

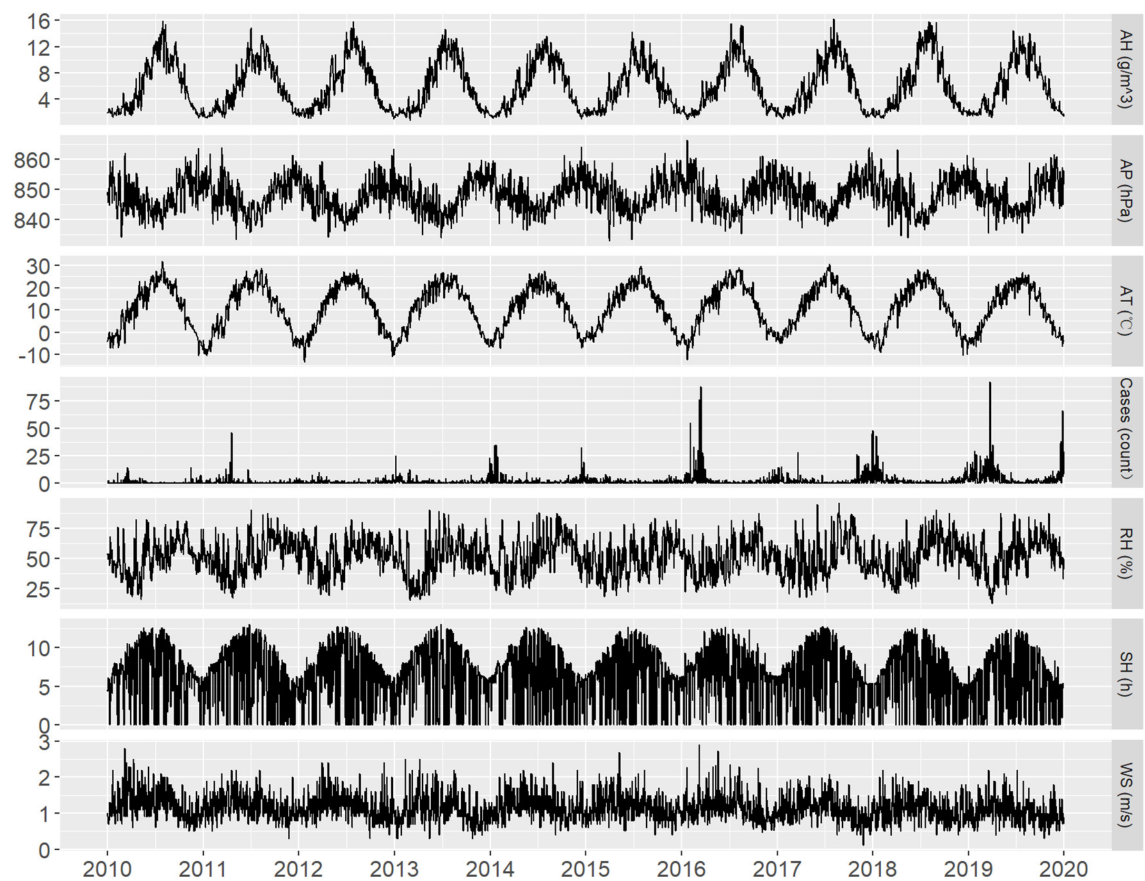

FIGURE 1 | Time-series distribution of daily influenza case counts and daily meteorological parameters in Lanzhou, China during 2010–2019.

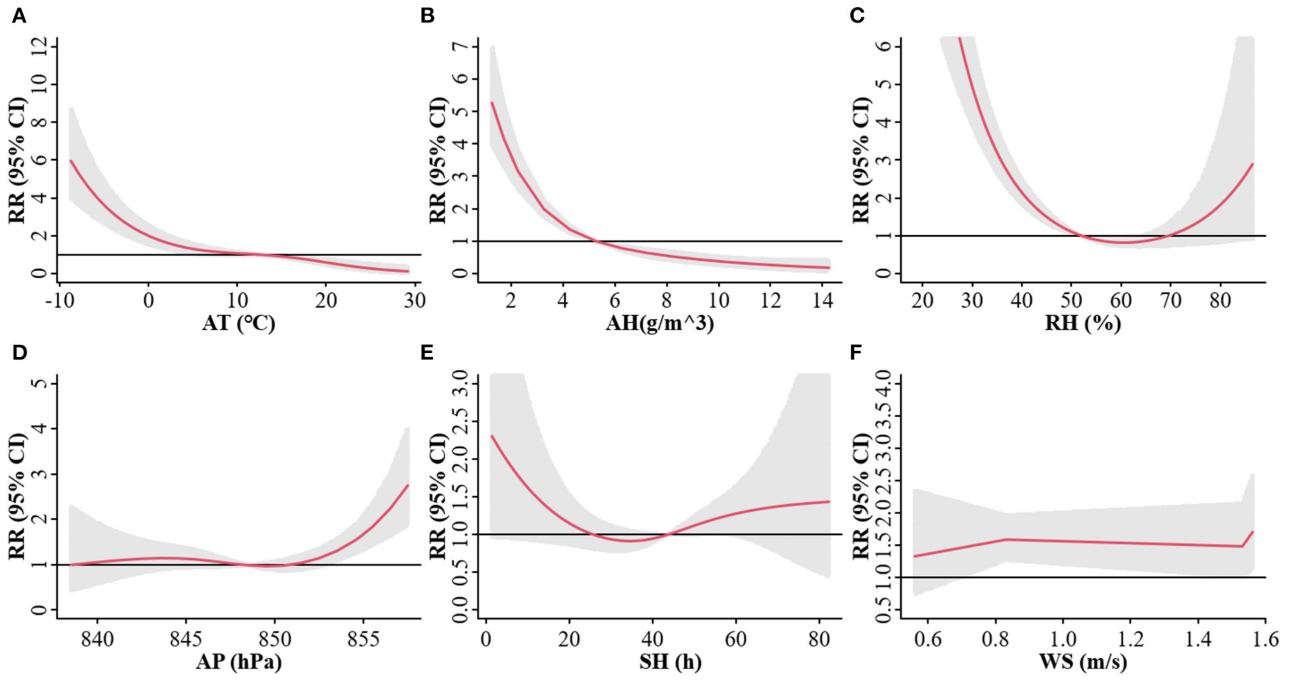

FIGURE 2 | Exposure-response relationship between the risk of influenza and AT **(A)**, AH **(B)**, RH **(C)**, AP **(D)**, SH **(E)**, and WS **(F)** at a three-week lag in Lanzhou, China during 2010–2019. The red line represents the cumulative relative risk (RR) of influenza, and the gray shaded region represents the 95% confidence interval (CI).

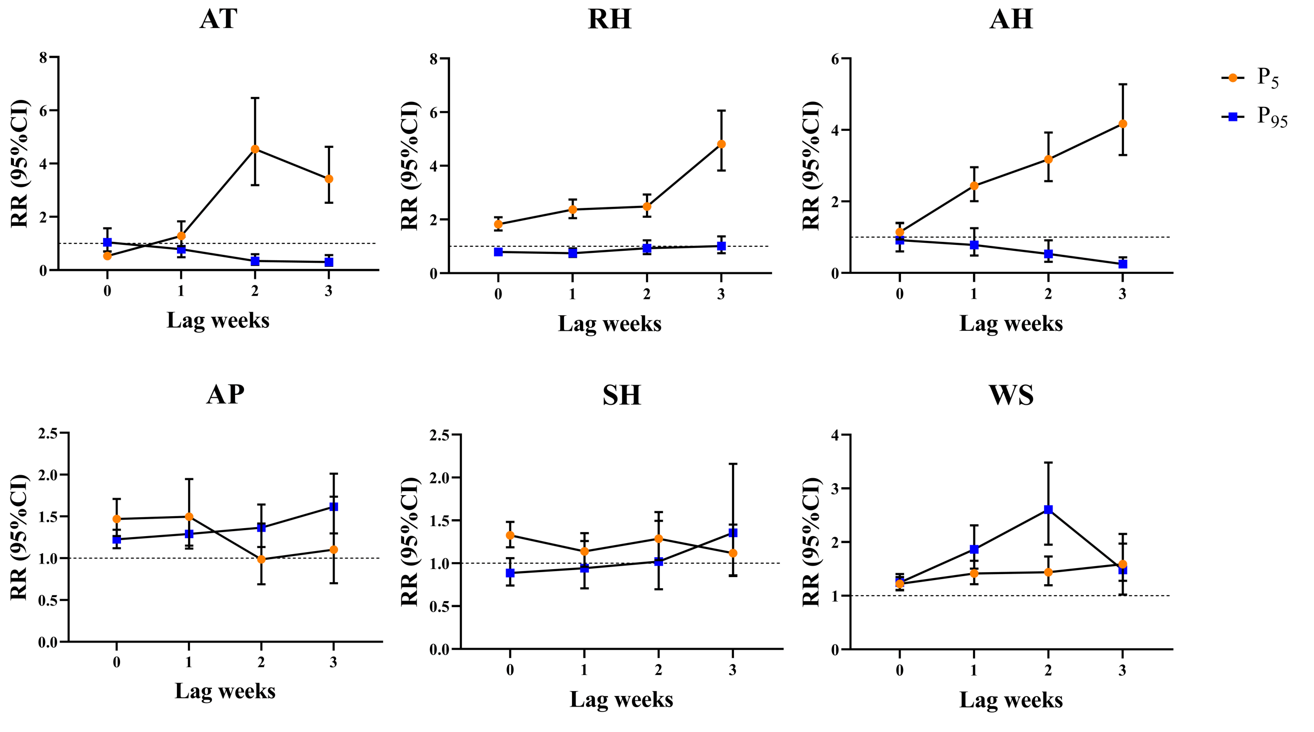

FIGURE 3 | Cumulative lag effect of meteorological parameters on the onset of influenza under extreme conditions at different lag weeks in Lanzhou, China during 2010–2019. P_5 represents the 5th percentile. P_{95} represents the 95th percentile.

effect of AP and WS was not significant, and a dangerous effect was observed at every lag week. The significant extreme effect of SH on influenza incidence showed that lesser SH increased the risk of influenza.

Interaction Effect of Meteorological Parameters on Influenza Incidence

Because Lanzhou is a typical temperate semi-arid climate, the interaction effect of RH with other meteorological parameters on influenza incidence was studied. The hierarchical model analysis is shown in **Table 3**. At lag 3 weeks, there was an interaction effect of Low-RH with AT, AP, and WS ($P < 0.05$) on influenza incidence, while the interaction effect of High-RH was not significant. An increase in AT by 1°C led to an estimates of percent change (95%CI) of 3.12% (−4.75 to −1.46%) decrease in the weekly influenza case counts with in the Low-RH environment. Influenza case counts were affected by various meteorological parameters and the interaction between various meteorological parameters. The interactive model also showed that there was an obvious interaction effect of RH with AT and AP on influenza incidence (**Figure 4**). In three-dimensional analysis, the strongest interaction was observed under conditions of low RH, low AT, and high AP.

TABLE 3 | Estimates of percent change (95% CI) in weekly influenza cases associated with a 1-unit increase in other meteorological parameters stratified by RH.

	Low-RH	High-RH
AT	−3.12% (−4.75%, −1.46%)*	0.42% (−2.38%, 3.30%)
AP	−5.42% (−7.99%, −2.22%)*	−1.03% (−1.03%, 3.99%)
WS	97.80% (29.78%, 201.46%)*	104.90% (−42.85%, 634.27%)

""represents significance at the level of 0.05. Taking the 5th and 95th percentiles as tangent points of the binary categorical variables, relative humidity (RH) was divided into two levels of "low" and "high." When RH was less than the 5th percentile, the environment was defined as Low-RH. When RH was greater than the 95th percentile, the environment was defined as High-RH.*

DISCUSSION

The antigenic drift and transfer of the influenza virus are constantly changing, imposing huge economic losses and disease burdens to the public on a global scale (5, 26–28). In this study, the relationship between meteorological parameters and influenza incidence was analyzed in a semi-arid area (Lanzhou) for the first time. Low AT, low humidity (AH and RH), and high AP could accelerate the spread of influenza with obvious lag effects. Moreover, in this dry area, the interaction effect of low RH with low AT and high AP on influenza incidence was significant.

From January 1, 2010 to December 31, 2019, a total of 6701 influenza cases were reported in Lanzhou. Children under the age of 14 years were a high-risk group, accounting for 53.93% of the total influenza patient population, consistent with other studies (9, 29). The seasonality of change trend demonstrated in previous studies (30–32) has indicated that the incidence of influenza peaks in winter and spring, particularly when the AT is the lowest. In an animal experiment, the airborne transmission of influenza virus was enhanced when guinea pigs were housed at a low AT (5°C), while at a high AT (30°C), the spread was interrupted under all conditions of RH (33). The reasons for low AT facilitating the spread of influenza may be as follows: (1) Influenza virus can survive at 0–4°C for several weeks and for a long time below −70°C or after freeze-drying, but its infectivity is quickly lost at room temperature. The average temperature during winter in Lanzhou is close to its optimum growth temperature, making it easier to spread and infect. Some studies also indicated that the influenza virus envelope was more complete and the survival time was longer at low temperatures than at high temperatures (34, 35). (2) Children under the age of 14 years were at high risk for influenza, probably because they had poor awareness of disease prevention, habit of hygiene, and immune system, making this population group more susceptible to be infected in cold weathers (36). (3) People spend more time indoors during cold weather, which could lead to higher infection rates and epidemics (37).

In this study, low humidity (RH and AH) was more beneficial to the activity of influenza, and a significant dry effect of RH and

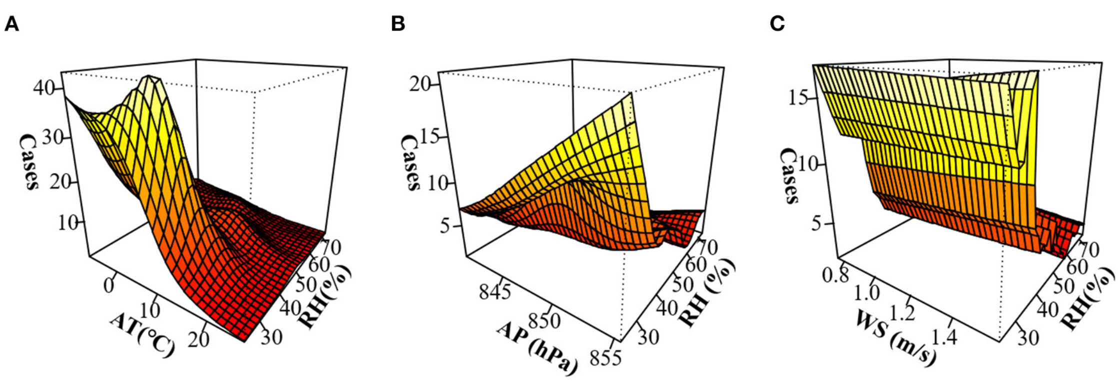

FIGURE 4 | Three-dimensional map of the interaction effect of relative humidity (RH) with other meteorological parameters on influenza incidence in Lanzhou, China during 2010–2019 after a lag of 3 weeks. **(A)** Interaction effect of RH with AT. **(B)** Interaction effect of RH with AP. **(C)** Interaction effect of RH with WS.

AH was observed during 0–3 lag weeks. The results of this study were consistent with those of studies on the impact of humidity on influenza (12, 38, 39). It is suggested that low humidity improves the survival stability of the virus when the salt content of droplets in winter allows the virus to maintain high vitality at low RH (<50%), and the viability of influenza virus increased with decreasing RH (40). Low humidity exposure impaired host responses to infection, resulting in higher viral burden such as decreasing mucociliary clearance in mouse trachea (41). However, conflicting views have been reported regarding the impact of RH on influenza. The findings of the current study on RH were not in line with those reported by studies in Poland, Zhejiang, and Chongqing, in which the influenza incidence was moderately positively correlated with RH, and higher RH could increase the risk of influenza incidence (42–44). The difference in the results may be because of the difference in the latitude, climate type, demographic characteristics of the study area, and the statistical methods and models used. Therefore, the reported associations related to influenza incidence are specific to the regions.

The interaction model in this study showed the interaction effect of RH with other meteorological parameters. The condition of low RH with low AT could increase the influenza case counts. Recent laboratory and epidemiological evidence have confirmed that influenza virus transmission depends on RH and AT, and the onset of influenza exhibits a synchronous change pattern with cold and dry climate conditions, revealing that low RH with low AT increases the risk of influenza epidemic (33, 45, 46). Temperature and humidity were the lowest when influenza was most active during winter and spring. Therefore, temperature and humidity play important roles in the spreading of influenza. Previous studies had been carried out in temperate or humid regions, but the present study shows how temperature and humidity influence the incidence of influenza in an arid region.

Besides the commonly studied parameters of temperature and humidity, other meteorological parameters (WS, SH, and AP) were also analyzed in this study. The risk of influenza rapidly increased as AP increased, when the AP was >853.47 hPa, and the interactive effect of low RH with high AP could increase the incidence of influenza, revealing a synergistic effect. A study similarly reported that under high pressure, the number of influenza cases increased when AP was >1,005 hPa (47). It is well-known that high AP usually accompany cold and dry weather, which promote indoor activities and more communication among people, this may increase the spread risk of influenza infection. Besides, the cold and dry weather would also make the nasal mucosa vulnerable to be cracked, which may increase the risk of influenza invasion.

Limitations

This study deepens the understanding of the effects of meteorological parameters on influenza incidence by using weekly data in a temperate semi-arid region. However, some limitations must be acknowledged. First, individuals most often overlook influenza and choose to isolate themselves at home due to its relatively mild symptoms, increasing the chances of a missed diagnosis. Second, the influenza virus was not classified in this study, and the impact of meteorological parameters may be different on different types of influenza viruses. Third, sandstorms, smog, and other extreme weather events in Lanzhou during peak times and air pollutants can also affect influenza seasonality (10, 42, 48–50). The number of days of extreme weather are increasing each year due to global climate change, which may pose more threats to public health. Finally, this is an ecological study, so the ecological bias could not be avoided. But it at least provide a hypothesis and indicate the significant effect of environmental factors on the influenza infection, which may be important for the government to place suitable medical cares against influenza in different weathers.

CONCLUSIONS

Low AT, low humidity (RH and AH), and high AP increased the risk of influenza. Moreover, the interaction effect of low RH with low AT and high AP can aggravate the incidence of influenza. Considering these significant effects of meteorological parameters, relevant government departments could actively implement appropriate measures to optimize influenza-related public health policies such as monitoring the mutations of influenza virus in a timely manner and providing increased vaccine coverage during the cold and dry season.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JW: methodology, software, data curation, and writing—original draft preparation. LZ: methodology, software, visualization, and writing—original draft preparation. RL: methodology and data curation. PL: investigation. SL: conceptualization, supervision, formal analysis, and writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.833710/full#supplementary-material

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Is Cold Apparent Temperature Associated With the Hospitalizations for Osteoporotic Fractures in the Central Areas of Wuhan? A Time-Series Study

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Osteoporosis is alarming problem due to aggravation of global aging, especially in China. Osteoporotic fracture (OF) is one of the most severe consequents of osteoporosis. Many previous studies found that environmental factors had adverse effects on human health. Cold temperature was associated with OF and bone metabolism in prior observational and experimental researches. However, few studies had been conducted on the acute effect of low temperature and OF. Data on daily meteorological factors and hospitalizations for OF were collected from Wuhan, China, between January 1, 2017 to December 24, 2019. Apparent temperature (AT), comprehensively considered a variety of environmental factors, was calculated by ambient temperature, relative humidity and wind speed. A generalized linear regression model combined with distributed lag non-linear regression model (DLNM) with quasi-Poisson link was used to explore the association between AT and the number of hospitalizations for OF. Subgroup analyses stratified by gender, age and the history of fracture were applied for detecting susceptible people. The exposure-response curve of AT and OF were generally U-shaped with lowest point at 25.8°C. The significant relationship of AT-OF existed only in cold effect (−2.0 vs. 25.8°C) while not in warm effect (37.0 vs. 25.8°C). Statistically significant risks of OF for cold effects were only found in females [RR = 1.12 (95%CI: 1.02, 1.24) at lag 2 day], aged <75 years old [RR = 1.18 (95%CI: 1.04, 1.33) and 1.17 (95%CI: 1.04, 1.33) at lag 2 and 3 days, respectively] and people with history of fracture [RR = 1.39 (95%CI: 1.02, 1.90) and 1.27 (95%CI: 1.05, 1.53) at lag 1 and 2 days, respectively]. The significant associations of AT on OF were only found in cold effect. The females, people aged <75 years and people with history of fracture possibly appeared to be more vulnerable. Public health departments should pay attention to the negative effect of cold AT and take measures in time.

Keywords: apparent temperature, distributed lag non-linear model, osteoporotic fracture, time-series study, hospitalization

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by a reduction in bone mass and micro-architectural deterioration of bone tissue (1). With the advancement of world population aging, the prevalence of osteoporosis was alarming and experts estimated that outnumbering 200 million people were suffering from osteoporosis (2, 3). Osteoporotic fractures (OF) is one of the most severe consequents of osteoporosis. According to the International Osteoporosis Foundation (IOF), there are nearly 9 million osteoporotic fractures worldwide every year, which means that a new case occurs every 3–4 s (4). One-third women and one-fifth men over the age of 50 years are predicted to suffer first time of osteoporotic fracture leading to limitations in quality of life (5, 6). All-cause death risks in the elderly with 1 years of bone fracture will increase 10–20%, and less than half of them were able to return to pre-fracture activity levels (7). About 300,000 people suffered from osteoporotic fracture accounting for nearly 2 million hospital bed days in the UK every year (8). In the United States of America, more than 2 million cases for osteoporotic fracture were reported and over 20 billion dollars of direct health cost were occurred in just 1 year (9). In Japan, family members as caregivers for patients with osteoporotic fracture leaded to over 20,000 dollars annual productivity loss per head (10).

Growing evidence pointed out that genetic, lifestyle, and environmental factors play roles in osteoporotic fracture to some extent (11–14). Fraenkel et al. found the daily rates of osteoporotic hip fractures in winter (1.1 cases per day) were significantly higher than summer (0.79 cases per day), autumn (0.90 cases per day) and spring (0.91 cases per day) (15). Compare with summer, the number of operations, length of hospital stays and cost for osteoporotic fractures of wrist in males were greatly increased in winter (8). A study conducted in Spain revealed the incidence of hip fracture was significantly associated with the coldest time of the year (16). Prior researchers also found that cold stimulus induced oxidative stress and inflammatory response (17, 18), which associated with exacerbating bone loss and enlarging the risks of osteoporotic fractures among the elderly (19, 20). An experimental study in New Zealand white rabbits found that short-term local cooling diminished bone healing by reducing bone blood flow (21). Compared with aging rats kept in a sedentary condition, the changes of bone mineral metabolism (such as the concentration of Ca, Mg, P, and key hormones) and bone mineral density were found in aging rats immersed in cold water (22). Exposures to low temperatures (−20∼-15°C) in a short time affect bone growth by inducing premature arrest of the epiphyseal plate, destruction of the epiphysis, and reactive-endosteal and periosteal bone formation (23). The above literatures hint that cold temperature especially short-term exposure to low temperature might be a noteworthy factor affecting the occurrence of osteoporotic fractures. Myriad environmental epidemiological studies had chiefly chosen daily mean temperature and its variations as the indicators to investigate the relationship with health outcomes (24–26). However, apparent temperature (AT) comprehensively considered a variety of environmental factors (e.g., temperature, relative humidity, and wind speed) and can reflect the actual feeling of human body to the degree of heat, particularly in cold temperature environment (27, 28). Former studies found that AT was more sensitive to the association with mortality than other temperature variables (29, 30). Nevertheless, to the best of our knowledge, there was no study adapting AT as the indicator to investigate the health effects on osteoporotic fractures in China.

In this study, we aimed to use generalized linear model combined with distributed lag non-linear regression model to estimate the associations between short-term exposure to AT and the daily number of hospitalizations for osteoporotic fractures in urban population of Wuhan, China. Moreover, subgroup analyses were applied to detect potential susceptible population.

MATERIALS AND METHODS

Study Area and Population

Wuhan, located in the middle reaches of Yangtze River, is the top 10 metropolises in China. The typical subtropical monsoon climate of Wuhan has extremely high temperature and much rain in the warm season and the opposite in the cold season. Wuhan Hospital of Traditional Chinese and Western Medicine is a large third-class public hospital situated in central of Wuhan (**Supplementary Figure S1**) with 4,260 beds and the number of outpatient/emergency visits and discharged patients are more than 3,000,000 and 100,000 per year, respectively (http://www.whyyy.com.cn/yygk/single/show/1.aspx).

Data Collection

The data on hospitalization for osteoporotic fractures were retrieved from the health information system of Wuhan Hospital of Traditional Chinese and Western Medicine from January 1, 2017 to December 24, 2019. The medical information data after cleaning and quality controlling included the date of hospitalization, gender, age, the history of fracture and main diagnosis (code: M80) according to the International Classification of Diseases (10th revision). We summarized the number of hospitalizations for osteoporotic fractures in each calendar day to establish a new database for analyzing.

Data on meteorological factors in this study period were collected from China National Meteorological Science Data Center (http://data.cma.cn/), including daily mean temperature, relative humidity, wind velocity, sunshine duration and rainfall. Daily mean fine particulate matter ($PM_{2.5}$), inhalable particles (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide(CO), and ozone (O_3) were collected at the nearest monitoring station from Wuhan Environmental Protection Bureau (http://hbj.wuhan.gov.cn/). Apparent temperature (AT) was calculated by some meteorological factors as follows (28).

$$wvp = \frac{Rh}{100} \times 6.105 \times e^{\frac{17.27 \times Ta}{237.7 + Ta}} \tag{1}$$

$$AT = Ta + 0.33 \times wvp - 0.70 \times WS - 4.00 \tag{2}$$

Where *wvp* was water vapor pressure (hPa); *Rh* was relative humidity (%); *Ta* was ambient temperature (°C); *WS* was wind speed (m/s).

Statistical Analysis

Demographic and meteorological factors were described as mean, standard deviation, and quantile. The Spearman analyses were carried out to estimate the correlations of meteorological factors. In this study, a generalized linear regression model combined with distributed lag non-linear regression model (DLNM) with quasi-Poisson link was used to explore the associations between AT and the number of hospitalizations for osteoporotic fractures. Natural cubic smoothing splines with degrees of freedom (dfs) of 5 and 3 were used for exposure-response and lag-response associations in cross-basis function, respectively (31). The effect of apparent temperature exposure was speculated using a natural cubic spline with four internal equally spaced values knots (20th, 40th, 60th, and 80th) and the lagged-response association was modeled with a natural cubic spline with 1 internal knot at equally spaced value (31). Due to the potential delayed effects of AT on the number of hospitalizations for osteoporotic fractures, after exploratory test (**Supplementary Figures S2**, **S3**), this study set up 10 days as maximum lag (31). Covariates included time, rainfall, sunshine duration, public holiday (PH), and day of week (DOW) were incorporate in the final model as follows (32–38):

$$\mathrm{Log}\,(\mathrm{Yt}) = \alpha + \beta \times \mathrm{AT}_{\mathrm{t,l}} + ns\left(time,\ df\right) + ns\left(rainfall,\ df\right) + ns\left(sunshine\ duration,\ df\right) + \gamma \times \mathrm{PH} + \delta \times \mathrm{DOW}$$

Where Yt is the daily number of hospitalizations for osteoporotic fractures in day t; α is the intercept of the model; $AT_{t,l}$ is the matrix of the daily mean apparent temperature obtained from the cross-basis function in the DLNM; β is the coefficient vector of matrix of $AT_{t,l}$, and l was the lag days; *ns* is natural cubic smoothing function for the nonlinear variables such as time, rainfall, and sunshine duration; *df* means the degree of freedom; According to previous literature and pre-analysis results (**Supplementary Figures S4**, **S5**), we defined 1 df per year for time trends and 3 df per year for daily mean rainfall and sunshine duration in the final model, respectively (31, 37).

According to preliminary analyses, optimum apparent temperature (OAT) was 25.8°C, which defined as the lowest risks of AT-OF in the exposure-response curve (**Supplementary Figure S6**). Cold and warm effects were defined as the effect values of 2.5th (−2°C) and 97.5th (37°C) AT percentiles compared with OAT, respectively, to exhibit the associations between AT and osteoporotic fractures. We furtherly analyzed the association between AT and the number of hospitalizations for osteoporotic fractures in different gender (males and females) age (0–75 and over 75 years old) and the history of fracture (yes and no) groups. The potential interaction in subgroups (gender, age, and the history of fracture) were analyzed by *Z*-test (39). After estimating the health effects of AT in the initial model, four sensitivity analyses were conducted to assess the robustness of effects of AT on the number of hospitalizations for osteoporotic fractures. The first was compare the result of the cold effect of absolute temperature [optimum absolute temperature was 297.1 K (for the convenience of comparison, the temperature scale of Celsius degree is adopted, so 297.1 K = 24.0°C) (**Supplementary Figure S7**)] and AT; The second was adding six air pollutants ($PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3) in the model one by one; The third was changing the maximum lag days (from 10 to 9 or 11) and dfs (for AT from 5 to 4 or 6, for lag from 3 to 2 or 4) for the cross-basis function of daily mean temperature; The last one was changing the dfs for time (from 1 to 2 or 3), rainfall and sunshine duration (from 3 to 2 or 4) to examine the robustness of the results in our study.

Consistent with previous studies, the effects of AT were reported as relative risk (RR) and 95% confidence interval (CI). All statistical analyses were conducted by "dlnm" and "splines" packages in R software (version 4.0.5). Results with a 2-sided and $p < 0.05$ were statistically significant.

RESULTS

Table 1 shows the descriptive statistics of hospitalization data due to osteoporotic fracture (OF) as well as daily average meteorological factors in Wuhan, from January 1, 2017 to December 24, 2019. A total of 1,488 hospitalizations for osteoporotic fracture were collected from Wuhan Hospital of Traditional Chinese and Western Medicine. Males and patients with a history of fracture accounted for 22.04 and 20.56% of the whole patients. Approximately half of the patients were aged 75+ years. For meteorological factors, the daily mean AT and temperature were 18.5 and 17.5°C, respectively. During the study period, the daily mean relative humidity, wind speed, sunshine duration, and rainfall were 79.0%, 1.6 m/s, 4.6 h, and 3.0 mm, separately.

Supplementary Figure S8 shows the variations of daily mean apparent temperature, temperature, relative humidity, and wind speed from January 1, 2017 to December 24, 2019. Similar trends were observed between AT and temperature which were both reaching the peak in summer and dropping into low ebb in winter. Relatively higher values of AT than temperature were mainly found in warm season. However, no obvious trend changes were observed in relative humidity and wind speed. Spearman correlation coefficients between meteorological variables were shown in **Supplementary Figure S9**. The relationships of AT and relative humidity, wind speed, and rainfall were almost negative. The largest positive correlation with statistical significance were found between AT and temperature (correlation coefficient = 0.998, $P < 0.01$), as seen in **Supplementary Table S1**.

Supplementary Figure S6 illustrates the exposure-response curve between apparent temperature and the relative risks of hospitalization visits for osteoporotic fractures at lag 10 day. In general, a wide U-shape with large opening and lowest point at 25.8°C was observed, which corresponding to the minimal risks of AT. **Figure 1** shows the estimated values with 95%CI of cold and warm effects on the number of hospitalizations for osteoporotic fractures. Statistically significant relationships of lag-response were only found in cold effects. The largest RR values (−2.0 vs. 25.8°C) were 1.17 (95%CI: 1.01, 1.36) at lag 1 day in single-lag effects and 2.10 (95%CI: 1.34, 3.30) along 0–7 days in cumulative-lag effects (**Supplementary Table S2**). No associations between warm effect (37.0 vs. 25.8°C) and

TABLE 1 | The descriptions of hospitalizations for osteoporotic fracture and meteorological factors.

	All (%)	Mean	SD	Min	P25	Median	P75	Max
Hospitalization visits	1,488	1.4	1.3	0.0	0.0	1.0	2.0	8.0
Gender								
Male	328 (22.04)	0.3	0.6	0.0	0.0	0.0	0.0	3.0
Female	1,158 (77.82)	1.1	1.1	0.0	0.0	1.0	2.0	7.0
Age (years)								
<75	755 (50.74)	0.7	0.9	0.0	0.0	0.0	1.0	6.0
75+	733 (49.26)	0.7	0.9	0.0	0.0	0.0	1.0	5.0
History of fracture								
Yes	306 (20.56)	0.3	0.6	0.0	0.0	0.0	0.0	5.0
No	1,180 (79.30)	1.1	1.1	0.0	0.0	1.0	2.0	8.0
Meteorological factors								
AT (°C)	–	18.5	11.9	−7.1	7.9	18.9	28.7	40.3
Temperature (°C)	–	17.5	9.4	−3.8	9.2	18.1	25.8	33.9
Relative humidity (%)	–	79.0	10.6	41.0	72.0	79.0	87.0	100.0
Wind speed (m/s)	–	1.6	0.9	0.2	0.9	1.4	2.1	6.3
Sunshine duration (h)	–	4.6	4.2	0.0	0.0	4.4	8.4	13.0
Rainfall (mm)	–	3.0	9.4	0.0	0.0	0.0	1.1	174.7

Min, minimum; Max, maximum; SD, standard deviation.

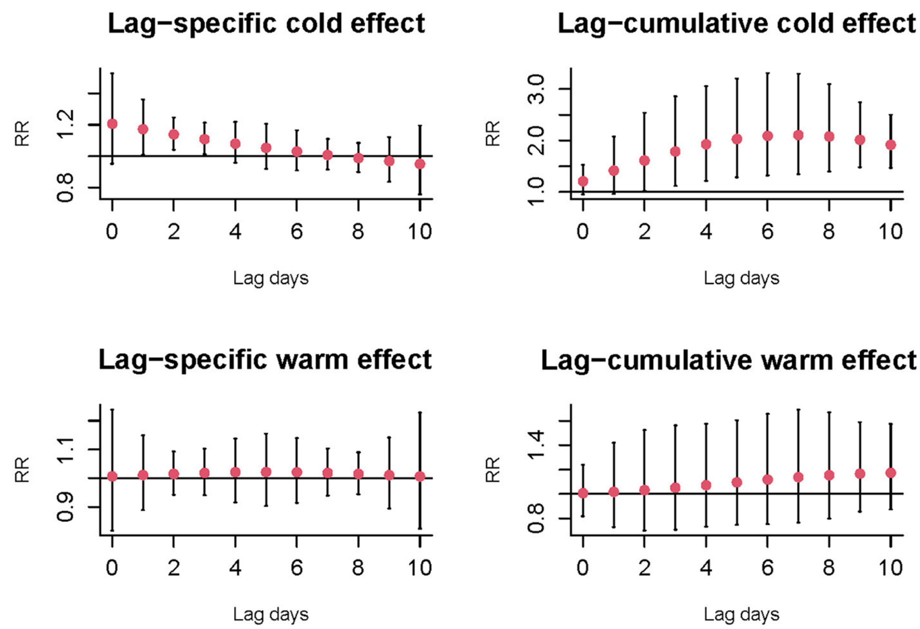

FIGURE 1 | The relative risks and 95%CI of cold (−2.0 vs. 25.8°C) and warm effect (37.0 vs. 25.8°C) on the number of hospitalizations for osteoporotic fractures at single and cumulative lag days.

osteoporotic fractures were identified in single and cumulative lag days.

Figure 2 shows the cold effects on the hospitalizations for osteoporotic fractures stratified by gender, age, and history of fracture. Significant risks of osteoporotic fractures for cold effects were only found in females [RR = 1.12 (95%CI: 1.02, 1.24) at lag 2 day], aged <75 years old [RR = 1.18 (95%CI: 1.04, 1.33) and 1.17 (95%CI: 1.04, 1.33) at lag 2 and 3 days, respectively] and history of fracture [RR = 1.39 (95%CI: 1.02, 1.90) and 1.27 (95%CI: 1.05, 1.53) at lag 1 and 2 days, respectively] (**Supplementary Table S3**). No significant associations of warm effects and osteoporotic fractures were observed in subgroup analyses, as seen in **Supplementary Figure S10** and **Supplementary Table S4**. The results of Z-test for the differences within each subgroup for the risks of cold effects at lag 2 day were shown in **Figure 3**. No statistically significant differences were found in gender, age, and

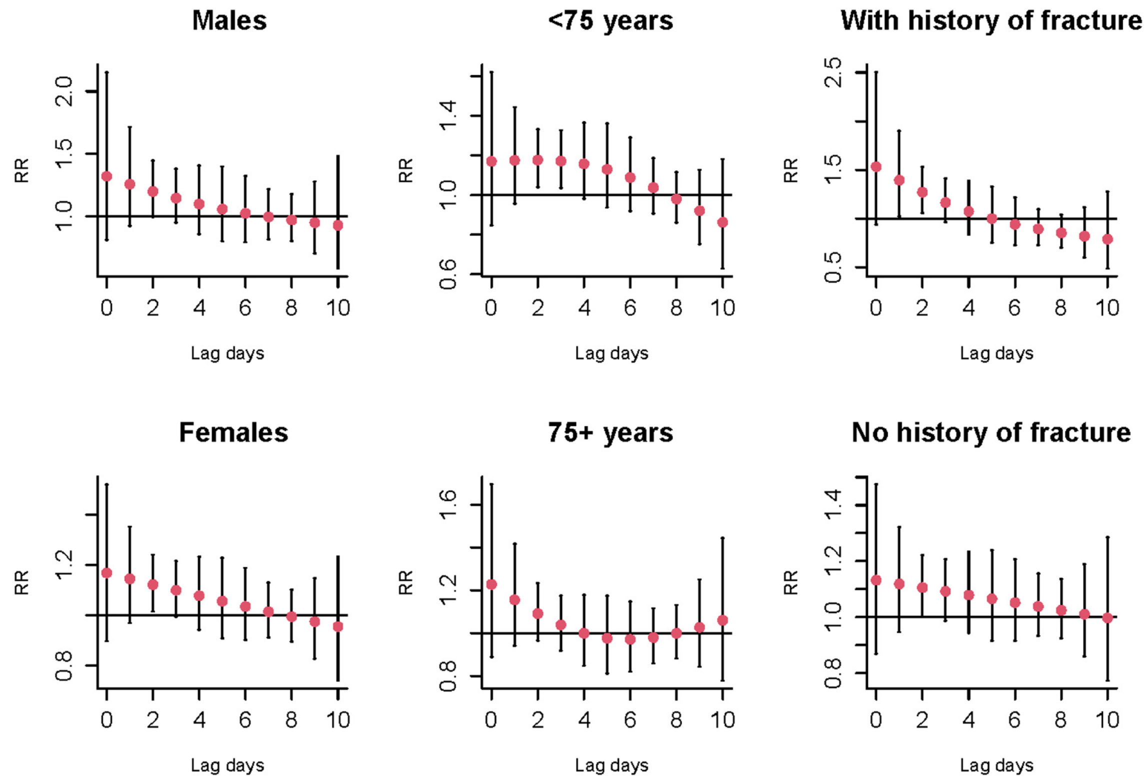

FIGURE 2 | The relative risks and 95%CI of cold effect (−2.0 vs. 25.8°C) on the number of hospitalizations for osteoporotic fractures stratified by gender, age, and history of fracture at different lag days.

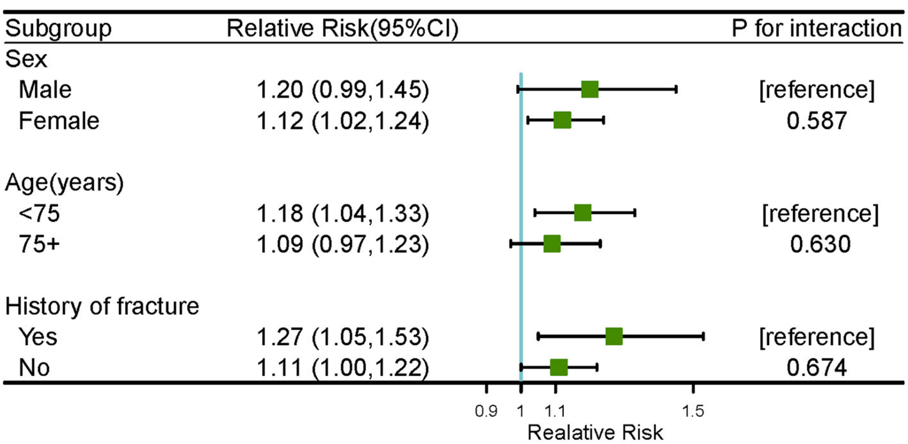

FIGURE 3 | The results of *Z*-test for cold effect (−2.0 vs. 25.8°C) on the number of hospitalizations for osteoporotic fractures within subgroup analyses at lag 2 day.

history of fracture subgroups (*P* for interaction were 0.587, 0.630, and 0.674, respectively).

Table 2 shows the relative risks and 95%CI of cold effect of absolute temperature and apparent temperature on the number of hospitalizations for osteoporotic fractures at lag 2 day. Similar effect patterns were observed in this two indicators. However, compared with absolute temperature, AT might be more sensitive to people who had the history of fracture [RR = 1.27, 95% CI: (1.05, 1.53)]. As seen in **Table 3**, though the values of RR were slightly changed after adjusting for air pollutants one by one, the cold effect of AT remained statistically significant. **Supplementary Table S5** summaries the relative risks and 95%CI of osteoporotic fractures for cold effects at lag 2 day in sensitive analyses. After changing the parameters for AT and maximum

TABLE 2 | The relative risks and 95%CI of cold effect of absolute temperature and apparent temperature on the number of hospitalizations for osteoporotic fractures at lag 2 day.

	Absolute temperature*	Apparent temperature**
	Cold effect	Cold effect
All	**1.14 (1.04, 1.25)**	**1.14 (1.04, 1.25)**
Gender		
Male	1.19 (0.97, 1.45)	1.20 (0.99, 1.45)
Female	**1.12 (1.01, 1.24)**	**1.12 (1.02, 1.24)**
Age		
<75	**1.19 (1.06, 1.35)**	**1.18 (1.04, 1.33)**
75+	1.12 (0.98, 1.29)	1.09 (0.97, 1.23)
History of fracture		
Yes	1.22 (0.98, 1.50)	**1.27 (1.05, 1.53)**
No	1.10 (1.00, 1.22)	1.11 (1.00, 1.22)

*Bold represents statistically significant; *Cold effect (0.5 vs. 24.0°C) of absolute temperature; **Cold effect (–2.0 vs. 25.8°C) of apparent temperature.*

TABLE 3 | The relative risks (95% CI) of cold effect after adjusting for air pollutants at lag 2 day.

	RR (95% CI)
Final model	**1.139 (1.041, 1.247)**
$+PM_{2.5}$	**1.135 (1.034, 1.246)**
$+PM_{10}$	**1.129 (1.028, 1.241)**
$+SO_2$	**1.138 (1.040, 1.246)**
$+NO_2$	**1.137 (1.040, 1.243)**
+CO	**1.136 (1.035, 1.246)**
$+O_3$	**1.115 (1.014, 1.226)**

Bold represents statistically significant.

lag days in cross-basis functions and the degrees of free for time (from 1 to 2 or 3), rainfall and sunshine duration (from 2 to 3 or 4) in the initial model, most of RR values also remained statistically significant, which meant our results and model were robust.

DISCUSSION

In this study, we applied generalized linear model combined with DLNM to explore the associations of AT and osteoporotic fractures in urban population of Wuhan, China. To our knowledge, this study was the first to analyze the effect of AT on hospitalizations for osteoporotic fractures in China. For all groups, only cold effect of AT had significantly nonlinear and delayed effects on hospital admissions for osteoporotic fractures was found. In addition, the female patients, patients aged <75 years and patients with history of fracture appeared to be more vulnerable to cold effect of AT since significant correlations were only observed in their subgroups, respectively. These findings might provide evidence that more targeted and effective preventive measures conducted by relative departments need to be adopt to these susceptible people.

We found significant association between low AT and the hospitalizations for osteoporotic fractures in the current study. In view of the highly identity between AT and air temperature, the cold effect was consistent with previous studies focused on temperature and fractures (8, 15, 40). As early as 2004, a Hungarian study pointed out that the prevalence of hypovitaminosis D during spring (71%) was higher than that in summer (46.3%) (35), which may affect bone health due to the limited absorption of calcium increased bone resorption (41). Lower AT usually accompanied by ice and snow weather may also lead to falls in the elderly, increasing the incidence of osteoporotic fractures (16, 42). In Australia, lower daily temperatures were significantly associated with higher hospitalization rates for fall related hip fractures in people aged over 75 years old (40). However, the significant difference of incidence of fractures in different temperatures, temperature changes, seasons and months were not observed in Southern England (33). The possible explanation might be that the climate and people's tolerance for temperature were different in various regions.

The specific biological mechanisms of the cold effect of AT and the hospitalizations for osteoporotic fractures were not clear yet. According to available studies, some possible mechanisms were exhibited in the followings: First, in cold environment, the duration of sunshine is usually short and the available vitamin D is limited, which aggravates the occurrence of osteoporosis and leads to osteoporotic fractures (35). Second, physical activity was proved to be linked with high bone mineral density, superior neuromuscular function, while lower temperature was a cause of reduced physical activity (36, 43). Third, lower temperature leads to impaired flexibility, decreased neuromuscular function and shortened response time, or has an impact on hemodynamic status and blood pressure, increasing the risk of falls (34, 44, 45). Fourth, lower temperature was associated with higher fracture rates only in people without influenza vaccination suggesting that influenza outbreaks may increase the risk of hip fractures (15). Finally, mice experiments revealed that cold stress could reduce the proliferation of bone marrow mesenchymal stem cells (BMMSCs), which were the main source of osteoblasts (46, 47).

Our results showed that the females seemed to be more vulnerable to cold effect than males. The subgroup analysis of gender was similar with some earlier studies focusing on the relationship between temperature and osteoporotic fractures (8, 35). A former study found the prevalence of low vitamin D disease associated with high incidence of osteoporosis was higher in females than males (35). Estrogen, promoted the proliferation and differentiation of osteoblasts by binding with estrogen receptor (ER) on osteoblasts, played an important role in bone metabolism (48). The decrease of estrogen secretion caused by menopause in women with higher plasma dipeptide peptide 4 (DPP4) levels will lead to an increase in bone turnover and the prevalence of osteoporotic fractures (49). However, the significant association between low temperature and fracture was also observed in males, which was thought to represent a vulnerable fracture in males who spend more time outdoors than women (8). More studies were warranted to provide evidence about whether females with postmenopausal osteoporosis have lower tolerance of cold effect.

In this study, the connection between cold effect of AT and risk of hospitalizations for osteoporotic fractures was only found in people aged <75 years. Levy et al. (32) reported similar findings with our study that the effect of cold weather on hip fracture rates was highest in younger persons. Younger people might have more exposure opportunities for cold effect of AT due to longer duration of time in outdoors, so that they would have a higher risk of hospitalization for osteoporotic fractures. However, significant association between lower daily air temperature with higher fall-related hip fracture hospitalizations in 75+ years old was also found in an Australian study (40). The inconsistent outcomes in these studies may be caused by different populations and lifestyle.

In single-day lag analysis of this study, the risk of hospitalizations for osteoporotic fractures associated with low AT were only found in people with a history of fractures. Former studies pointed out that 23% of subsequent fractures occur within 1 year and 54% within 5 years after the first fracture (50, 51). A meta-analysis found that regardless of the type of initial fracture, the risk of re-fracture was about twice that of people without a history of fracture, especially higher in patients with postmenopausal osteoporotic fractures (52). It is plausible that with bone mass rapidly lost due to the bed-rest and immobilization during the acute period after the fracture, the bone mineral density will continue to decline in following 3–6 months (53). This may explain the people with a history of fracture were more vulnerable to cold effect and increasing the risk of hospitalizations for osteoporotic fractures.

Prior epidemiological studies pointed out that warm effect of AT was associated with all-cause mortality and hospital admissions for cardiovascular diseases (54–56). However, no statistical significance was found in the warm effect of AT on the risk of hospitalizations for osteoporotic fractures in this study. A study conducted in Taiwan observed significant negative associations between ambient temperature and hip fractures, which indicated that higher temperature may have a protective effect in fractures and will not increase the risk of hospitalizations for osteoporotic fractures (36). The difference findings may be due to people living in different climatic environments with different tolerances to temperature. In addition, there may be certain time temporal trends in the association of ambient temperature and health (57, 58).

There were some strengths in this study. First, AT, the new comprehensive index about heat, may be more realistic and objective as an early warning indicator than temperature itself, which is widely accepted in earlier studies (37, 59, 60). Second, we compared the differences of subgroups affected by the cold effect. It may be conducive to more focused policy implementation in relevant prevention work. And the difference between subgroups with or without fracture history was also mentioned in similar studies for the first time. Third, this paper found a significant relationship between AT and osteoporotic fractures. This may provide a new idea for the following related research. Finally, the application of DLNM was scientific dealing with non-linear exposure–response relationships and delayed effects (61, 62).

Several limitations in this study should be recognized. First, meteorological data was obtained from one fixed-site meteorological monitoring station and the use of mean AT as proxies for personal exposure were inevitably expected to cause exposure misclassification (63, 64). More accurate ways, for example, estimating individual's exposure by simulating and calculating using satellite data based on home address, were warranted. Second, we could not acquire the data of individual diet, medication and physical activity, which might be confounding factors of the association of AT and bone strength. Lastly, the region we selected was limited to Wuhan, and the sample of hospitalizations is relatively small, lacking generalizability to other populations.

Findings of this study may provide some references for public health policy. In this study, AT has a cold effect on the risk of hospitalizations for osteoporotic fractures. Early warning according to the predicted meteorological data can be formulate by public health department. For example, the female patients, patients aged <75 years and patients with history of fracture can be checked or inquired regularly through the community or hospital system. Especially in China, where the phenomenon of empty nesters is very common, the mortality rate can reach 21% within 1 year once osteoporotic fractures occur (65). It is necessary to identify potential patients and take precautions earlier according to the correlation between AT and osteoporotic fractures. And early medical allocation is also theoretically feasible. The effect of other possible risk factors needs to be addressed by future studies. It is hoped that this study can draw more researchers' attention to make more improvement and exploration.

CONCLUSIONS

In conclusion, we investigate the effects of AT on the daily hospitalizations for osteoporotic fractures from 2017 to 2019 in urban population of Wuhan, China. Results in this study showed that short-term exposure to cold effect of AT was linked with the increased risk of hospitalizations for osteoporotic fractures at Wuhan Hospital of Traditional Chinese and Western Medicine, which meant AT was a novel indicator to estimate the relationship between environment and disease. Female patients, patients aged <75 years and patients with history of fracture possibly appeared to be more vulnerable to cold effect of AT. Consequently, public health departments should consider not only the health impact of daily mean temperature, but also AT, to formulate better preventive measures.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was approved by the Ethics Committee of Wuhan University.

AUTHOR CONTRIBUTIONS

WZ and NX: conceived and designed the study. GZho, GZha, and SZ: collected and cleaned the data. FZ and XuZ: performed the data analysis and drafted the manuscript. WZ and XiZ: helped to revise the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Association of Metals and Metalloids With Urinary Albumin/Creatinine Ratio: Evidence From a Cross-Sectional Study Among Elderly in Beijing

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Background: Environmental exposure to toxic elements contributes to the pathogenesis of chronic kidney disease (CKD). Few studies focus on the association of urinary metals and metalloids concentrations with the urinary albumin/creatinine ratio (UACR) among elderly, especially in areas and seasons with severe air pollution.

Objective: We aimed to evaluate the associations of urinary metals and metalloids concentration with UACR, which is an early and sensitive indicator of CKD.

Method: We conducted a cross-sectional study among 275 elderly people in Beijing from November to December 2016, which has experienced the most severe air pollution in China. We measured 15 urinary metals and metalloids concentration and estimated their association with UACR using a generalized linear model (GLM). Bayesian kernel machine regression (BKMR) and quantile g-computation (qgcomp) models were also conducted to evaluate the combined effect of metal and metalloid mixtures concentration.

Results: Of the 275 elderly people included in the analysis, we found that higher urinary Cu concentration was positively associated with UACR using GLM ($\beta = 0.36$, 95% CI: 0.25, 0.46). Using the BKMR model, we found that the change in UACR was positively associated with a change in urinary Cu concentration from its 25th to 75th percentile value with all other metals and metalloids concentration fixed at their 25th, 50th, or 75th percentile levels. Urinary Cu concentration had the most significant positive contribution (59.15%) in the qgcomp model. Our finding was largely robust in three mixture modeling approaches: GLM, qgcomp, and BKMR.

Conclusion: This finding suggests that urinary Cu concentration was strongly positively associated with UACR. Further analyses in cohort studies are required to corroborate this finding.

Keywords: urinary Cu, kidney function, UACR, elderly, quantile g-computation, BKMR

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem that imposes heavy burden on both developed and developing countries (1). The overall prevalence of CKD in China increased to 10.8% (2), and global CKD-related mortality rates increased by ∼14% from 1990 to 2010 (9.6-1.1 per 100,000) (3). As an organ with the ability to metabolize, the kidney is a target organ for metal and metalloid toxicity (4), which can accumulate in the nephron, leading to renal dysfunction. The 2012 Kidney Disease Improving Global Outcome (KDIGO) guidelines define CKD by estimated glomerular filtration rate (eGFR) or markers of kidney damage, such as albuminuria [defined as urinary albumin/creatinine ratio (UACR) $\geq$ 30 mg/g)] (5). Clinically, UACR has been considered an early and sensitive indicator to determine CKD (6). UACR is beneficial in that it has low requirements for samples, as it is noninvasive and can be detected using a spot urine sample rather than 24 h urine (7).

Metals and metalloids may be contained in soil, drinking water, food, ambient air and consumer products (8–14). For example, Pb released into the environment by petrol, domestic Pb-based paints and cigarette smoke (15, 16). Exposure to Cu and Se is mainly dietary, and both are naturally found in seafood, nuts, rice, whole grains, and some fruits and vegetables (17). The general population can also be exposed to Mn *via* traffic-related emissions, due to the use of Mn as an antiknock additive in gasoline (18). It is difficult to evaluate the real exposure of human body through a single or several external exposure media (i.e., air or water). Previous studies have reported that metals can enter the body through oral, inhalational, or transdermal routes, they circulate in the blood and are excreted in the kidney as urine (19–21). Urinary metal concentrations were mostly regarded as a reliable indicator of exposure as they can integrate multiple exposure sources (22, 23). Therefore, the study assessed human exposure to multiple metals by detecting metals in urine.

Metals and metalloids are known to be a risk factor of CKD (24), which may result in end-stage renal disease and increase the risk for all-cause mortality and cardiovascular disease (25). Although several studies have suggested an association between metals and metalloids concentration and kidney function (26–28), studies focusing on the possible relationship between multiple metals and metalloids concentration and UACR have been limited, especially among elderly. Additionally, humans are typically exposed to complex mixtures rather than single agents (29); thus, it is important to explore the health effects of metal and metalloid mixtures.

The traditional generalized linear model (GLM) was broadly used to estimate the association of a single metal or metalloid concentration with health outcomes based on the hypothesis that the association was linear. In recent years, weighted quantile sum (WQS) regression, quantile g-computation (qgcomp) and Bayesian kernel machine regression (BKMR) model have been proposed to investigate the effects of combined exposure. To further assess the contributing effects of individual metals or metalloids, WQS regression analysis was employed to estimate the combined and discrete effects of multiple predictors in the context of correlated high-dimensional mixtures (30). However, WQS regression should be based on the assumption of directional homogeneity, and individual exposures have linear and additive effects as well (31). A study reported that qgcomp is an adaptive method of WQS regression to estimate the association of metals and metalloids in mixtures in environmental epidemiology (32). The method has advantages over WQS, including that directional homogeneity of effect estimates is unnecessary (33). Considering the possibility of nonlinearity and interaction, BKMR was proposed to explore the relationship between metal and metalloid mixtures and health outcomes. Although these methods are gradually being applied, few studies have compared these models together to understand the stability of the results.

In this cross-sectional study, we selected 275 elderly who lived in Beijing for at least 1 year by November and December 2016, the season with the most severe air pollution. The association of multiple urinary metals and metalloids and their mixtures with UACR was examined. We selected 15 metals and metalloids (aluminum [Al], arsenic [As], barium [Ba], cadmium [Cd], cobalt [Co], chromium [Cr], cesium [Cs], copper [Cu], iron [Fe], manganese [Mn], nickel [Ni], lead [Pb], selenium [Se], strontium [Sr] and zinc [Zn]) based on demonstrated developmental nephrotoxicity in animal models (34, 35) and evidence from existing literature that identified associations with kidney parameters in people (19, 36, 37). We applied multiple models, including the GLM, BKMR and qgcomp models, to estimate the association of urinary metals and metalloids concentration with UACR and to explore the stability of the results among different models.

MATERIALS AND METHODS

Study Design and Participants

We conducted a cross-sectional study and utilized data based on communities distributed from south to north in Beijing, which experienced the nation's highest levels of $PM_{2.5}$ during the last 20 years (38). In 2016, the annual average concentration of $PM_{2.5}$ reached 73 $\mu g/m^3$ in Beijing according to the Ministry of Environmental Protection of China, while the China National Air Quality Standard for $PM_{2.5}$ is 35 $\mu g/m^3$ (39). Medical examinations and testing were administered to participants between November and December 2016 during the winter heating period, when Beijing became a hot spot for anthropogenic heavy metal emissions with the increase in coal burning, worsening the air pollution situation (40). Eligible participants were above 60 years of age and lived at least 1 year. We excluded subjects who were unable to complete anthropomorphic examinations or questionnaires. Furthermore, we excluded participants who had malignant tumors, liver disease and endocrine disease. We further excluded participants with missing or insufficient urine samples for detection, as well as missing other variables of interest. A total of 275 subjects were finally included in the analyses. Written informed consent was obtained from all participants. In addition, the study was approved by the institutional ethics committees of the Institute of Basic Medicine in the Chinese Academy of Medical Sciences.

TABLE 1 | Baseline information of the study participants ($n = 275$).

Characteristic	All participants ($n = 275$)
Age [years], mean ± SD	68.9 ± 6.8
BMI [kg/m^2], mean ± SD	24.5 ± 3.8
Sex, *n* (%)	
Male	122 (44.4)
Female	153 (55.6)
Education, *n* (%)	
Primary school or below	131 (47.6)
Middle school	55 (20.0)
High school or above	87 (31.6)
Refuse to answer	2 (0.7)
Smoking status, *n* (%)	
Never	187 (68.0)
Current	42 (15.3)
Former	41 (14.9)
Refuse to answer	5 (1.8)
Drinking status, *n* (%)	
Never	157 (57.1)
Current	21 (7.6)
Former	90 (32.7)
Refuse to answer	7 (2.5)
Urinary creatinine [μg/g], median (IQR)	9.3 (5.5–12.1)
UACR [mg/g], median (IQR)	6 (3–18)

BMI, body mass index; IQR, interquartile range; SD, standard deviation; UACR, urinary albumin/creatinine ratio.

Determination of Urinary Metal and Metalloid Concentrations and UACR

Morning first void urine samples were collected in polypropylene containers and stored at −80°C. We measured 15 urinary metals and metalloids, including Al, As, Ba, Cd, Co, Cr, Cs, Cu, Fe, Mn, Ni, Pb, Se, Sr and Zn, using inductively coupled plasma-mass spectrometry (ICP-MS) with a Nexion 300D (Perkin-Elmer SCIEX, USA), which has been described in detail in previous study (41). The urine samples were thawed at room temperature for subsequent processing. One milliliter of urine was made up to 15 mL with 0.5% (v/v) HNO_3 and 0.02% Triton X-100 and treated by sonication in an ultrasonic water bath for 1 h at 60°C. In terms of quality control procedures, urinary metals and metalloids were measured three times and averaged for analysis. Rhodium (Rh) element standard solution (Central Iron and Steel Research Institute, National Testing Center for Iron and Steel Materials) was used as the internal standard solution, diluted to 10.0μg/L with blank solution. Besides, the urine quality control samples of trace element (Trace Element Urine L-1 ROU, REF: 210613, LOT: 1706877, Seronorm, Norway) was used as certificated reference material (CRM), and the measured concentrations of each metal is within the 95 % CI provided by CRM. Moreover, the spiked recovery samples were measured every 20 specimens to ensure the correct analysis of urine samples. Only when the quality control sample is within the normal range (e.g., the recovery rate is in the range of 80-120%) will we proceed with the subsequent analysis. Additionally, the intra-assay and inter-assay coefficients were <10% (see **Supplementary Tables S1, S2** for more validation parameters for urinary metals and metalloids). The value below the limit of detection (LOD) was assigned LOD/2.

Considering the concentration dilution of urine, the concentrations of urinary metals and metalloids were all corrected by urinary creatinine. Creatinine-adjusted urinary metal and metalloid concentrations were included in subsequent analyses. We measured urinary creatinine and albumin (mg/dL) on a Beckman Coulter analyzer (AU5800 Analyzer, Beckman Coulter, Brea, CA, USA) from morning first void spot samples. Urinary creatinine was measured by the sarcosine oxidase method, and albumin was measured by immunoturbidimetry. UACR (mg/g), which is an indicator of albuminuria, was determined. Elevated UACR is defined as an abnormally high urine albumin concentration (42).

Covariate Assessment

Information on demographic characteristics and lifestyle factors was collected by registered physicians using standard questionnaires, including age, sex (male/female), education level (primary school or below, middle school, high school or above), smoking status (never, current, former), drinking status (never, current, former), hypertension (yes/no) and diabetes (yes/no). Current smokers were identified as smoking more than one cigarette or cigar or water pipe/day over the last 6 months. Current drinking was identified as drinking alcoholic beverages at least once per week over the last 6 months. Former smokers/drinkers were identified as quitting smoking/drinking for more than six months.

Participants were examined according to a standardized protocol by registered physicians, including weight, height, systolic blood pressure (SBP) and diastolic blood pressure (DBP). BMI (kg/m^2) was calculated as weight divided by height squared. Blood pressure was measured on the right arm after a 15 min rest period in the sitting position by a mercury sphygmomanometer. SBP and DBP were calculated as follows: if the second and third measurements are <5 mmHg, take the average value; otherwise, re-measure until the difference is <5 mmHg. Hypertension was defined using SBP≥140 mmHg and/or DBP≥90 mmHg, intake of any antihypertensive drug, or both (43). Diabetes was defined using fasting glucose ≥7.0 mmol/L, 2 h glucose ≥11.1 mmol/L, intake of any antidiabetic drug, or both (44). According to the KDIGO (45), (a) an eGFR of <60 mL/min/1.73 m^2, (b) albuminuria (defined as UACR ≥ 30 mg/g), or (c) a medication regimen for treating renal dysfunction is sufficient for CKD diagnosis (46).

Statistical Analysis

Descriptive statistics were used to describe the frequency and proportion of the demographic and clinical characteristics. We described normally distributed data using means with standard deviations (SD), and the median and interquartile range (IQR) were used to describe data with skewness distribution. Both creatinine-adjusted urinary metals and metalloids and UACR

TABLE 2 | Detection rates and distribution for 15 adjusted urinary metals and metalloids.

Element (μg/g creatinine)	%>LOD[a]	GM(GSD)[b]	Quartiles of adjusted urinary elements			
			25th	50th	75th	90th
Al	100.00	4.358 (2.144)	2.484	4.264	7.274	12.776
As	99.99	2.063 (2.200)	1.377	1.954	3.347	5.235
Ba	99.97	0.307 (3.424)	0.169	0.288	0.776	1.445
Cd	99.95	0.049 (3.295)	0.038	0.066	0.109	0.153
Co	99.99	0.104 (2.386)	0.051	0.105	0.212	0.338
Cr	100.00	0.274 (1.668)	0.189	0.267	0.381	0.569
Cs	100.00	0.947 (1.898)	0.716	0.966	1.324	1.724
Cu	99.99	1.082 (1.750)	0.749	1.093	1.601	2.118
Fe	100.00	3.903 (2.096)	2.170	3.850	6.474	10.753
Mn	61.80	0.031 (4.236)	0.008	0.027	0.094	0.235
Ni	100.00	0.311 (3.202)	0.188	0.375	0.736	1.077
Pb	99.86	0.118 (3.831)	0.042	0.141	0.325	0.631
Se	100.00	3.391 (2.153)	1.667	3.926	6.168	8.911
Sr	100.00	11.499 (1.909)	7.926	11.872	18.078	24.720
Zn	100.00	46.847 (1.776)	32.610	47.838	68.342	102.643

[a] *% > LOD, detection rate above limit of detection.*
[b] *GM, geometric mean; GSD, geometric standard deviation.*

were required to logarithmically convert to an approximate normal distribution.

GLM Analysis

GLMs were used to analyze the association of individual urinary metal and metalloid concentrations with UACR. We conducted linear regression to explore the associations [estimated by regression coefficient β and its 95% confidence interval (CI)] between log–transformed urinary metal and metalloid concentrations as continuous independent variables and UACR as continuous dependent variables. Multiple comparisons were accounted for using the Benjamini and Hochberg method for false discovery rates (FDR) (47). In addition, the urinary metal concentrations were divided into 3 categories in terms of the tertile distribution. The tertile with the lowest value of urinary metal concentration was regarded as reference, regression coefficient β and 95% CI were also reported to indicate the association between urinary metal concentration and UACR in each tertile, respectively. Based on prior knowledge and literature accumulation (7, 48, 49), we adjusted age, sex, BMI, education levels, smoking status, drinking status, hypertension and diabetes in the model.

BKMR Analysis

To further consider the possibility of nonlinearity and interaction and explore the health effects of metals and metalloids in mixtures, we also conducted a BKMR model to estimate the associations between metal concentration and kidney function (50). Combining Bayesian and statistical learning methods, BKMR was introduced to regress an outcome variable on a nonparametric term of exposure mixture (50). We explored the overall association of metal and metalloid mixtures concentration in relation to UACR and conducted the dose-response association of single metals and metalloids, as other metals and metalloids concentration were fixed at the 50th percentile. In addition, we estimated the risk difference between a single exposure at the 75th percentile and an exposure at the 25th percentile, and all remaining metals were fixed at the 25, 50, or 75th percentile level. We also further explored the specific interactions exposed on UACR. In addition, we estimated risk differences when a single metal or metalloid was at the 75th percentile compared to 25th percentile, and other metals and metalloids were fixed at their 25, 50, or 75th percentile levels. The specific interactions between metals and metalloids on UACR were further explored. We used Markov chain Monte Carlo algorithm to implement BKMR variable selection model with 25,000 iterations. The confounding factors that were adjusted in the BKMR were the same as those in the GLM.

qgcomp Analysis

Individual associations of metals and metalloids in the mixture with health outcome can be inverse; thus, qgcomp was introduced. Unbiased estimation of the overall mixture effects is produced within the coverage of small sample size and acceptable CI. qgcomp used a parametric GLM-based application of g-calculation to evaluate the effect of increasing all metals and metalloids in the mixture by a quarter simultaneously (31). The advantage of qgcomp is that metals and metalloids can interact with outcomes in any direction (21). This method is applied in following steps. First, all elements were transformed into quantiles. Second, a linear model was fit between the elements, UACR and covariates, including age, sex, BMI, education levels, smoking status, drinking status, hypertension and diabetes. Third, weights are defined for each element, corresponding to the

TABLE 3 | Estimated associations between urinary elements and UACR in GLM[a].

Elements (μg/g creatinine)	β (95% CI)	R^2	*P*-value	P_{FDR}
Al	0.00 (−0.09, 0.09)	0.25	1.00	1.00
As	0.05 (−0.06, 0.16)	0.25	0.36	0.61
Ba	0.04 (−0.03, 0.10)	0.25	0.26	0.61
Cd	0.03 (−0.04, 0.10)	0.25	0.46	0.61
Co	0.03 (−0.06, 0.12)	0.25	0.53	0.61
Cr	0.03 (−0.10, 0.17)	0.25	0.64	0.68
Cs	0.09 (−0.04, 0.22)	0.26	0.18	0.61
Cu	**0.36 (0.25, 0.46)**	0.39	**<0.01**	**<0.01**
Fe	0.12 (0.02, 0.22)	0.27	0.02	0.14
Mn	−0.02 (−0.07, 0.03)	0.25	0.45	0.61
Ni	0.03 (−0.04, 0.11)	0.25	0.39	0.61
Pb	0.03 (−0.03, 0.09)	0.25	0.33	0.61
Se	0.06 (−0.05, 0.17)	0.25	0.29	0.61
Sr	0.04 (−0.08, 0.16)	0.25	0.53	0.61
Zn	0.14 (0.01, 0.28)	0.27	0.04	0.19

[a]The Model was adjusted for age, sex, BMI, education levels, smoking status, drinking status, hypertension and diabetes.
Boldface type indicates effect estimates were statistically significant (p-value < 0.05).

strength of the relationship between the element and UACR. The overall effect of the mixture can be interpreted as the change in UACR per quantile of change in all elements while controlling for covariates. If the element has different effects in different directions, the positive or negative weights are interpreted as the percentage of exposure effects that have a negative (or positive) effect on UACR.

Sensitivity Analyses and Stratify Analysis

Considering that CKD status may be a collider between urinary metals and UACR, we did not adjust for CKD status in the main model. However, to examine whether CKD status may confound the association between urinary elements and UACR, we further added the CKD status (yes/no) in sensitivity analyses. We also eliminated the outliers of urinary Cu which above the mean concentration ±3 SD to explore the stability of the results.

In the stratified analysis, we conducted the stratified analysis by age (<65 years/above age 65 or more), gender (male/female), smoking status (yes/no), and drinking status (yes/no). Multiple comparisons were also accounted by P_{FDR}.

All analyses were carried out in R software (R version 3.6.2) and with the packages "bkmr", "gqcomp" and "ggplot" for plotting the quantification and visualization results of the BKMR model.

RESULTS

Demographic Characteristics

Table 1 presents the demographic and clinical characteristics of the 275 study participants (122 men and 153 women), with a mean age of 68.9 years and a mean BMI of 24.5 kg/m^2. More than half of the participants never smoked (68.0%) or drank (57.1%). The median (25, 75th percentile) of clinical values were 6 (3, 18) mg/g UACR and 9.3 (5.5, 12.1) μg/g urinary creatinine. The LOD, geometric mean concertation (GM), geometric standard deviation (GSD) and distribution of 15 urinary elements are shown in **Table 2**. The concentrations of most urinary metals and metalloids were higher than the LOD.

Results of Main Analysis

Association Between Urinary Element Concentrations and UACR in GLM

The relationships between individual adjusted urinary elements and UACR in GLM are shown in **Table 3.** We observed that urinary Cu, Fe and Zn concentrations were positively associated with UACR after adjustment for age, sex, BMI, education levels, smoking status, drinking status, hypertension and diabetes in a single metal and metalloid model. Urinary Cu had the highest estimate effect ($\beta = 0.36$, 95% CI: 0.25 to 0.46; $R^2 = 0.39$, *P*-value $= 2.82 \times 10^{-10}$), followed by Fe ($\beta = 0.12$, 95% CI: 0.02 to 0.22; $R^2 = 0.27$, *P*-value $= 0.02$) and Zn ($\beta = 0.14$, 95% CI: 0.01 to 0.28; $R^2 = 0.27$, *P*-value $= 0.04$). After FDR adjustment, only urinary Cu concentration was remained significantly and positive associated with UACR ($P_{\text{FDR}} < 0.05$). Comparing with the lowest tertile, the total population demonstrated significant increased UACR in the third tertile of urinary Cu ($\beta = 0.55$, 95% CI: 0.37-0.73) and urinary Fe ($\beta = 0.29$, 95% CI: 0.10-0.49) (**Supplementary Table S3**).

Association Between Urinary Element Concentrations and UACR in qgcomp

In the qgcomp mixtures approach (**Figure 1**), a marginal association was observed between the urinary element mixture concentration and higher UACR ($\beta = 0.07$, 95% CI: −0.08, 0.22). Urinary Cu (59.15%) concentration had the greatest positive contribution to the overall effect, and urinary Mn (29.15%) concentration had the largest negative weight.

Association Between Urinary Element Concentrations and UACR in the BKMR Model

We estimated the overall association analysis that regarded the urinary elements as a mixture and found a marginal positive correlation trend with UACR, which was similar to the result of qgcomp (**Figure 2A**). To further explore potential nonlinear relationships, we conducted univariate exposure-response functions (**Figure 2B**). The plot indicates a nonlinear association between urinary Cu concentration and UACR. We further estimated univariate summaries of the change in the UACR associated with a change in a single metal or metalloid from its 25th percentile to 75th percentile, where all of the other pollutants are fixed at a particular threshold (25, 50, or 75th percentile) (**Figure 2C**). Urinary Cu is the only element displaying a significant effect, and its positive association with UACR appears stronger at lower percentiles of other elements. An approximately S-shaped dose-response curve for Cu was observed, and the CI became wider as observations became less frequent for high and low Cu concentrations. The single-pollutant estimates from **Figure 2D** suggested that most elements have no interaction with each other except for Cu and Cs and Cu and Zn.

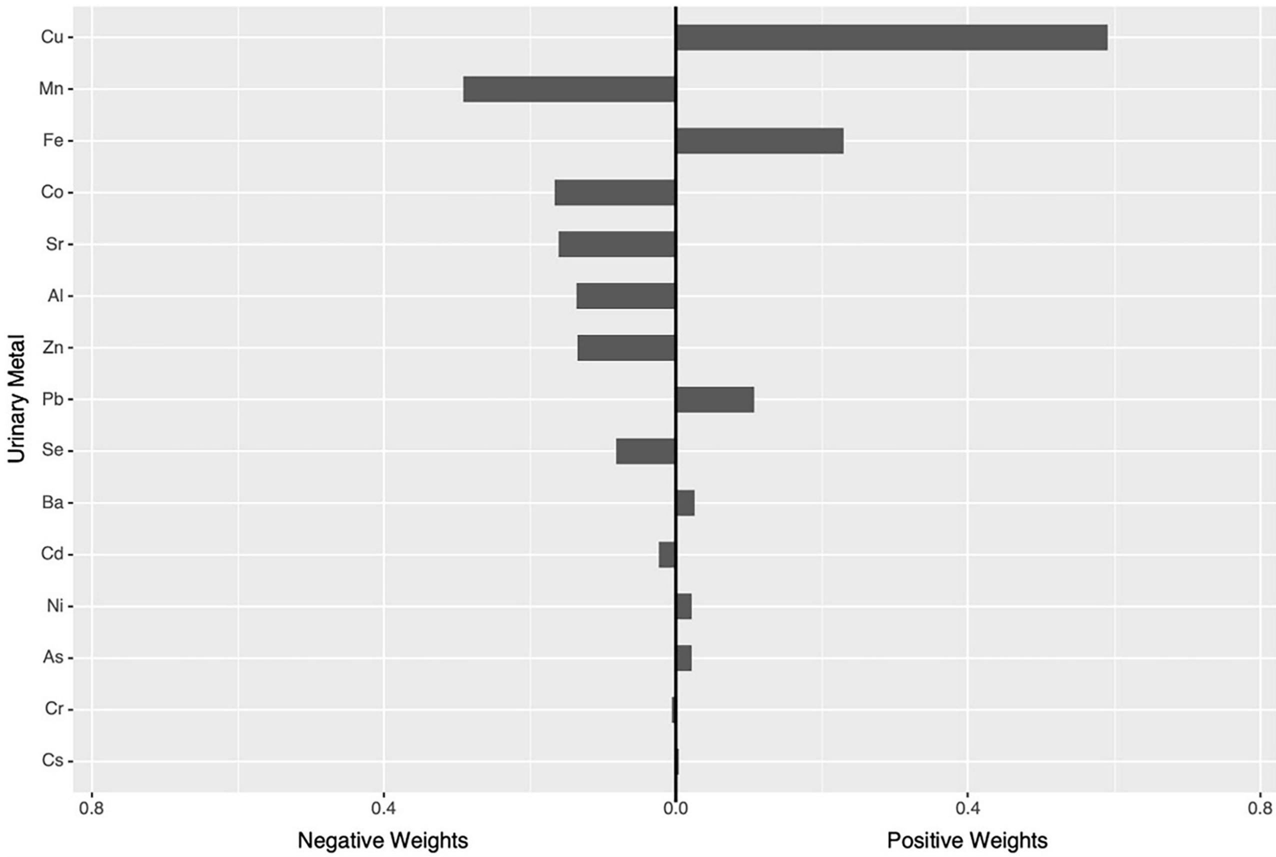

FIGURE 1 | qgcomp model[a] regression index weights for UACR. [a]The Model was adjusted for age, sex, BMI, education levels, smoking status, drinking status, hypertension and diabetes.

Results of Sensitivity and Stratification Analysis

The results of the sensitivity analysis suggested that our findings were robust. **Supplementary Figure S1** shows that urinary Cu remained significantly positively associated with UACR after additionally adjusting for CKD status ($\beta = 0.17$, 95% CI: 0.09, 0.25). We observed that the CI of the two tails in is very wide in **Figure 2B**, which may be due to the influence of outliers on the results. Thus, we excluded the outliers of urinary Cu concentration which above the mean concentration ±3 SD and found a linear positive association between urinary Cu and UACR in BKMR (**Supplementary Figure S2**).

Stratified analysis of our data showed significantly positive associations between urinary Cu and UACR in all stratified analyses ($P < 0.05$) (**Supplementary Tables S4,S5**). The estimated effects were higher in the above 65-year-old, female, smoking and drinking populations.

DISCUSSION

In this study, the association of multiple urinary elements and element mixtures concentration with UACR was investigated in typical severe air polluted areas and seasons. We found that urinary Cu concentration was significantly and positively associated with UACR in GLM, BKMR and qgcomp, which indicates that Cu was associated with an increased risk of albuminuria. To better understand the results, we also supplemented the assumptions, advantages and disadvantages of each model in supplementary (**Supplementary Table S6**).

To compare the concentration of urinary metals with published studies, we have searched and included several studies if they had an observational design; were conducted on general participants without environmental or occupational exposure; and reported data on exposure to metals of interest in this study (36, 51–54). By comparing with other studies (**Supplementary Table S7**), we found that most of urinary metals concentration in this study are lower than published studies, such as Cu, Al, Co, Fe, Mn and Sr. On the contrary, the concentrations of Cs, Se and Zn were higher than published studies. Besides, some metals, such As, Ba, Cd, Cr, Ni, and Pb, are in the range of published studies.

Cu exists widely in nature and can enter the human body through air, soil, water and food. It has been reported that Cu was one of the most abundant particulate matter components, and it was consistently quantified in urine (55). Additionally, Cu

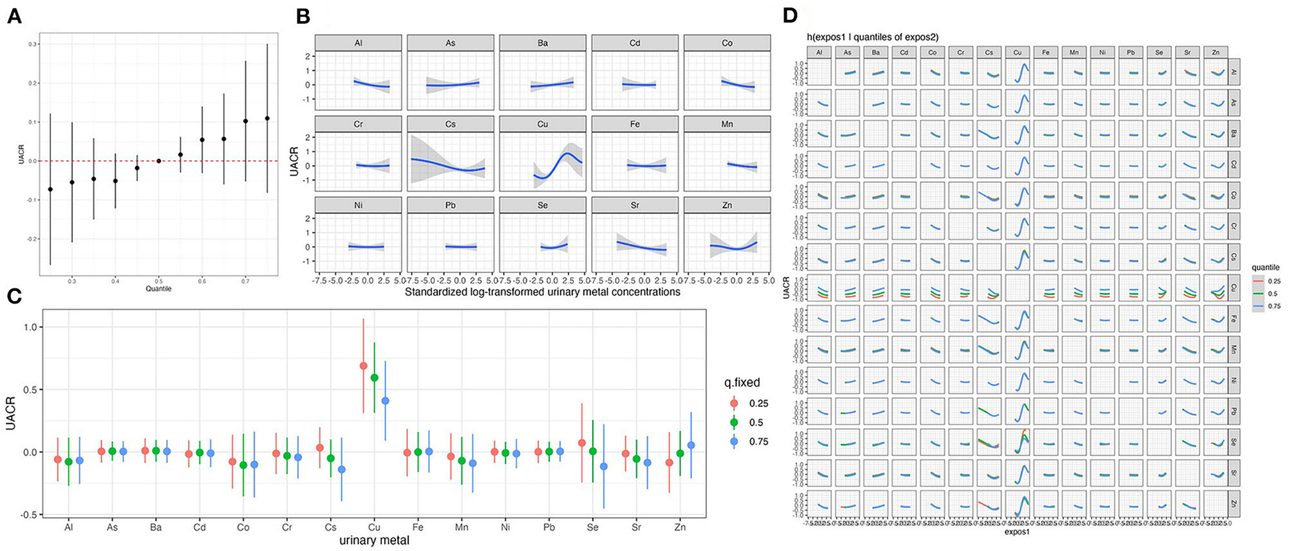

FIGURE 2 | Joint effect of the urinary metal and metalloid mixture on UACR by Bayesian Kernel Machine Regression[a]. **(A)** Overall associations between the urinary metal and metalloid mixtures and UACR. **(B)** Univariate exposure-response curves for individual metal. **(C)** The single-exposure effect of each metal. **(D)** Bivariate exposure response functions for each of the urinary metal and metalloid. [a]The Model was adjusted for age, sex, BMI, education levels, smoking status, drinking status, hypertension and diabetes.

remains in the upper part of the soil for a few centimeters, and the majority of Cu in water results from the natural runoff of soil Cu (56). Foods with relatively high Cu content include whole grains, dried fruits, mushrooms, beans, etc. The concentration of Cu in food varies from 0.2 to 44 ppm by wet weight (57). As a relatively short half-life, urinary Cu is mostly regarded as a reliable indicator of recent exposure. Therefore, urinary Cu concentration are typically used to assess Cu exposure, as they can integrate multiple exposure sources, such as air, soil, water and food (22, 23).

Albuminuria is an early indicator of glomerular damage, and it can lead to changes in glomerular filtration rate. Some studies have observed the effect of albuminuria on renal function (58). Increased albuminuria can determine whether immediate therapeutic intervention is required (59). Our study revealed a stable positive association between urinary Cu concentration and UACR. In the GLM, urinary Cu concentration was positively associated with UACR (β = 0.36, 95% CI: 0.25, 0.46) after adjusting for age, sex, BMI, education level, smoking status, drinking status, hypertension and diabetes. The GM (GSD) of the adjusted urinary Cu concentration was 1.08 (1.75) µg/g creatinine, which was lower than other studies (60). A cross-sectional analysis from China (Taiwan, $N = 2{,}447$ adults) showed that urinary Cu (15 µg/L) concentration was positively associated with albuminuria (36). Consistently, another China Study [Hunan, $N = 3{,}553$ adults] demonstrated positive dose-response relationships between urinary Cu concentration (median: 14.57 µg/L) and abnormal eGFR (odds ratio [OR] = 3.70, 95% CI: 1.92, 7.14) (19). Johnson et al. (61) found that among participants with CKD, a majority of participants were female. This study supported this finding in females, resulting in a higher likelihood of albuminuria. Urinary Cu concentration were found to be higher in males than in females in a study conducted in Wuhan among 226 individuals with a mean age of 43.6 years (60), which indicated more chronic exposure for males.

Cu is an essential trace element and cofactor of several enzymes, and it is involved in physiological pathways such as heme synthesis and iron absorption (62). Previous histopathological examination found that Cu could cause kidney dysfunction, characterized by degeneration of tubule cells (apoptotic or necrotic) (63, 64). An experimental study showed a time-dependent increase in apoptosis in chickens exposed to Cu. Increased apoptosis index and leakage of blood urea nitrogen (BUN) and creatinine suggest that Cu may lead to kidney dysfunction (65). Previous studies have shown that Cu can induce kidney dysfunction through oxidative damage, mitochondria damage (65, 66). The toxicity of excessive Cu is primarily involved in the generation of reactive oxygen species (ROS), which in turn lead to inhibited levels of antioxidant enzyme and lipid peroxidation, ultimately causing the elevations of BUN and creatinine may lead to the elevations of BUN and creatinine (67, 68). In addition, excessive endogenous ROS alters mitochondrial inner membrane structure, resulting in leakage of cytochrome-c, which further activates caspases (69). Caspase-3 executes the apoptosis phase and acts as a significant contributor to nephrotoxicity (70).

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There are some limitations in our study. The long-term clinical outcomes and causal relationships could not be confirmed given the cross-sectional study design. Long-term cohort studies are needed to verify our results, including serial measurements of heavy metals and renal function. Besides, this study was carried out among elderly over 60 years old and in a single city, so the extrapolation of the results needs to be further discussed.

The present study also has several strengths. First, we focused on an early indicator of glomerular damage, UACR, which is noninvasive and provides an early warning. Second, multiple statistical methods, including GLM, BKMR and qgcomp, were used to verify the stability of the results. Third, the study conducted in areas with high levels of air pollution and during periods of high levels of air pollution provides evidence to further understand the effects of urine metals on humans.

CONCLUSION

In the area and time of serious air pollution, we found a stable positive association between urinary Cu and UACR. Future research may focus on prospective studies of mixture exposure and renal function, as well as a better understanding of the complex biological mechanisms of chemical mixtures affecting the kidneys and other organ systems.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Ethics Committees of the Institute of Basic Medicine in the Chinese Academy of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AL and JZ: conceptualization, investigation, data curation, methodology, data analysis, writing—original draft preparation, reviewing and editing, and funding acquisition. LL, YM, QZ, MZ, JX, and XG: resources, data collection—organization and completion of filed research work, and writing—reviewing and editing. QX: writing—reviewing and editing, supervision, and funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.832079/full#supplementary-material

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Association Between Sulfur Dioxide and Daily Inpatient Visits With Respiratory Diseases in Ganzhou, China: A Time Series Study Based on Hospital Data

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Background: Sulfur dioxide (SO_2) has been reported to be related to the mortality of respiratory diseases, but the relationship between SO_2 and hospital inpatient visits with respiratory diseases and the potential impact of different seasons on this relationship is still unclear.

Methods: The daily average concentrations of air pollutants, including SO_2 and meteorological data in Ganzhou, China, from 2017 to 2019 were collected. The data on daily hospitalization for respiratory diseases from the biggest hospital in the city were extracted. The generalized additive models (GAM) and the distributed lag non-linear model (DLNM) were employed to evaluate the association between ambient SO_2 and daily inpatient visits for respiratory diseases. Stratified analyses by gender, age, and season were performed to find their potential effects on this association.

Results: There is a positive exposure-response relationship between SO_2 concentration and relative risk of respiratory inpatient visits. Every 10 $\mu g/m^3$ increase in SO_2 was related to a 3.2% (95% CI: 0.6–6.7%) exaltation in daily respiratory inpatient visits at lag3. In addition, SO_2 had a stronger association with respiratory inpatient visits in women, older adults ($\geq$65 years), and warmer season (May-Oct) subgroups. The relationship between SO_2 and inpatient visits for respiratory diseases was robust after adjusting for other air pollutants, including PM_{10}, NO_2, O_3, and CO.

Conclusion: This time-series study showed that there is a positive association between short-term SO_2 exposure and daily respiratory inpatient visits. These results are important for local administrators to formulate environmental public health policies.

Keywords: sulfur dioxide, air pollution, respiratory disease, inpatient visits, time-series analysis, generalized additive models, distributed lag non-linear models

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INTRODUCTION

Air pollution is one of the most important public health problems around the world (1). Sulfur dioxide (SO_2), mainly comes from various industrial processes, transportation, and vehicles, power plants, and fuel (coal) combustion, is one of the most common and irritant air pollutants in developing countries and industrialized areas (2–5). Several epidemiological studies have revealed that SO_2 exposure is related to human respiratory health (6, 7), including stimulating the respiratory tract (8), leading to the decline of pulmonary function (9, 10), and the increased mortality due to respiratory diseases (11, 12). However, there are few studies on the relationship between SO_2 and respiratory morbidity in developing countries. Inpatient visit is an important indicator of morbidity and has been widely used to assess the adverse effects associated with atmospheric pollutants (13). Therefore, it will be helpful to understand the impact of SO_2 on the respiratory system by evaluating the relationship between ambient air SO_2 and the number of hospitalized cases of the respiratory system.

Ganzhou is located in the southern part of Jiangxi Province. The ambient temperature and lifestyle of Ganzhou are typical of southern China. In 2019, the mean concentrations of PM_{10}, SO_2, NO_2, O_3, and CO in Ganzhou were 51, 12, 22, 74, and 1.2 mg/m^3, respectively. Except for SO_2, the concentrations of other air pollutants in Ganzhou were lower than the mean concentration of 337 Chinese cities (63 μg/m^3 for PM_{10}, 11 μg/m^3 for SO_2, 27 μg/m^3 for NO_2, 148 μg/m^3 for O_3, and 1.4 mg/m^3 for CO, respectively) (14). Compared with lower levels of other air pollutants, the concentration of SO_2 in Ganzhou is higher than that of the national average in China, drawing more attention to the potential respiratory health damage caused by SO_2.

In this study, the daily average concentrations of air pollutants, including SO_2 from 2017 to 2019, were collected from the local Environmental Protection Bureau. The respiratory inpatient visits were recorded during the same period in the biggest hospital in Ganzhou. We analyzed the association between the level of SO2 exposure and the daily respiratory inpatient visit, investigated populations more sensitive to SO_2 exposure, assessed the potential impact of seasonal changes on SO_2 lagging effects, and explored the exposure-response relationship between SO_2 concentrations and different population subgroups.

METHODS

Study Area

Ganzhou (24°29′ - 27°09′ N; 113°54′ - 116°38′ E) is located in the southern region of China. The terrain of the area is dominated by mountains and hills. Ganzhou has a total population of 9.82 million and an area of 39,379 km^2, accounting for 23.6% of the total area of Jiangxi. The area is characterized by a subtropical monsoon climate. The average annual rainfall in Ganzhou in 2020 is 1,706.4 mm; the average temperature is 19.9°C; the average sunshine hours is 1,637.9 h (15).

Data Collection

In this time-series analysis study, we extracted the daily respiratory inpatient visits from January 1, 2017, to December 31, 2019, from the medical database of the largest hospital (the First Affiliated Hospital of Gannan Medical University) in Ganzhou. A total of 9,668 respiratory inpatient visits were recorded during the study period. The respiratory inpatients were identified by the primary code of admission diagnosis (ICD-10: J00–J99). The concentration data of atmospheric pollutants in this study came from the Ganzhou Environmental Protection Bureau. There were five air monitoring stations in the city, and the mean daily concentrations of ambient PM_{10}, SO_2, NO_2, O_3, and CO were collected by these fixed monitoring stations. The daily temperature and humidity data during the study period were collected from the Ganzhou Meteorological Bureau. The daily air pollutant concentrations and meteorological data were not missing.

Statistical Analysis

Daily inpatient visits are generally considered to be rare events and have a Poisson distribution. Therefore, this study used the generalized additive model (GAM) and the distributed lag non-linear model (DLNM) to investigate the relationship between SO_2 and respiratory daily hospitalizations. Due to potential non-linear effects, natural spline functions were used to control the confounding factors, such as long-term trends, relative humidity, temperature, day of the week effect, and the effect of holidays. The GAM was selected to evaluate the health effects of SO_2 under different lag days (including single-day lag effects and multi-day lag effects). Referring to previous studies (16, 17), the model of the hysteresis effect of SO_2 is as follows:

$$Log[E(Y_t)] = \beta X_t + ns(time,\ df = 7/per\ year) + ns(Temp, df = 3) + ns(RH, df = 3) + DOW + \ Holiday + \alpha$$

where $E(Y_t)$ means the expected number of inpatient visits for the respiratory system at day t; X_t and β represent the concentration of SO_2 in the atmosphere on day t and the regression coefficient, respectively; ns is natural spline function; df refers to the degrees of freedom; DOW means the day of the week; Holiday indicates the effect of holidays; α refers to a constant.

The DLNM was used to reflect the exposure-response relationship between SO_2 concentrations and the relative risk of respiratory inpatient visits based on the hysteresis effect. The cross-basis function can combine the two dimensions of atmospheric pollutant concentration and lag days. Referring to related research (18–20), the model of the exposure-response relationship is as follows:

$$Log(u_t) = \beta X_{t,i} + ns(time, df = 7/peryear) + ns(Temp, df = 3) + ns(RH, df = 3) + DOW + \ Holiday + \alpha$$

where $E(Y_t)$ denotes the expected number of respiratory inpatient visits at lag day t; $X_{t,I}$ and β represent the cross-basis function of SO_2 and the regression coefficient, respectively.

Several analyses were adopted to investigate the relation between SO_2 and respiratory inpatient visits. Firstly, single-pollutant model, including single-day lag (from lag0, which meant current day estimated effect, to lag7, which meant the previous 7th day estimated effect) and multi-day lag (from lag0–1, which represented the mean of the current day effect and lag1 effect, to lag0–7, which represented the mean of the current day effect and the previous 7 days' effects), was selected to research the lag pattern of SO_2. Secondly, the expose-response relationship between the SO_2 concentration and the relative risk of respiratory inpatient visits was plotted. Thirdly, the stratified analysis was selected to explore the relationship between the SO_2 level and the inpatient visits for respiratory diseases in different gender, ages, and season subgroups. Finally, the multi-pollutant model was used to evaluate the stability of the single pollutant model after adjusting for other atmospheric pollutants, such as PM_{10}, NO_2, O_3, and CO.

The results of the exposure-response relationship were presented as the relative risk (RR) of respiratory inpatient visits caused by SO_2 exposure as a continuous variable. The rest of the results were presented as the percentage changes (PC) and 95% CI in daily respiratory inpatient visits each 10 $\mu g/m^3$ increment of SO_2 levels. In this study, two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were conducted in R 4.0.2 using the "mgcv" and "dlnm" packages.

RESULTS

Table 1 presents descriptive results for ambient air pollutant concentrations, meteorological parameters, and daily respiratory inpatient visits. During the 1,095 days from January 1, 2017, to December 31, 2019, the average daily concentrations (standard deviation) of atmospheric pollutants were 62.7 (34.6) $\mu g/m^3$ for PM_{10}, 18.5 (11) $\mu g/m^3$ for SO_2, 24.2 (13) $\mu g/m^3$ for NO_2, 71.7 (34.5) $\mu g/m^3$ for O_3, and 1.3 (0.3) mg/m^3 for CO, respectively. Moreover, the daily mean relative humidity and temperature were 74% and 19.6°C, respectively. A total of 9,668 respiratory inpatient visits were recorded from 2017 to 2019; the daily mean count of inpatient visits was 9. Women accounted for ∼34.1% of all the cases, and younger people (<65 years) accounted for ∼48.1% of all the cases.

The correlations between meteorological parameters and atmospheric pollutants are shown in **Table 2**. All the correlation coefficients between the meteorological factors and the atmospheric pollutants were statistically significant. The daily concentration of SO_2 was positively correlated with other air pollutants (PM_{10}, NO_2, O_3, and CO) and temperature (correlation coefficient = 0.07–0.71) and negatively correlated with relative humidity (correlation coefficient = −0.41). Moreover, PM_{10} and NO_2 had positive associations with other air pollutants (correlation coefficient = 0.12–0.71), while there was a negative correlation between CO and O_3 (correlation coefficient = −0.16). The temperature was also negatively associated with relative humidity (correlation coefficient = −0.31).

Table 3 shows the percent changes in daily respiratory inpatient visits associated with a 10 $\mu g/m^3$ increase in SO_2 on different lag days in different gender and age subgroups. The delayed effects of SO_2 were significant at lag3, lag4, lag0–3, lag0–4, lag0–5, lag0–6, and lag0–7, with the maximum effect observed at lag4 (PC: 3.4%; 95% CI: 0.4–6.4%) in single-lag days. The maximum effect of multi-lag days was at lag 0:5 with 6.9% (95% CI: 1.6–12.5%). For men, the association between SO_2 exposure and respiratory admission was not statistically significant at any lag days. The SO_2 concentration was significantly correlated with women at lag1, lag4, and all the multi-lag days, with the largest effect observed at lag1 (PC: 7.1%; 95% CI: 1.9–12.6%) in the single-lag day model. For younger people (<65 years), there is no statistically significant relationship between SO_2 and inpatient visits for respiratory diseases at any lag days. For the elderly (≥65 years), daily respiratory inpatient visits were significantly associated with SO_2 concentration at lag1, lag4, and all the multi-lag days except lag0:7; the strongest association was observed at lag1 (PC: 5.5%; 95% CI: 1–10.2%) in single-lag day model.

Figure 1 presents a positive exposure-response relationship between the SO_2 concentration and the relative risk of respiratory

TABLE 1 | Data for ambient air pollutants, weather conditions, and respiratory inpatient visits in Ganzhou from 2017 to 2019.

		Mean ± SD	Minimum	P (25)	Median	P (75)	Maximum
PM_{10} ($\mu g/m^3$)		62.7 ± 34.6	11	38	54	79	258
SO_2 ($\mu g/m^3$)		18.5 ± 11.0	3	11	16	23	73
NO_2 ($\mu g/m^3$)		24.2 ± 13.0	8	15	20	29	84
O_3 ($\mu g/m^3$)		71.7 ± 34.5	5	46	70	94	194
CO (mg/m^3)		1.3 ± 0.3	0.6	1.1	1.3	1.5	2.9
Temperature (°C)		19.6 ± 8.1	0	13	21	27	32
Relative humidity (%)		74.0 ± 12.5	36	64	74	84	99
Daily inpatients visits		8.8 ± 3.9	0	6	9	11	25
Gender	Male	5.8 ± 2.9	0	4	6	8	18
	Female	3.0 ± 1.9	0	2	3	4	10
Age	≥65	4.6 ± 2.6	0	3	4	6	18
	<65	4.2 ± 2.4	0	3	4	6	15
Season	Cold	9.1 ± 4.1	0	6	9	12	25
	Warm	8.5 ± 3.6	1	6	8	11	21

TABLE 2 | Spearman's correlation of air pollutants and weather conditions.

	PM_{10}	SO_2	NO_2	O_3	CO	Temperature	Relative humidity
PM_{10}	1	0.71	0.69	0.38	0.29	−0.13	−0.46
SO_2		1	0.56	0.30	0.12	0.07	−0.41
NO_2			1	−0.07	0.38	−0.44	−0.13
O_3				1	−0.16	0.40	−0.65
CO					1	−0.39	0.18
Temperature						1	−0.31
Relative humidity							1

All correlation coefficients are statistically significant ($p < 0.05$).

TABLE 3 | Percentage change (95% CI) of inpatient visits for respiratory diseases per 10 $\mu g/m^3$ increase in concentrations of SO_2 for different lag days in the single-pollutant model.

Lag type	Lag day	Total	Male	Female	<65	≥65
Single-lag days	0	1.8 (−1.5/5.3)	0.7 (−3.3/4.9)	3.7 (−1.9/9.5)	−0.7 (−5.0/3.7)	4.7 (−0.2/9.8)
	1	2.9 (−0.2/6.1)	0.9 (−2.7/4.8)	**7.1 (1.9/12.6)**	0.9 (−3.2/5.1)	**5.5 (1.0/10.2)**
	2	2.1 (−0.8/5.2)	1.4 (−2.2/5.1)	2.7 (−2.2/7.9)	1.5 (−2.5/5.5)	2.3 (−1.0/5.7)
	3	**3.2 (0.6/6.7)**	2.7 (−0.9/6.4)	4.5 (−0.4/9.5)	3.8 (−0.1/7.9)	2.7 (−0.6/6.1)
	4	**3.4 (0.4/6.4)**	2.1 (−1.5/5.8)	**5.1 (0.2/10.2)**	0.8 (−3.1/4.8)	**4.5 (1.2/7.9)**
	5	0.9 (−2.0/3.9)	−0.7 (−4.2/2.9)	3.8 (−1.1/8.9)	−0.3 (−4.2/3.7)	1.6 (−1.6/4.9)
	6	−1.4 (−4.2/1.6)	−1.5 (−5.0/2.1)	−1.4 (−6.1/3.5)	0.6 (−3.3/4.6)	−3.2 (−6.3/−0.1)
	7	0.6 (−2.3/3.6)	1.4 (−2.2/5.0)	−1.31 (−5.9/3.5)	2.0 (−1.8/6.1)	−0.9 (−4.1/2.3)
Multi-lag days	0–1	3.4 (−0.4/7.2)	1.1 (−2.4/5.7)	**7.7 (1.3/14.4)**	0.2 (−4.7/5.3)	**7.1 (1.5/13.0)**
	0–2	3.5 (−0.3/8.3)	1.8 (−3.2/7.0)	**7.9 (0.9/15.5)**	1.1 (−4.3/6.7)	**7.2 (1.1/13.7)**
	0–3	**5.5 (0.9/11.2)**	3.1 (−2.3/8.8)	**9.8 (2.1/18.1)**	3.1 (−2.8/9.3)	**8.1 (1.4/15.2)**
	0–4	**6.8 (1.9/12.1)**	4.0 (−1.8/10.2)	**12.3 (3.9/21.4)**	3.4 (−2.9/10.1)	**10.9 (3.6/18.7)**
	0–5	**6.9 (1.6/12.5)**	3.4 (2.8/10.0)	**14.1 (5.0/24.0)**	3.3 (−3.5/10.5)	**11.4 (3.6/18.9)**
	0–6	**6.0 (0.4/11.8)**	2.6 (−4.0/9.6)	**12.8 (3.2/23.3)**	3.2 (−4.0/10.9)	**9.3 (1.0/18.2)**
	0–7	**6.5 (0.5/12.8)**	3.4 (−3.6/11.0)	**12.53 (2.3/23.7)**	4.6 (−3.1/13.0)	8.7 (−0.1/18.1)

Bold font indicates statistical significance ($P < 0.05$).

inpatient visits. The exposure-response curves of the total population, men, women, and the elderly (≥65 years) were raised relatively faster in the range of 0–20 $\mu g/m^3$, which meant that the risk of respiratory hospitalization increases rapidly under relatively low concentrations of SO_2 exposure; the curves in the range of 20–50 $\mu g/m^3$ were relatively flat, indicating that the risk of hospitalization remains at a relatively high level with the increase of SO_2 concentration. The curve for younger people (<65 years) decreased slightly in the range of 0–10 $\mu g/m^3$ and increased at higher concentration (20–50 $\mu g/m^3$), which showed the risk of hospitalization for younger people's respiratory system does not change much under relatively low concentration of SO_2 exposure.

As shown in **Figure 2**, the association between the SO_2 concentration and the daily respiratory inpatient visits was stronger in the warm season (May–Oct) rather than in the cold season (Nov–Apr). For the elderly (≥65 years), the positive association between the SO_2 concentration and the respiratory inpatient visits was statistically significant only in warm seasons. **Table 4** summarizes the percent changes for daily respiratory inpatient visits associated with each 10 $\mu g/m^3$ increase of SO_2 concentration in multiple pollutant models. We used the data from lag3 and lag4 because the single-day lag effect of SO_2 was statistically significant in the above lag days. The results from the multi-pollutant model indicated that the relationship between SO_2 and respiratory inpatient visits was meaningless at lag3 after PM_{10} was controlled. When adjusted for all atmospheric pollutants, including PM_{10}, NO_2, O_3, and CO, the association between SO_2 and inpatient visits was still statistically significant at lag4. The effects of SO_2 on respiratory inpatient visits were slightly decreased after adjusting for PM_{10}, O_3, and CO (2.6–3.3%) at lag4 and the percent change of inpatient visits became 3.8% after adjusting for NO_2.

DISCUSSION

Our research is a quantitative evaluation of the relevance between SO_2 and daily respiratory inpatient visits in Ganzhou

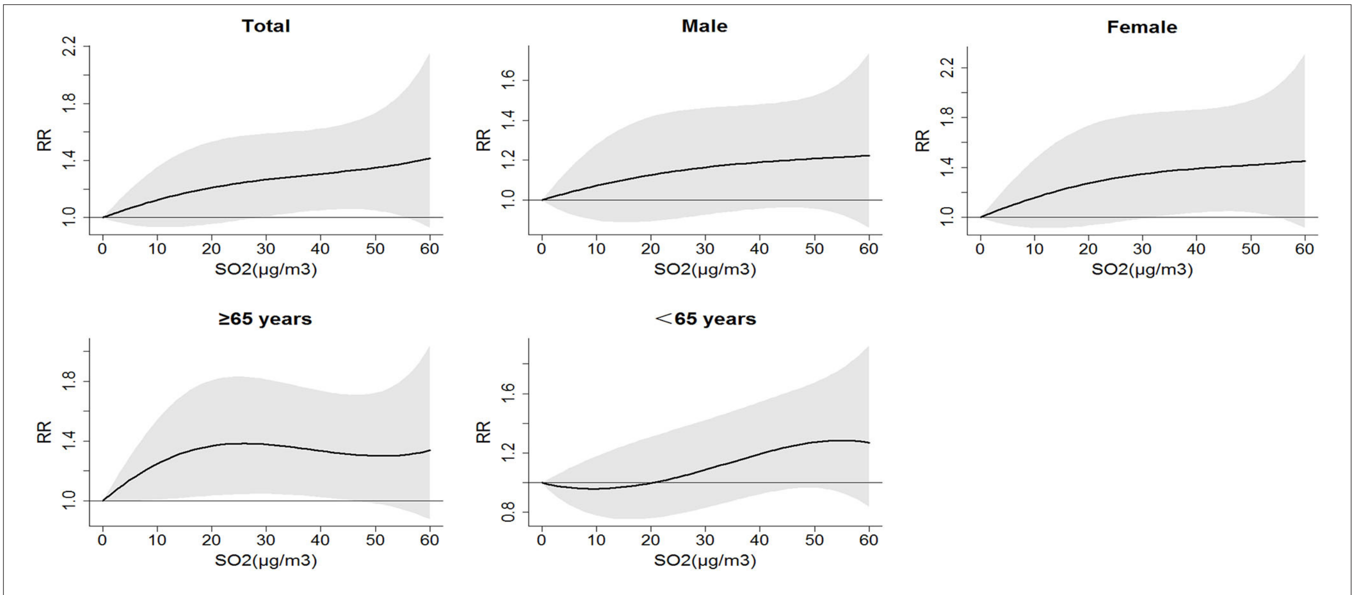

FIGURE 1 | Relative risk (RR) of respiratory inpatient visits caused by different SO_2 concentrations.

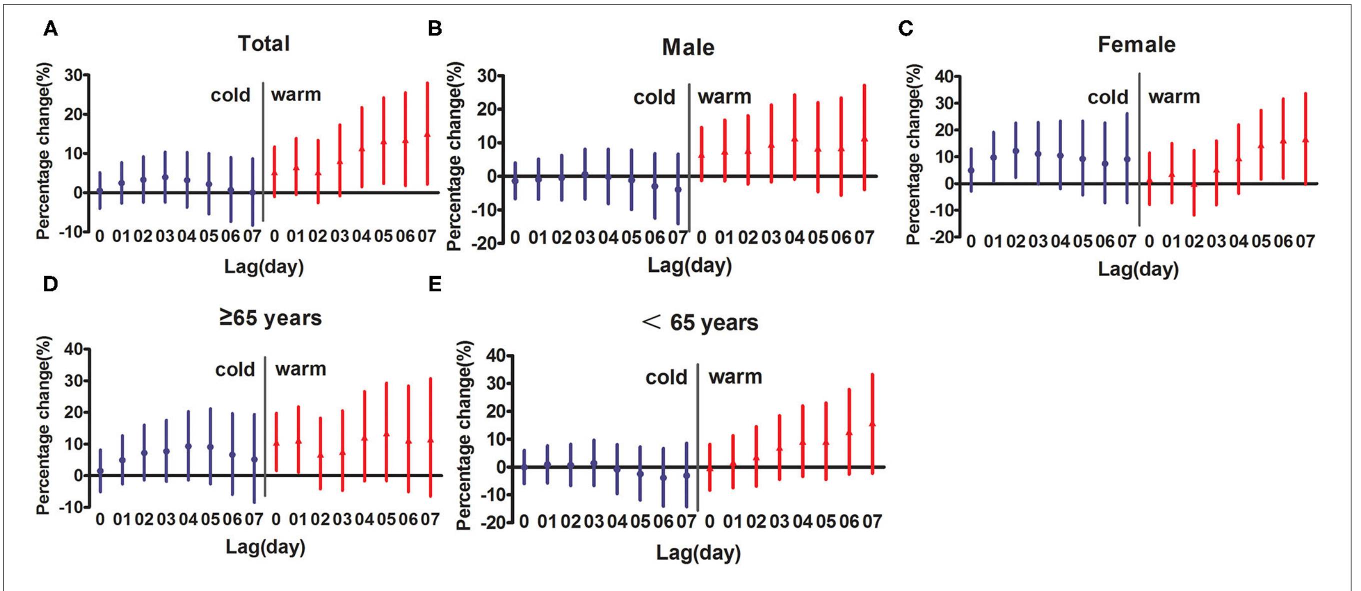

FIGURE 2 | Percentage change (95% CI) of inpatient visits per 10 μg/m^3 increase in concentrations of SO_2 for different lag days in different seasons. **(A)** represents total people; **(B)** represents male; **(C)** represents female; **(D)** represents the elderly people (≥65 years); **(E)** represents younger people (<65 years).

from 2017 to 2019 using the GAM and the DLNM. The results indicated that the elevation in SO_2 concentration was significantly associated with an increase in respiratory inpatient visits, especially in the warm season (May–Oct), women, and elderly (≥65 years) subgroups. This association was stable after adjusting for other atmospheric pollutants. The exposure-response curves of the SO_2 concentrations and the relative risk of respiratory inpatient visits were nearly non-linear with no obvious thresholds.

This study showed significant cumulative effects of SO_2 concentration in a single pollutant model, with the peak at lag0–5. At this point, per 10 μg/m^3 elevation of SO_2 concentration was associated with a 6.9% (95% CI: 1.6–12.5%) increment in daily respiratory inpatient visits. The results of the previous studies were consistent with ours, indicating that the SO_2 concentration was positively related to respiratory diseases (21). Early *in vivo* studies have observed that SO_2 exposure causes bronchoconstriction and induces respiratory diseases (22). A study conducted in Thailand indicated that a 10 μg/m^3 increase in the SO_2 concentration was associated with a 1.83% (95% CI: 1.2–2.4%) enhancement in total respiratory hospital admissions at lag0–4 (23). Similarly, the positive relationship

TABLE 4 | Percentage change (95% CI) of inpatient visits associated with 10 $\mu g/m^3$ increase of SO_2 under multiple pollutant models.

Lag day[a]	Model type	Percentage change	95% CI
3	SO_2	3.2	(0.6, 6.7)*
	$SO_2 + PM_{10}$	3.0	(−0.3, 7.2)
	$SO_2 + NO_2$	3.7	(0.7, 7.0)*
	$SO_2 + O_3$	2.9	(0.3, 5.9)*
	SO_2 + CO	3.0	(0.8, 5.6)*
4	SO_2	3.4	(0.4, 6.4)*
	$SO_2 + PM_{10}$	3.3	(0.3, 6.5)*
	$SO_2 + NO_2$	3.8	(1.1, 6.8)*
	$SO_2 + O_3$	2.6	(0.2, 5.6)*
	SO_2 + CO	3.3	(1.1, 5.7)*

*$p < 0.05$.

[a]*The association between SO_2 exposure and daily respiratory inpatient visits was statistically significant at lag3 and lag4 in a single-lag model.*

between respiratory admissions and SO_2 was observed at lag 4 [relative risk (RR): 1.12; 95% CI: 1.05–1.21] in Malaysia (24). A systematic review also suggested that every 10 $\mu g/m^3$ increase of the SO_2 levels corresponded to 0.7% (95% CI: 0.1–1.4%) increment respiratory morbidity at lag0 (25). An ecological study reported that in Shenyang, a typical heavily polluted city in China, per 10 $\mu g/m^3$ increase in SO_2 was related to 0.7% (95% CI: 0–1.4%) increase in respiratory admissions at lag0 (26). The earliest observed positive relation between SO_2 exposure and respiratory inpatient visits in our study was at lag3 in a single-day lag model. After comparing the average SO_2 concentrations in Ganzhou (18.5 $\mu g/m^3$) and Shenyang (55 $\mu g/m^3$) during the study period, we speculated that the exposure of higher concentrations of SO_2 had intraday effects on the respiratory health, while the exposure of relatively low concentrations of SO_2 had a delayed effect.

In this study, the earliest observed association between the SO_2 concentration and the daily inpatient visits with respiratory diseases was at lag0–3 in the multi-day lag model. Conversely, some earlier studies indicated that the strongest effects were observed on the current day (25) or lag0–1 (23). A plausible explanation for the longer-than-normal hysteresis effect observed in Ganzhou may be that long-term exposure to SO_2 leads to a decrease in the sensitivity of residents to SO_2. In addition, the differences in the estimated effects and lagged patterns of SO_2 may be related to different outcome indicators of the study, local economic development, and the gender structure of the total population in different regions. A retrospective study from Switzerland suggested that the relationship between the SO_2 exposure and the hospital admissions for respiratory diseases was not statistically significant (27). This might reflect the difference in population sensitivity caused by different cultural backgrounds and dietary structures.

The stratified analysis suggested that women and elderly (≥65 years) are more sensitive to SO_2 exposure, which is consistent with previous studies (28, 29). An observational study conducted in Lanzhou, China, found that the estimated effect size of SO_2 on respiratory hospital admissions was slightly larger in women than in men (30). Physiological factors, such as lower red blood cell count and higher airway response, may be important reasons that cause women to be more sensitive to atmospheric pollutant exposure (31, 32). Moreover, the health differences according to sex may be affected by smoking, drinking, and other unhealthy living habits and occupational environment. Interestingly, in an earlier multi-city time series analysis, gender differences in the impact of SO_2 were not observed, and this study pointed out that the insignificant gender differences may be due to factors, such as study design, sample size, and modeling strategy (33).

Consistent results have been reported on the effects of ambient air pollution on specific age groups. Qiu et al. found that each 10 $\mu g/m^3$ increase in SO_2 corresponds to a 3.4% (95% CI: 2.3–4.5%) increase in overall respiratory hospital admissions among the elderly (>65 years) in the Sichuan Basin (33). Similarly, earlier studies observed that SO_2 was more associated with hospital admissions for respiratory diseases in older adults (>65) than in other age subgroups (26). The elderly are more susceptible to pathogen exposure due to the weaker immune defenses and respiratory functions (34). This may be an important reason for their increased sensitivity to SO_2 exposure.

The health effects of SO_2 in different seasons have long been debated. The results showed a positive relation between SO_2 and daily respiratory inpatient visits during the warm season. Two study indicated that the relationship between SO_2 and respiratory disease morbidity could be observed only during the cold season (heating season) (30, 35). It was worth mentioning that the research site is located in northern China, where temperatures are well below freezing in winter, and fossil fuels need to be burned for heating. The SO_2 level in the cold season in northeast China was much higher than that in the warm season. However, there was no statistical difference in the SO_2 concentration in Ganzhou during the cold and warm seasons (**Supplementary Table 1**). A recent study, also from southern China, was consistent with our findings, confirming a statistically significant association between SO_2 and respiratory disease mortality during warm seasons (36). People in warm seasons tend to spend longer times outdoors. Even indoors, residents often open windows during warm seasons, and the indoor SO_2 level is closer to the ambient SO_2 level. Moreover, the different meteorological conditions (especially extreme temperatures) in different regions may be one of the important reasons for the variability (37–39).

Understanding the exposure-response curves of atmospheric pollutants is very important for the making of environmental and public health policies. As shown in **Figure 1**, we found that even at very low exposure levels, a positive correlation between SO_2 and daily respiratory inpatient visits could be observed in the elderly subgroups. Similarly, several studies demonstrated adverse effects of SO_2 at relatively low concentrations (40, 41). The health effect of SO_2 as a single pollutant or with other atmospheric pollutants has long been controversial. In this study, the association between the SO_2 concentration and the respiratory inpatient visits was stable after adjusting for other air pollutants at lag4. A study in Japan by Yorifuji et al. (42) also suggested that the relationship between SO_2 exposure and respiratory system mortality can still be observed after adjusting for atmospheric pollutants, such as nitrogen dioxide and particulate matter. Yang et al. (43) proposed that multi-pollutant models increase the standard error, so the effects of multi-pollutant models tend to be slightly lower than those of single-pollutant models, which was consistent with the results of this study. However, a systematic review suggests that after adjusting for PM_{10} and NO_2, no association between respiratory morbidity and SO_2 had been observed (25). It is worth noting that there is a strong correlation between atmospheric pollutants, and it is difficult to accurately assess the adverse effects of a single pollutant even if multi-pollutant models are used (44).

In this study, the generalized additive model was adopted to adjust for the influence of confounding factors, such as long-term trends of the time, meteorological conditions, weekend, and holiday effects. Our study revealed a positive correlation between the SO_2 concentration and the morbidity of respiratory diseases in China. Nevertheless, the study has several limitations. Firstly, the average concentration at fixed air monitoring stations was used as a proxy for individual exposure, which may underestimate the adverse effects of SO_2 (45). Secondly, even if multi-pollutant models were used, the independent effects of SO_2 could not be fully explored because there are no data on other particulate pollutants except PM_{10} in this study. Thirdly, the main model of this study did not include several confounding factors, such as daily activities and socioeconomic status, which may not fully reflect the association between SO_2 and respiratory inpatient visits.

The relationship between the elevated SO_2 concentrations and the daily respiratory inpatient visits was observed in Ganzhou, a subtropical city in southern China, even though the average daily SO_2 concentrations were lower than the minimum allowable exposure concentration set by the WHO (46) and China (47). We call on scholars in different regions to research on the health damage caused by common air pollutants to provide a theoretical basis for local health promotion and environmental health policy formulation. Future investigations should require more rigorous experimental designs (e.g., a combination of animal experiments and population epidemiological investigations) to identify the subgroups susceptible to respiratory damage caused by the SO_2 exposure.

CONCLUSION

Our study indicated that SO_2 concentration is positively associated with daily inpatient visits for respiratory disease. The association is closer in women, elderly people ($\geq$65 years), and warmer seasons (May–Oct) subgroups. These results provide further evidence to support the potential health effects of exposure to SO_2. We hope that our study can remind researchers and managers to pay more attention to the adverse effects of SO_2 in developing countries.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: the disclosure and use of inpatient information requires the consent of the relevant departments of the hospital. Requests to access these datasets should be directed to https://www.gyyfy.com/.

AUTHOR CONTRIBUTIONS

XZho carried out literature retrieval, determined the research direction and data analysis according to the existing literature, and wrote the article. YG participated in the data collection of articles and assisted in statistical analysis. DW and WC explained the data results, discussed them in combination with existing articles, and assisted in writing the first draft of the article. XZha was mainly responsible for contacting the hospital to provide the data required for this study and putting forward modification opinions on the first draft of the article. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.854922/full#supplementary-material

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A Time-Series Study for Effects of Ozone on Respiratory Mortality and Cardiovascular Mortality in Nanchang, Jiangxi Province, China

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Objective: Most evidence comes from studies show that ambient ozone(O_3) pollution has become a big issue in China. Few studies have investigated the impact of ozone spatiotemporal patterns on respiratory mortality and cardiovascular mortality in Nanchang city. Thus, this study aimed to explore the health effect of ozone exposure on respiratory mortality and cardiovascular mortality in Nanchang, Jiangxi Province.

Methods: Using the daily mortality data, atmospheric routine monitoring data and meteorological data in Nanchang from 2014 to 2020,we performed a generalized additive model (GAM) based on the poisson distribution in which time-series analysis to calculate the risk correlation between respiratory mortality and cardiovascular mortality and ozone exposure level (8h average ozone concentration, O_3-8h). Besides, analyses were also stratified by season, age and sex.

Results: In the single-pollutant model, for every 10 $\mu g/m^3$ increase in ozone, respiratory mortality increased 1.04% with 95% confidence interval (CI) between 0.04 and 1.68%, and cardiovascular mortality increased 1.26% (95%CI: 0.68 $\sim$ 1.83%). In the multi-day moving average lag model, the mortality of respiratory diseases and cardiovascular diseases reached a relative risk peak on the cumulative lag5 (1.77%,95%CI: 0.99 $\sim$ 2.57%) and the cumulative lag3 (1.68%,95%CI: 0.93 $\sim$ 2.45%), respectively. The differences were statistically significant ($P < 0.05$). Results of the stratified analyses showed the effect value of respiratory mortality in people aged ≥65 years was higher than aged <65 years, whereas the greatest effect of cardiovascular mortality in people aged <65 years than aged ≥65 years. Ozone had a more profound impact on females than males in respiratory diseases and cardiovascular diseases. In winter and spring, ozone had a obvious impact on respiratory mortality, and effects of ozone pollution on cardiovascular mortality were stronger in summer and winter. There was a statistically significant difference of respiratory mortality in winter and spring and of cardiovascular mortality in summer and winter ($P < 0.05$).

Conclusions: In the long run, the more extreme the pollution of ozone exposure, the higher the health risk of residents' respiratory mortality and cardiovascular mortality.

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Therefore, the government should play an important role in the prevention and control ways of decreasing and eliminating the ozone pollution to protect the resident's health. The findings provide valuable data for further scientific research and improving environmental policies in Nanchang city.

Keywords: ozone pollution, cardiovascular mortality, respiratory mortality, time-series analysis, stratified analysis

INTRODUCTION

With the rapid development of modern industrialization, the air quality around us is increasingly affected (1). The World Health Organization (WHO) estimated that air pollution causes the deaths of 4.2 million people each year, which accounts for 6% of total deaths worldwide (2). Based on the analysis of atmospheric environment in 1,600 cities and regions around the world, it was found that only 12% of the study areas met the safety standards stipulated by WHO (3), indicating that the status and development of global air pollution cannot be ignored. Since the Chinese government implemented China's Action Plan of Prevention and Control of Air Pollution in 2013, atmospheric particulate matter has dropped significantly (4). Nevertheless, along with the rapid development of urban basic infrastructure and growth in motor vehicle number, ozone concentration has dramatically increased recently (5). Ozone is a secondary pollutant, its formation is due to the interaction between the hydrocarbons and oxides of nitrogen released from car exhaust and sunlight (UV), leading to photochemical smog. It can affect air quality at local, regional and even global scales, beside, it has an important impact on animal health, plant growth, climate change and global ecological balance. At the same time, the adverse effects on human life and ecological environment are gradually increasing (6). The more serious the air pollution is, the more the residents' medical expenses will increase (7).

According to the 2020 China Ecological Environment Bulletin, ozone has been become an important pollutant besides particulate matter ($PM_{2.5}$, PM_{10}) at the national level (8). Compared with Japan, South Korea, Europe and the United States, the magnitude and frequency of high-ozone events in China are much more significant (9). China experiences high ozone concentrations with highest annual 8-h maximum concentration in eastern China of 78 $\mu g/m^3$ and was followed by southern (73$\mu g/m^3$), north-western (69$\mu g/m^3$), northern (68$\mu g/m^3$), central (67$\mu g/m^3$), north eastern (65$\mu g/m^3$) and south-western China (59$\mu g/m^3$) (10). The majority of the Chinese population lives in the eastern part of China, especially in the three most developed regions, Jing-Jin-Ji (Beijing-Tianjin-Hebei), the Yangtze River Delta (including Shanghai-Jiangsu -Zhejiang-Anhui), and the Pearl River Delta (including Guangzhou, Shenzhen, and Hong Kong). These regions consistently have the highest emissions of anthropogenic precursors, which have led to severe region-wide air pollution (11). Studies showed that according to monitoring results from 74 Chinese cities, the mean daily 8-h maximum concentrations of ozone increased from approximately 69.5 ppbv in 2013 to 75.0 ppbv in 2015, while the percentage of non-compliant cities increased from 23 to 38% (5, 10). Jiangxi Province lies on the southern bank of the Yangtze River's lower and middle sections, it has a sub-tropical climate, warm and humid. Kan (12) using the data of environmental monitoring stations data in Jiangxi Province from January 2017 to June 2020, showed that from 2017 to 2019, the time and mass concentration of ozone exceeding the limit showed an increasing trend year by year. April to June and August to October were the periods of high incidence of ozone pollution. Nanchang City is the Central City of Jiangxi Province, and it is one of the first cities to implement new ambient air quality standards. The daily 8-hour maximum concentration of ozone in Nanchang from 2013 to 2015 was analyzed, showing that the seasonal variation of ozone was high in spring and summer and low in autumn and winter (13).

Many epidemiological studies had been conducted to assess the characteristics of ozone pollution exposure in China, related research showed that the concentration of ozone in Yangtze River Delta, Beijing-Tianjin-Hebei, Pearl River Delta and Chengdu-Chongqing cities was increasing year by year (14–17). There is a growing interest in studying the potential effect of ozone levels, and its subsequent effects on public health. Epidemiological and toxicological studies had shown that ozone exposure is not only associated with adverse health outcomes (18–22), but also leads to significant economic burdens (23). A series of epidemiological studies reported that short-term ozone exposure is strongly associated with the death risk of cardiovascular diseases (24, 25) and respiratory diseases (26). China recorded 93,351 (95%CI: 11,001–169,898) ozone related premature mortality in 2015 with 42,673 (95%CI: 11,001-69,586) respiratory mortality and 50,678 (95%CI: 0–100,312) cardiovascular mortality. Northern and eastern China recorded high ozone related mortality with 18,230 (95%CI: 4,700–29,727), 12,261 (95%CI: 3,161–19,993) respiratory, 21,662 (95%CI: 0–42 877) and 14,528 (95%CI:0–28 757) cardiovascular deaths respectively (11). Kamal and Anil (27) showed that the proportion of all-cause, cardiovascular and respiratory premature deaths attributed to short-term environmental ozone exposure in China in 2019 increased by 19.6, 19.8, and 21.2% in comparison with those in 2015. Ozone is one of the most powerful oxidizing molecule to which living beings can be exposed. Accordingly, ozone inhalation may cause oxidative damages and inflammation, which could expand from the respiratory system to the periphery and to the brain, for which the nose and olfactory pathway is another portal of entry (28). Animal and human exposure studies had been proved that ozone has a stimulating effect on human mucosa through the eyes, nose, and mouth into the lungs, which will also cause damage to the lung tissue. Therefore, excessive ozone concentration will increase the probability of human suffering from respiratory diseases, and also aggravate the condition of patients with respiratory diseases such as asthma and chronic lung diseases (29). Some scholars pointed out that Short-term ozone exposure at levels was associated with platelet activation and blood pressure increases, suggesting a possible mechanism by which ozone may affect cardiovascular health (30). The proposed mechanisms include systemic inflammation and oxidative stress, autonomic nervous system imbalance, and abnormal epigenetic changes (31).

In areas with good air quality, ozone has gradually become the main pollution factor affecting the air quality compliance rate, which is closely related to climate change, and its composition is complex and difficult to control. In the preparation of the "14th Five-Year Plan" ecological and environmental protection plan, it is necessary to pay attention to the coordinated treatment of $PM_{2.5}$ and ozone in view of the prominent problems of ozone pollution (32). Among China's 2030 climate target, as the largest developing country in the world, China has overcome its own economic and social difficulties, implemented a series of strategies, measures and actions to cope with climate change, participated in global climate governance, and achieved positive results in addressing climate change. China has always attached great importance to non-carbon dioxide greenhouse gas emissions and China has accepted the Kigali Amendment to the Montreal Protocol on Substances that Deplete the Ozone Layer, which has entered a new stage in protecting the ozone layer and responding to climate change (33). Nitrogen oxides (NOx) and volatile organic compounds (VOCs) are important precursors to ozone formation. In order to control ozone pollution during the "14th Five-Year Plan" period, Jiangxi will promote the energy structure, adjustment and optimization of industrial structure and traffic structure to reduce NOx and VOCs emissions from the source (34). Nanchang is an important central city in the middle and lower reaches of the Yangtze River in China, due to the city is a lack of research on the effects of ozone pollution, and the association of human health with ambient ozone have not been fully understood. Therefore, the main objective of this study is to evaluate the association between ozone exposure and respiratory mortality and cardiovascular mortality, at the same time, we aimed to evaluate individual characteristics (sex and age) and season as potential effect modifiers of the ozone-mortality association, which providing a basis for further research and formulation of local environmental prevention and control policies in Nanchang City.

MATERIALS AND METHODS

Study Area

Nanchang is located in the north-central part of Jiangxi Province, at the end of the Ganjiang River and the Fuhe River. It is the capital of Jiangxi Province and is considered to be a provincial political, economic, cultural, scientific, technological and information center. Importantly, it is the core city of the Poyang Lake Ecological Economic Zone, which promotes the economic development and urbanization of the province (35). The study area is a typical subtropical monsoon climate with mild climate, sufficient sunshine, abundant rainfall and four distinct seasons with a long frost-free period, spring and autumn are short, while winter and summer are long. In recent years, with the optimization of economic structure and industrial overall layout of Nanchang, people's living standards have improved significantly, but also brought a series of air pollution problems.

Data Collection

The daily mortality data of the respiratory diseases and cardiovascular diseases in Nanchang from 2014 to 2020 were selected, included sex, age, death time and underlying cause of death code (ICD-10), which were cardiovascular diseases death (I05–I52) and respiratory diseases death (J00–J99), respectively. The data were derived from the death cause registration system of Chinese Center for Disease Control and Prevention. Atmospheric pollutant data and meteorological data of Nanchang City are from the Nanchang Environmental Monitoring Center and Meteorological Bureau of Nanchang Municipality during the same period, respectively. Atmospheric pollutants included O_3-8h($\mu g/m^3$), SO_2($\mu g/m^3$), NO_2($\mu g/m^3$), $PM_{2.5}$($\mu g/m^3$), PM_{10}($\mu g/m^3$), CO(mg/m^3), which is the arithmetic mean of the data from eight nationally controlled monitoring sites in Nanchang city; meteorological data included daily average temperature (°C), daily average relative humidity (%), daily average air pressure (kPa) and daily average wind speed (m/s). The World Health Organization proposed that daily 8-h maximum ozone concentration as an appropriate indicator to study the relationship between environmental ozone exposure and health in 2020 (36). It is usually divided into four seasons according to the position of the earth around the solar orbit. In China, March to May is generally counted as spring (MMA), June to August as summer (JJA), September to November as autumn (SON), and December to February as winter (DJF).

Time-Series Analysis

Generalized additive model based on Quasi-Poisson regression was used to estimate the correlation between O_3-8h exposure and respiratory mortality and cardiovascular mortality in Nanchang city. The model was specified as follows:

$$\begin{aligned}\text{Log}[\text{E}(\text{y}_\text{i})] &= \alpha + \beta_\text{i}\text{X}_\text{i} + \text{ns}(\text{time, df}) + \text{ns}(\text{Z}_\text{i}, \text{df}) \\ &\quad + \text{DOW} + \text{PH} \end{aligned} \tag{1}$$

In this equation, i refers to the day of the observation; E (y_i) is the expected number of non-accidental mortality of residents on day i; α is the intercept; x_i refers to the concentration level of O_3-8h ($\mu g/m^3$) on day i; βi represents the regression coefficient of the corresponding air pollutants; ns is the natural smoothing spline function, and df represents the degree of freedom. Previous studies have usually set the degrees of freedom of time to 5 to 7 and meteorological factors to 6 (22, 37); DOW as the variables of weeks; PH is the holiday effect; Zi as the meteorological factor of day i, including daily average temperature and daily average relative humidity; time is the date variable, the appropriate degree of freedom is selected by using the minimum sum of the absolute values of the partial autocorrelation function (PACF) of the basic model residual to effectively control the long-term and seasonal fluctuation trend of the pollution-death series data. The excess risk of non-accidental death (ER) caused by 10 $\mu g/m^3$ increase of O_3-8h concentration was calculated by formula (2).

$$ER = [\exp(\beta_i \times 10) - 1] \times 100\% \quad (2)$$

The O_3-8h pollutant model was introduced to analyze the concentration of O_3-8h on the same day (Lag0) and the number of non-accidental deaths of residents. Meanwhile, the lag effect and cumulative lag effect were analyzed. According to the significance of the model analysis results, Lag0-Lag7 was selected for analysis (38, 39). Lag0 represents the average concentration of O_3-8h on the day and Lag1 represents the average concentration of O_3-8h on the lag one day, and so on. Previous studies have shown that the cumulative effect of multi-day lag is greater than that of single-day lag of air pollutants (40, 41). Therefore, we further used the moving average of air pollutant concentrations from 2nd day to 8th day (lag01 to lag07) in the analysis, where Lag01 represents the moving average concentration of O_3-8h on the current day and the previous day, Lag02 represents the moving average concentration of O_3-8h on the current day and the previous 2 days, and so on.

Statistical Analysis

The data did not conform to the normal distribution, so the median (M), quartile spacing (P_{25}, P_{75}), minimum and maximum values were used to describe the air pollutant level, meteorological factors and respiratory mortality and cardiovascular mortality in the study period. In addition, we conducted stratified analyses by age, sex and season. Spearman rank correlations were performed to evaluate the relationship between O_3-8h and other atmospheric pollutants and meteorological conditions. Temporal changes of air pollutant were summarized by Origin 8.0 software; SPSS 23.0 was used to describe the air pollutants, meteorological factors and the number of daily mortality in respiratory and cardiovascular disease. Non-normal distributions are performed using independent sample nonparametric tests (Kruskal-WallisTest). The time-series statistical analysis was conducted using R software, version 4.1.2. The statistical significance of all analyses was set as $P < 0.05$.

RESULTS

Overview of Air Pollution in Study Area

From 2014 to 2020, we monitored eight ozone monitoring sites and obtained ozone concentration and meteorological data in Nanchang City (**Figure 1**). During the study period, the average annual concentrations of $PM_{2.5}$, PM_{10}, and SO_2 all showed a steady downward trend, from 49.63 $\mu g/m^3$, 82.02 $\mu g/m^3$, 24.32 $\mu g/m^3$ in 2014 to 31.75 $\mu g/m^3$, 55.07 $\mu g/m^3$, 8.49 $\mu g/m^3$ in 2020 in Nanchang City. The average annual concentration of NO_2 increased firstly, reached the peak in 2017 (40.44 $\mu g/m^3$) and then began to decline, and fell to 26.98 $\mu g/m^3$ in 2020. The annual concentration of CO increased firstly, then decreased rapidly to 0.6 mg/m^3 in 2020. Among the six air pollutants, the average annual concentration of O_3-8h is increasing year by year, reaching 90.98 $\mu g/m^3$ in 2020 (**Figure 2**).

The Basic Situation of Air Pollution, Meteorological Factors and Daily Mortality

The number of mortality from respiratory diseases was 28,938, with 19,015 males and 9,920 females, accounting for 65.7 and 34.3%, respectively. The number of respiratory mortality in people aged $\geq$65 years was 23,943 and aged <65 years was 4,993, accounting for 82.7 and 17.3%, respectively. Besides, There were 29,481 deaths of cardiovascular diseases, 15,457 deaths of males and 14,002 deaths of females, accounting for 52.4 and 47.6%, respectively. The number of cardiovascular mortality in people aged $\geq$65 years was 25,757 and aged <65 years was 3,703, accounting for 87.4 and 12.6%, respectively. The median of daily respiratory mortality was 11 (8–14) and cardiovascular mortality was 11 (8–15). The daily median concentrations of SO_2, NO_2, O_3-8h, CO, $PM_{2.5}$ and PM_{10} were 11.50 (7.27–18.67)$\mu g/m^3$, 28.15 (21.20–39.08)$\mu g/m^3$, 85.00 (55.00–115.23)$\mu g/m^3$, 0.89 (0.70–1.08)mg/m^3, 33.00 (21.00–50.67)$\mu g/m^3$, 61.14 (39.66–91.77)$\mu g/m^3$, respectively. During the research period in Nanchang city, the median of daily average air pressure, daily average temperature, daily average relative humidity and daily average wind speed were 1,009.80 (1,002.20–1,016.85) hpa, 20.20 (11.40–26.30)°C, 75.00 (64.80–85.00)% and 1.70 (1.30–2.40)m/s, respectively. As important meteorological factors affecting atmospheric pollutants, daily average temperature and daily average relative humidity are significantly different in four seasons. The maximum of daily average relative humidity in spring is 77.65 (66.00–86.45)%, whereas the minimum of daily average relative humidity is 73.00 (62.55–83.00)% in autumn. Besides, the median of average temperature in summer is the highest, that is 29.00 (26.50–31.18)°C, and the median of average temperature in winter is the lowest, the value is 8.10 (5.90–10.30)°C. The distribution characteristics of atmospheric pollutants, meteorological indicators and daily mortality of respiratory and cardiovascular disease in Nanchang was shown in **Table 1**.

Moreover, the Spearman correlation analysis in **Table 2** showed that O_3-8h exposure is positively correlated with NO_2 and CO ($P < 0.05$), but not related to $PM_{2.5}$ ($P > 0.05$). It is negatively correlated with daily average air pressure, daily average relative humidity, and precipitation, whereas positively correlated with daily average temperature, but has nothing to do with daily average wind speed. It was remarkably observed that meteorological indicators are one of the significant factors affecting ozone pollution.

The Health Effect of O_3 Exposure

This study emphatically analyzed the effect of ozone exposure on respiratory mortality and cardiovascular mortality in different sex, age and season. By drawing the exposure-response relationship between ozone and the risk of death of residents in **Figure 3**, it can be seen that the increase of ozone concentration is positively correlated with the excessive risk of death on respiratory diseases and cardiovascular diseases. The influence curve of ozone on the death of residents is approximately linearly increasing, and there is no discernible threshold. At low concentrations, it also has a certain impact on the death of

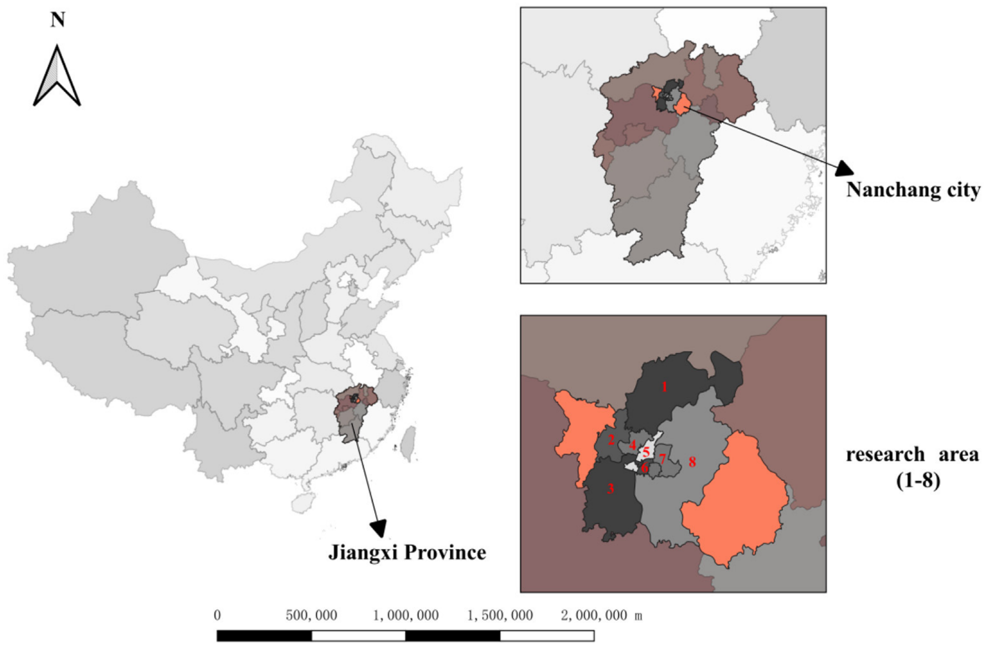

FIGURE 1 | Ozone monitoring sites in Nanchang city, Jiangxi province, 2014–2020.

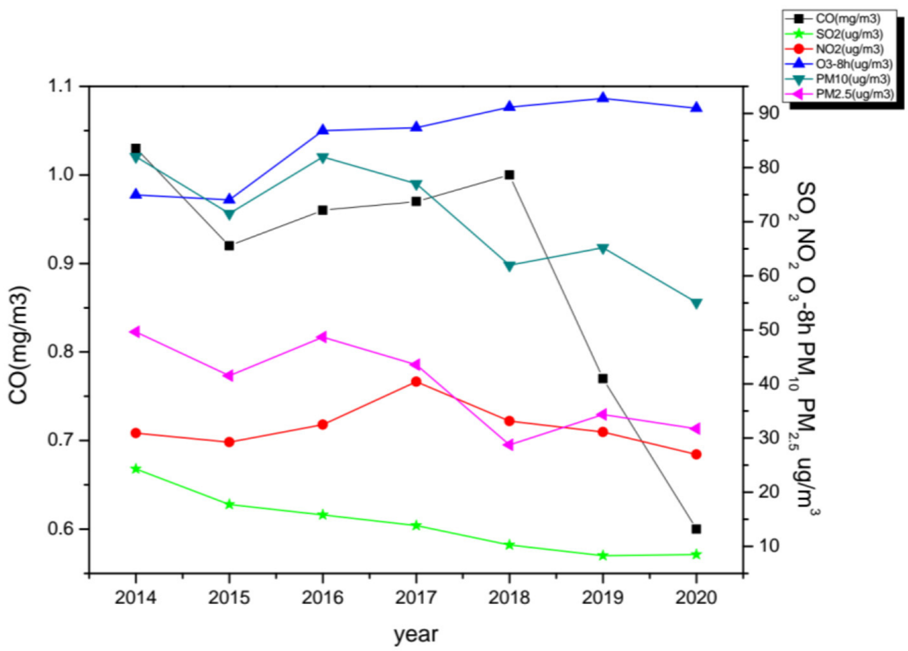

FIGURE 2 | The annual change trend of air pollutants in Nanchang city, 2014–2020.

residents. **Figure 4** indicates that the estimated lag structure of the effects of a 10 μg/m^3 increase in O_3-8h concentration on respiratory diseases and cardiovascular diseases for the whole group. After adjusting for time, meteorological factors, day of the week effects, holiday effects and other confounding factors, it is focused on that under different hysteresis models with the average concentration of O_3-8h increase of 10μg/m^3 leads to respiratory mortality and cardiovascular mortality (ER,95%CI). For the single lag model, the strongest effect of O_3-8h on respiratory mortality and cardiovascular mortality on the current

TABLE 1 | Distribution characteristics of air pollutants, meteorological indicators and non-accidental deaths in Nanchang City, 2014–2020.

Variables	Min	P_{25}	M	P_{75}	Max
Air pollutants					
SO_2 (μg/m^3)	2.00	7.27	11.50	18.67	78.50
NO_2 (μg/m^3)	6.10	21.20	28.15	39.08	123.00
CO (mg/m^3)	0.20	0.70	0.89	1.08	2.70
O_3-8h (μg/m^3)	5.70	55.00	85.00	115.23	217.40
PM_{10} (μg/m^3)	5.20	39.66	61.14	91.77	362.20
$PM_{2.5}$ (μg/m^3)	4.00	21.00	33.00	50.67	304.00
Meteorological indicators					
Daily mean air pressure (hpa)	989.00	1,002.20	1,009.80	1,016.85	1,038.20
Daily mean wind speed (m/s)	0.40	1.30	1.70	2.40	10.00
Daily mean relative humidity (%)	31.00	64.80	75.00	85.00	100.00
Spring (MAM)	34.00	66.00	77.65	86.45	98.00
Summer (JJA)	44.00	67.00	76.00	85.00	99.00
Autumn (SON)	33.50	62.55	73.00	83.00	100.00
Winter (DJF)	31.00	60.00	74.00	85.00	97.00
P	$P < 0.05$				
Daily mean temperature (°C)	−1.30	11.40	20.20	26.30	34.90
Spring (MAM)	3.70	14.40	19.50	23.10	31.60
Summer (JJA)	19.50	26.50	29.00	31.18	34.90
Autumn (SON)	4.00	16.50	20.50	24.90	31.80
Winter (DJF)	−1.30	5.90	8.10	10.30	22.30
P	$P < 0.05$				
Daily mortality counts of respiratory disease					
All	1	8	11	14	38
Male	0	5	7	10	24
Female	0	2	3	5	21
≥65	0	6	9	12	32
<65	0	1	2	3	11
Daily mortality counts of cardiovascular disease					
All	1	8	11	15	42
Male	0	4	6	8	24
Female	0	3	5	7	21
≥65	0	7	9	13	40
<65	0	0	1	2	12

TABLE 2 | Correlation analysis of air pollutants and meteorological indicators in Nanchang city.

O_3-8h (μg/m^3)	**Air pollutants**				**Meteorological conditions**			
	NO_2 (μg/m^3)	**CO (mg/m^3)**	**PM_{10} (μg/m^3)**	**$PM_{2.5}$ (μg/m^3)**	**Daily mean air pressure (hpa)**	**Daily mean temperature (°C)**	**Daily mean relative humidity (%)**	**Daily mean wind speed (m/s)**
r	−0.096	−0.14	0.282	0.03	−0.398	0.585	−0.573	0.053
P	<0.05	<0.05	<0.05	>0.05	<0.05	<0.05	<0.05	>0.05

day (lag0) and 1th day (lag1), respectively, that is, for every 10μg/m^3 increase in O_3-8h, the risk of death of respiratory diseases and cardiovascular diseases increased by 1.04% (95%CI: 0.40–1.68%), 1.26%(95%CI: 0.68–1.8%), respectively. The multi-day moving average lag model showed that respiratory mortality and cardiovascular mortality were the highest on the 15 day (1.77%, 95%CI:0.99–2.57%) and the third day (1.68%,95%CI: 0.93–2.45%) of the cumulative lag, respectively. The differences were statistically significant ($P < 0.05$). To avoid multiple colinearities, only the two-pollutant model was used to detect the robustness of the model (42). **Table 3** shows that in the two-pollutant models, the effect of O_3-8h were still significantly after

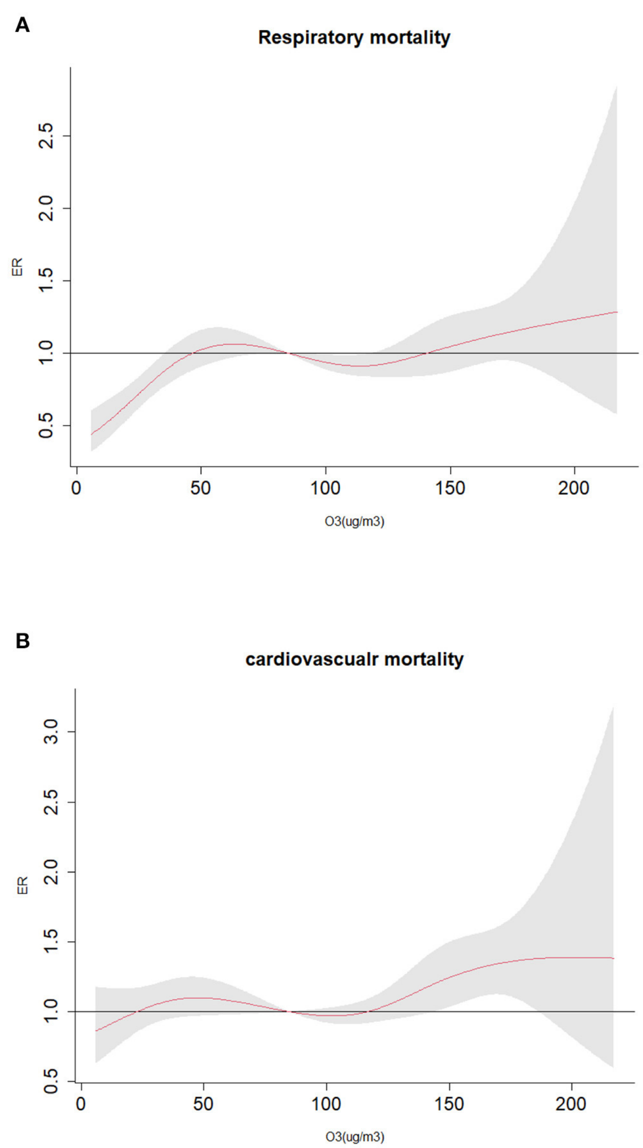

FIGURE 3 | Exposure-response curve of O_3-8h to major death causes of residents; **(A)** O_3-8h lead to respiratory mortality; **(B)** O_3-8h lead to cardiovascular mortality.

adding SO_2, NO_2, CO, $PM_{2.5}$ and PM_{10} on respiratory mortality and cardiovascular mortality. Besides, the effect of respiratory mortality had no significant change, while the risk of death from cardiovascular diseases caused by O_3-8h is reduced by 0.23, 0.23, 0.35, 0.38, and 0.27%, respectively.

Table 4 shows the excessive risk and 95% confidence intervals of mortality for respiratory diseases and cardiovascular diseases in the optimal lag days in the stratified analysis by age, sex, and season. Results of single-pollutant and multi-pollutant models from respiratory diseases for different age and sex are presented in **Figure 5**. In the cumulative lag model, for every 10 $\mu g/m^3$ increase of O_3-8h, the greatest excessive risk of respiratory mortality among people aged <65 years, aged ≥65 years, females and males at lag05, lag05, lag05, lag04 increased by 1.04% (95%CI: −0.45 ∼ 2.56%), 1.93%(95%CI: 1.09 ∼ 2.78%), 2.17% (95%CI: 0.99 ∼ 3.37%), 1.61% (95%CI: 0.76 ∼ 2.47%), respectively. When we analyzed the effect of a 10 $\mu g/m^3$ increase in O_3-8h on cardiovascular diseases, as presented in **Figure 6**, we saw a similar pattern to respiratory diseases. In this case, the greatest excessive risk of cardiovascular mortality in the cumulative lag model among people aged <65 years, aged ≥65 years, males, and females at lag06, lag03, lag01, lag03 increased by 2.11% (95%CI: 0.31 ∼ 3.96%), 1.67%(95%CI: 0.86 ∼ 2.48%), 1.44% (95%CI: 0.57 ∼ 2.31%), 2.03 (95%C I:1.06 ∼ 3.01%), respectively. Except that not statistically significant for age <65 years from respiratory mortality ($P > 0.05$), statistically significant associations were observed in different age and sex groups ($P < 0.05$). In summary, the female group had the highest association with ozone exposure compared to the male group, and the death effect value of respiratory diseases is higher for people age ≥65 years than age <65 years. Conversely, for cardiovascular diseases, the death effect value of people age <65 years is higher than age ≥65 years. Season-specific associations for respiratory and cardiovascular disease in single day lag and cumulative day lag models of O_3-8h are presented in **Figures 7**, **8**. The strongest effects of O_3-8h exposure of respiratory mortality in spring, summer, autumn, and winter at lag05, lag06, lag01, and lag03 increased by 0.88% (95%CI: −0.71 ∼ 2.49%), −0.61% (95%CI: −2.12 ∼ 0.92%), 0.61% (95%CI: −0.86 ∼ 2.11%), 5.87% (95%CI: 3.61 ∼ 8.18%), respectively. And the effects of O_3-8h concentration of cardiovascular mortality in spring, summer, autumn, and winter reached the maximum at lag02, lag06, lag06, lag03 increased by 0.45%(95%CI: −1.88 ∼ 2.10%), 1.51% (95%CI: −0.09 ∼ 3.12%), 0.41% (95%CI: −0.96 ∼ 1.79%), 4.14% (95%CI: 1.92 ∼ 6.40%), respectively. We did see statistically significant contributions from O_3-8h on respiratory mortality and cardiovascular mortality in winter ($P < 0.05$). Additionally, the season fluctuation of air pollution demonstrated that O_3-8h concentration had a stronger association with respiratory mortality in winter and spring and with cardiovascular mortality in summer and winter.

DISCUSSION

In this study, we found that air pollution has an important correlation with residents' health. This paper describes a approach to evaluate the health effect of ozone exposure on respiratory mortality and cardiovascular mortality in Nanchang City from 2014 to 2020. The exposure-response relationship reflects that ozone has an approximately linear positive correlation with the respiratory mortality and cardiovascular mortality. Studies in many cities in the United States, which showed that daily changes in ambient ozone exposure are linked to premature mortality, even at very low pollution level. And they also found robust evidence of the exposure-response relationship between ozone exposure and mortality showed an approximate linear curve (43). Moreover, the single- and two-pollutant models

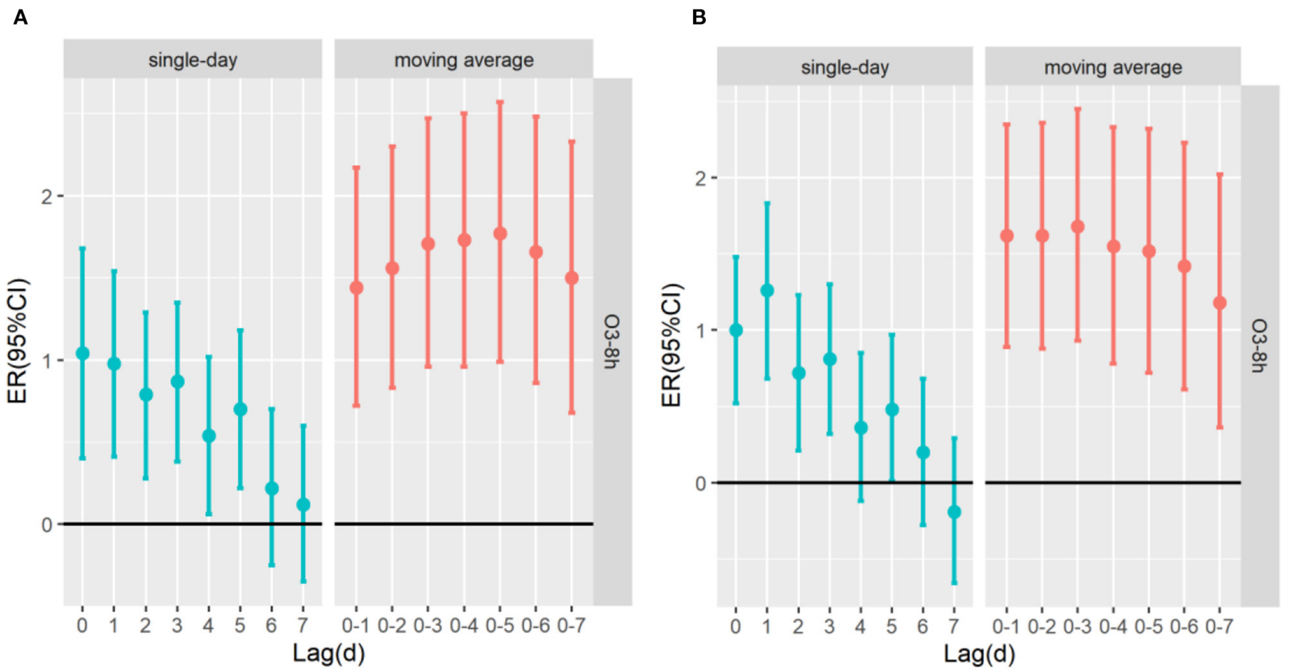

FIGURE 4 | The ER (95%CI) of mortality associated with 10 μg/m^3 increase of O_3-8h concentration; **(A)** O_3-8h lead to respiratory mortality; **(B)** O_3-8h lead to cardiovascular mortality.

TABLE 3 | The excess risk (95%CI) of air pollutant associated with 10μg/m^3 increase of O_3-8h concentration in the double-pollutant models.

Air pollutant models	ER (95%CI)	
	Respiratory mortality	Cardiovascular mortality
Single-pollutant model		
O_3-8h	1.04 (0.40,1.68)*	1.26 (0.68,1.83)*
Two-pollutant models		
O_3-8h+SO_2	1.05 (0.41,1.70)*	1.03 (0.38,1.68)*
O_3-8h+NO_2	1.03 (0.39,1.68)*	1.03 (0.38,1.68)*
O_3-8h+$PM_{2.5}$	0.99 (0.35,1.64)*	0.91 (0.26,1.56)*
O_3-8h+PM_{10}	0.96 (0.32,1.61)*	0.88 (0.23,1.54)*
O_3-8h+CO	1.03 (0.39,1.68)*	0.99 (0.35,1.64)*

*$P < 0.05$.

in our studies were constructed to further analyze the lag-response effect of ozone on the risk of death of residents, it was found a significant association for both O_3-8h and respiratory mortality and cardiovascular mortality with higher effects at the cumulative exposure level.

The results of survey showed that a correlation between O_3-8h and respiratory mortality and cardiovascular mortality, with percent changes in excessive risk of 1.04% (95%CI: 0.40 ∼ 1.68%) and 1.26% (95%CI: 0.68 ∼ 1.83%) for a 10 μg/m^3 increase in O_3-8h at lag0 and at lag1, respectively. The multi-day moving average lag effect showed that the greatest excessive risk of respiratory mortality and cardiovascular mortality at lag05 and lag03 increased by 1.77% (95%CI: 0.99 ∼ 2.57%), 1.68% (95%CI: 0.93 ∼ 2.45%), respectively, which is similar to the effect value of related research at home and abroad (42, 44, 45). In our studies, we found that ozone exposure had immediate effect on respiratory mortality and cardiovascular mortality, and the risk of death of cardiovascular diseases was especially susceptible to ozone pollution. But with the cumulative lag effect, it is worth noting that ozone has a greater impact on respiratory mortality. The association between O_3-8h exposure and respiratory mortality and cardiovascular mortality has been well documented in the epidemiological literature. Chao (41) also found that for every 10 μg/m^3 increase in O_3-8h concentration, a single-day lag of 1st-2nd day and multi-day cumulative lag of 3rd day had the greatest effect on cardiovascular disease mortality in Jiangsu Province. Qi's (21) research in Nanjing city discovered that the risk of cardiovascular mortality increased by 1.25% (95%CI: 0.78 ∼ 1.72%) for a 10 μg/m^3 increase in O_3-8h, while the effect of O_3-8h on the risk of respiratory mortality was not statistically significant. A study in Sichuan Province (46) consider that for every 10 μg/m^3 increase in ozone, respiratory mortality would increase by 0.78%(95%CI: 0.12 ∼ 1.44%). The same environmental and health cohort study followed up in Canada for 16 years showed that (47), for every 10 μg/m^3 increase in ozone on respiratory mortality and cardiovascular mortality will increase by 0.97%(95%CI: 0.95 ∼ 0.99%) and 1.03% (95%CI: 1.03 ∼ 1.05%), respectively. The inconsistency of research results in different regions may be related to temperature (5), population composition, geographical

TABLE 4 | The ER (95%CI) of respiratory mortality and cardiovascular mortality in the optimal lag days for different age, sex and season.

Variables	Respiratory mortality		Cardiovascular mortality	
	Lag(d)	O3-8h (μg/m3)	Lag(d)	O3-8h (μg/m3)
All	lag0	1.04 (0.40,1.68)*	lag1	1.26 (0.68,1.83)*
	lag05	1.77 (0.99,2.57)*	lag03	1.68 (0.93,2.45)*
Sex				
Male	lag0	0.95 (0.24,1.67)*	lag1	1.16 (0.48,1.84)*
	lag04	1.61 (0.76,2.47)*	lag01	1.44 (0.57,2.31)*
Female	lag0	1.20 (0.24,2.16)*	lag1	1.46 (0.72,2.20)*
	lag05	2.17 (0.99,3.37)*	lag03	2.03 (1.06,3.01)*
Age(years)				
≥65	lag1	1.11 (0.51,1.71)*	lag1	1.29 (0.68,1.90)*
	lag05	1.93 (1.09,2.78)*	lag03	1.67 (0.86,2.48)*
<65	lag0	1.12 (−0.10,2.35)	lag1	1.39 (0.12,2.67)*
	lag05	1.04 (−0.45,2.56)	lag06	2.11 (0.31,3.96)*
Season				
Spring	lag5	0.91 (0.09,1.73)*	lag1	0.24 (−0.75,1.24)
	lag05	0.88 (−0.71,2.49)	lag02	0.45 (−1.88,2.10)
Summer	lag6	0.41 (−0.44,1.27)	lag6	1.12 (0.23,2.02)*
	lag06	−0.61 (−2.12,0.92)	lag06	1.51 (−0.09,3.12)
Autumn	lag1	0.52 (−0.54,1.60)	lag5	0.51 (−0.31,1.33)
	lag01	0.61 (−0.86,2.11)	lag06	0.41 (−0.96,1.79)
Winter	lag1	3.71 (2.06,5.39)*	lag2	3.07 (1.58,4.58)*
	lag03	5.87 (3.61,8.18)*	lag03	4.14 (1.92,6.40)*

*$P < 0.05$.

structure and urbanization scale (16, 39, 44). In our studies, in the dual-pollution model, after adjusting for SO_2, NO_2, CO, $PM_{2.5}$, and PM_{10}, the death risk of respiratory diseases had no significant change, while the death risk of cardiovascular diseases caused by O_3-8h decreased by 0.23, 0.23, 0.35, 0.38, and 0.27%, respectively. Qi (21) and Yebin (25) discovered that O_3 had a certain degree of reduction in the risk of cardiovascular mortality after adjusting for $PM_{2.5}$,PM_{10}, NO_2, SO_2 and CO; Lihong (35) found that after adding $PM_{2.5}$ and NO_2, the risk of respiratory diseases was not significantly different from the effect value of O_3 single pollutant, which is consistent with our findings. Furthermore, there was a research showed (48) that after incorporating other pollutants into the single pollutant model, there was no difference in the impact on the health of residents before and after. The reason for the difference may be related to the constructed model, or the single air pollutant may be only considered in the single pollution model effect, and the effect of air pollutant may be affected by the co-linearity or spatial nature of other air pollutants (47).

Regarding gender differences, the effect of ozone exposure on excessive risk of respiratory mortality and cardiovascular mortality in female was greater than in male. It has been proved that females were more likely to suffer from the mortality of respiratory diseases and cardiovascular diseases than males, and females are more susceptible to O_3-8h than males, which is similar to the results of previous studies at home and abroad (48, 49). The reason for this result may be females have higher gas sensitivity, shorter respiratory tract and more susceptible to air pollutants compared with males (5, 37, 44). However, there is also evidence that males are more vulnerable to the effects of ozone on respiratory mortality than females. A study conducted in Li et al. (50) explained that pneumonia and bronchitis are more common in males with a history of smoking and exposure to different occupations, which may exacerbate the impact of O_3-8h on respiratory mortality in males. Mechanistically, as a result of reduced uptake of ozone into conducting airways, cigarette smoking may shift the longitudinal distribution of ozone uptake distally toward the respiratory airways, thereby leading to respiratory diseases in the population (51). However, there is no detailed study on whether the smoking rate of adults will affect the association between ozone exposure and cardiovascular diseases. Our studies have also exhibited that the elevated concentration of O_3-8h significantly increased the risk of respiratory mortality among residents aged ≥65 years (compared to aged <65 years), which is consistent with the results of previous studies (5, 19–22, 44). The structure of the respiratory system changes as we age, with decreased chest wall compliance, respiratory muscle strength, and vital capacity, which could lead to the risk of death of respiratory diseases in older people (52). As for the risk of cardiovascular mortality, the effect value of residents aged <65 years is higher than that of residents aged ≥65 years, which is inconsistent with previous researches found that people aged ≥65 years were more closely related to cardiovascular mortality risks (37, 48, 50). On the one hand, the younger with these cardiometabolic conditions had a

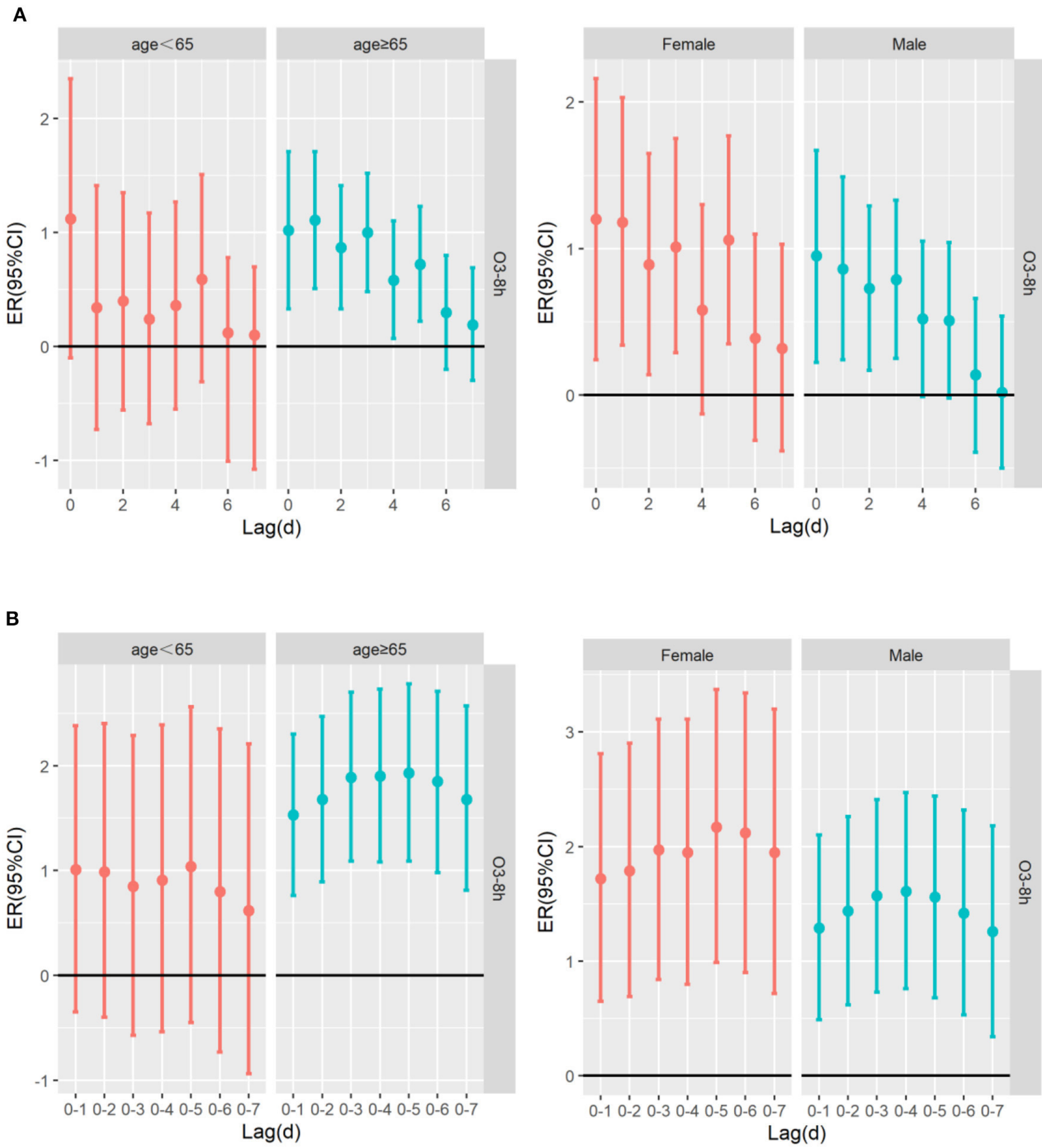

FIGURE 5 | The ER (95%CI) of respiratory mortality in age and sex lag-response relationship associated with 10 μg/m^3 increase of O_3-8h concentration; **(A)** The risks of respiratory mortality associated with 10 μg/m^3 increase of O_3-8h; **(B)** The cumulative risks of respiratory mortality associated with 10 μg/m^3 increase of O_3-8h.

higher prevalence of cardiovascular diseases in association with higher air pollution exposures than individuals without these cardiometabolic conditions (53). On the another hand, some scholars detected stronger associations between air pollutants and cardiometabolic risk factors in younger participants and for those with a family history of cardiovascular diseases (54). In summary, ozone exposure is closely related to the risk of respiratory mortality and cardiovascular mortality in people of different ages and sexes. Among them, females and people aged ≥65 years are sensitive groups. Nevertheless, ozone as an important air pollutant, we also should also be paid attention to the health risk of people aged <65 years because they are more closely linked to cardiovascular mortality for a 10 μg/m^3 increase in O_3-8h.

Climate change has a negative impact on human health due to increased exposure to adverse climate-related stresses (55). According to the climatic characteristics and the analysis of daily average temperature and daily average relative humidity of Nanchang City during the study period, it is known that the higher the temperature in the warm season (spring, summer),

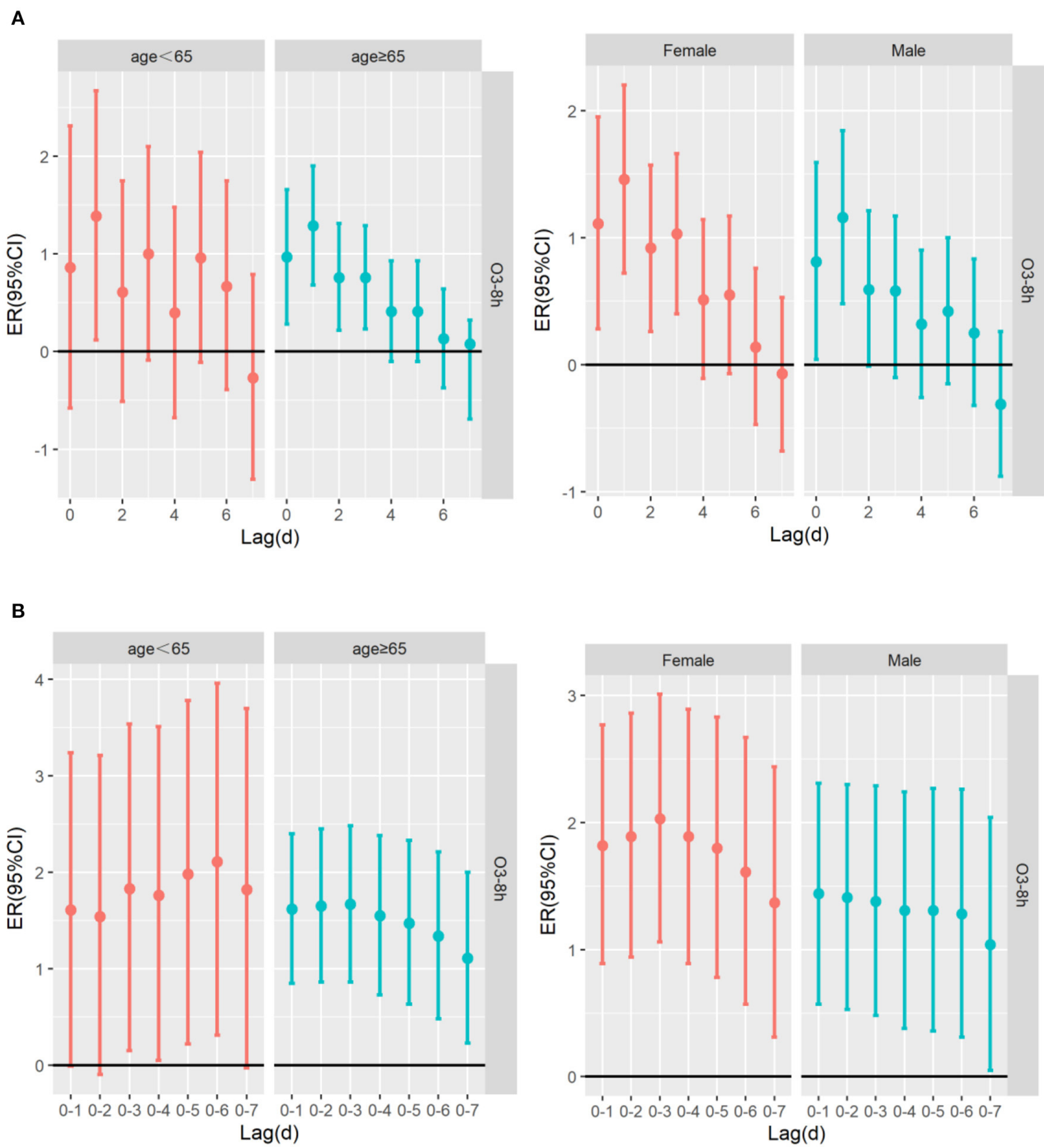

FIGURE 6 | The ER (95%CI) of cardiovascular mortality in age and sex lag-response relationship associated with 10 µg/m^3 increase of O_3-8h concentration; **(A)** The risk of cardiovascular mortality associated with 10 µg/m^3 increase of O_3-8h; **(B)** The cumulative risks of cardiovascular mortality associated with 10 µg/m^3 increase of O_3-8h.

the greater the humidity. When considering differential effects by season, it had been reported that seasonal changes will affect the impact of air pollutants on human health (56). We conducted that season-specific associations for the mortality risk of respiratory diseases showed stronger associations in winter and spring for a 10 µg/m^3 increase in O_3-8h, which is in agreement with the finding of the study by Yuqi (42) in Lishui district. And the risk of cardiovascular mortality was stronger associated with O_3-8h in summer and winter. In summer, ozone precursors in the air produce ozone more quickly with the increase of temperature (57). The reduced levels of nitrogen dioxide and carbon monoxide in summer months can be attributed to the contribution of these compounds to photochemical reactions occurring under the influence of solar radiation which result in the formation of ozone (58). Most importantly, we indicated the excessive risk of ozone pollution on respiratory mortality and cardiovascular mortality occurred earlier and had a greatest effect in winter than in the warm

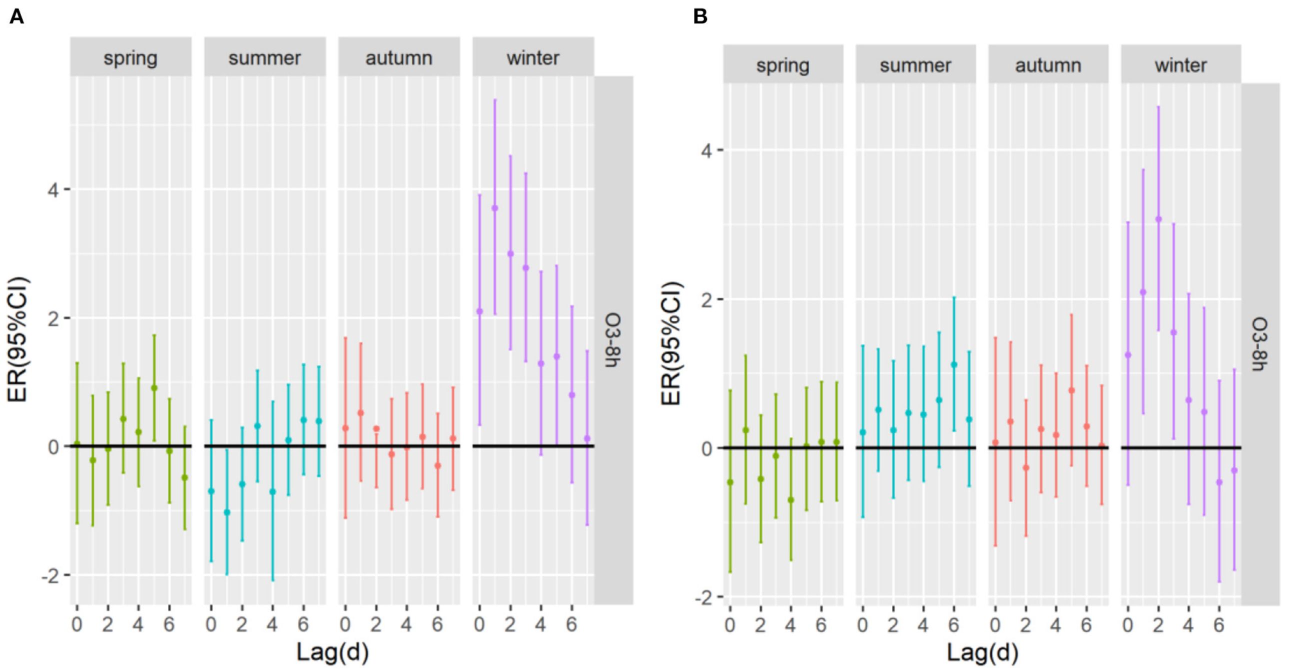

FIGURE 7 | The ER (95%CI) of mortality in season lag-response relationship associated with 10 μg/m^3 increase of O_3-8h concentration; **(A)** O_3-8h lead to respiratory mortality; **(B)** O_3-8h lead to cardiovascular mortality.

season. Higher levels of ozone pollution in winter months may also be associated with increased low emissions from local home furnaces, as well as more frequent in these periods, inversion of temperature resulting in smog events (59).

This study has several limitations that should be addressed. First, the air pollution exposure data of the study is the monitoring point data, which may be affected by distance, climate and other reasons, and cannot fully reflect the individual exposure (39, 40, 48), may overestimate the impact of air pollutants on the death of residents. Second, there exists another source of misclassification of ozone concentrations as this study did not use personal ozone exposure, because some personal behavior factors were not taken into consideration, such as air conditioner use, and time spent outdoors (60). Third, this study was conducted in a single city (Nanchang), thus, our findings cannot be generalized to other cities with different environmental and economic characteristics. Finally, the research only examined the correlation of respiratory mortality and cardiovascular mortality and ozone pollution, we were not able to involve more diseases, which is also a limitation of this study. As an important pollutant, ozone has independent health hazards. According to the source and changes of ozone in Nanchang city, government departments should strengthen the monitoring and control of ozone pollutant emissions, actively formulate energy-saving and emission reduction measures for ozone to reduce the heavy burden. In this vein, government departments also should promote actions and measures to enhance numerous aspects around the subject. Boosting education, training and public participation are some of the relevant actions for maximizing the opportunities to achieve the targets and goals on the crucial matter of ozone pollution. Without any doubt, technological improvements makes our world easier and it seems difficult to reduce the harmful impact caused by gas emissions, we could limit its use by seeking reliable approaches (61). When carrying out the prevention and control of ozone pollution, the relationship between $PM_{2.5}$ and ozone is often discussed. In winter, $PM_{2.5}$ treatment should be carried out, and in summer, the synergy between ozone and $PM_{2.5}$ should be explored. As a secondary pollutant, ozone has a complex reaction mechanism, and it is necessary to implement multi-target and multi-pollutant coordinated control. In the entire prevention and control work, more emphasis should be placed on the importance of atmospheric oxidation (62). Last but not least, taking appropriate protective measures for the entire population, sensitive groups, and high-risk groups to improve residents' awareness of self-protection. At the same time, identifying vulnerable subpopulations and the impact of ozone on these subpopulations will help in establishing air quality standards that will better protect these groups (53). A study (63) have shown that masks containing activated carbon interlayer have good protection against ozone at different pollution levels.

CONCLUSION

This study provides evidence of evaluating the effects of O_3-8h exposure on respiratory mortality and cardiovascular mortality in Nanchang city from 2014 to 2020. To our knowledge, results confirm that ozone pollution would increase the risk of

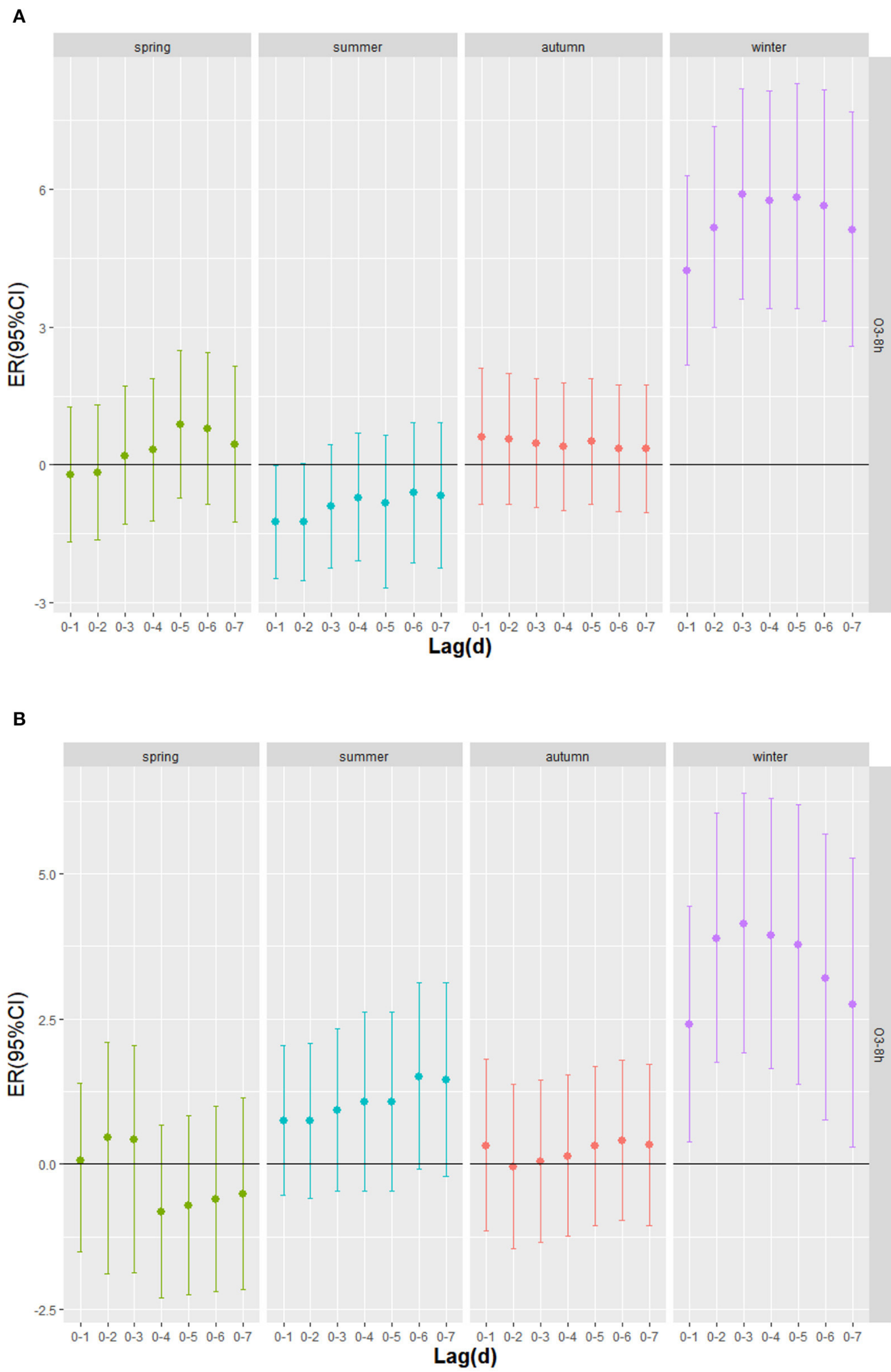

FIGURE 8 | The cumulative excess risk (95%CI) of mortality in season lag-response relationship associated with 10 μg/m^3 increase of O_3-8h concentration; **(A)** O_3-8h lead to respiratory mortality; **(B)** O_3-8h lead to cardiovascular mortality.

respiratory mortality and cardiovascular mortality. Our findings complement previous studies that are lacking by revealing that ozone pollutants have a lag effect on the health of the population in Nanchang city, China. With the rapid of economic growth and the development of processing industries such as electric power, gas and non-ferrous metal smelting in Nanchang city, the government should introduce corresponding control policies, take actions to reduce air pollution and make interventions for sensitive individuals to improve our health.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

HW and JF conceived and designed the work. HW led the study, carried out the time-series studies, analyzed the data, and approved the version to be published. KL involved in the study design and the interpretation of the results. JF helped to conceptualize the study, provided intellectual advice, and revise various drafts of the manuscript. All authors read and approved the final manuscript.

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Towards Integrated Air Pollution Monitoring and Health Impact Assessment Using Federated Learning: A Systematic Review

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Environmental issues such as environmental pollutions and climate change are the impacts of globalization and become debatable issues among academics and industry key players. One of the environmental issues which is air pollution has been catching attention among industrialists, researchers, and communities around the world. However, it has always neglected until the impacts on human health become worse, and at times, irreversible. Human exposure to air pollutant such as particulate matters, sulfur dioxide, ozone and carbon monoxide contributed to adverse health hazards which result in respiratory diseases, cardiorespiratory diseases, cancers, and worst, can lead to death. This has led to a spike increase of hospitalization and emergency department visits especially at areas with worse pollution cases that seriously impacting human life and health. To address this alarming issue, a predictive model of air pollution is crucial in assessing the impacts of health due to air pollution. It is also critical in predicting the air quality index when assessing the risk contributed by air pollutant exposure. Hence, this systemic review explores the existing studies on anticipating air quality impact to human health using the advancement of Artificial Intelligence (AI). From the extensive review, we highlighted research gaps in this field that are worth to inquire. Our study proposes to develop an AI-based integrated environmental and health impact assessment system using federated learning. This is specifically aims to identify the association of health impact and pollution based on socio-economic activities and predict the Air Quality Index (AQI) for impact assessment. The output of the system will be utilized for hospitals and healthcare services management and planning. The proposed solution is expected to accommodate the needs of the critical and prioritization of sensitive group of publics during pollution seasons. Our finding will bring positive impacts to the society in terms of improved healthcare services quality, environmental and health sustainability. The findings are beneficial to local authorities either in healthcare or environmental monitoring institutions especially in the developing countries.

Keywords: federated learning, health hazard, deep learning, machine learning, air pollution

INTRODUCTION

In today's globalization era, inhaling clean air has now become opulent. Environmental issues such as pollutions and climate change worsen due to the impacts of globalization. Air pollution refers to the environmental contamination that occurs either indoor or outdoor caused by any chemical, physical or biological agent that could change the natural characteristics of the atmosphere. According to World Health Organization (WHO), the impacts of ambient air pollution exposure which caused an estimated 4.2 million deaths annually have led to stroke, heart diseases, lung cancer, acute and chronic respiratory diseases (1). Meanwhile, WHO also reported that in the developing countries, one of the sources of indoor pollution are actually coming from household activities such as cooking. It has also become one of the leading causes of diseases such as respiratory diseases and premature death (1).

Pollutants such as particulate matter ($PM_{2.5}$ and PM_{10}), ozone (O_3), nitrogen dioxide (NO_2), etc. caused the ambient air quality to be below the healthy and normal limit (1). Other pollutants namely polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs) also contributed to ambient air pollution. On the other hand, the indoor air pollution is often contributed by exposure to PM2.5, smoke from tobacco and other sources, heating by burning substances namely coal and kerosene. Exposure to high levels of pollutants whether short-term or long-term contributes to a variety of adverse health outcomes. In this study, the ambient air pollutants and their impacts on health are keen to be explored.

Poor air quality has resulted from the high-level air pollution. To assess the air quality, it is important to monitor the air pollution exposure, and its potential health hazards to human. Hence, a robust predictive model for air quality monitoring is needed to anticipate risk factor due to air pollutant exposure. Recently, researchers have done significant studies on forecasting air pollution, understanding its interaction and associations with other pollutants. Myriad research have been conducted to understand the impacts of these pollutants on health (2–24). Air pollution prediction requires significant information on its contaminants, their sources and interaction with other particles. The outcome of the predictive model is crucial in assisting public to monitor their health conditions and aiding the healthcare management in providing an effective and comprehensive medical service as well as resources planning. In addition, lacking significant studies on air pollution prediction based on socioeconomic activities and forecasting of healthcare services during severe air pollution is still lacking. The following research questions were developed in aiding the process of developing this systemic review:

1. How are the significant pollutants that cause ambient air pollution can be characterized based on the socio-economic, location-specific and its significant associations to the health hazard?
2. What are the health hazards and potential diseases contributed by the pollutant?
3. How do the impacts of pollution contribute to healthcare services and resources planning?

The identification of the pollutants can assist in determining the pollution sources; hence, a mitigation plan can be proposed to reduce the risk of air pollution to human health. In addition, we reviewed the feasibility of predicting air pollution and monitoring air quality using artificial intelligence (AI) and/or machine learning (ML) techniques using pollutants' parameters based on the socio-economic activities, revealing the gap and the novelty of the study. The identified pollutants will be contributed to the air quality policies and management development, aiding the government in monitoring the air quality. Currently, there are limited studies that contributed to the aspects mentioned above. Therefore, by undertaking the systemic review of previous studies, this study aimed to identify the significant pollutants and the sources based on socio-economic activities, and subsequently identify the significant association with the health hazard.

MATERIALS AND METHODS

Literature Search

The systematic review was completed by referring to the standard namely Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PRISMA is performed in evaluating and analyzing related articles on air pollutions from the academic databases. The PRISMA process involves the searching using keywords and article selection and screening. In addition, the processes sorting of inclusion and exclusion criteria, data extraction and synthesis were performed thoroughly for relevant studies and the included studies were examined to fit the objective of systemic review in the subject field. The process of the PRISMA will be further explained in section 2.2 and section 2.3.

Resources

The relevant literature of this systematic review related to air pollution prediction was found from the two major databases, namely Scopus and Web of Science where both covered a variety of study fields. The study fields that are included in both databases are engineering, environmental research, artificial intelligence and health science. In this review study, a few additional databases were added to enhance the comprehensiveness and the possibility of searching the relevant articles of the study subject area. The additional selected databases are Science Direct, IEEE Xplore, Emerald, SAGE Journal and Dimensions. The systematic review of the articles was performed from the year of 2010 to 2022 to ensure only relevant and current state-of-the-art technologies are included in the study.

Article Selection

Article selection explains how the articles were selected based on PRISMA guideline. It involved three steps of identification, screening, and eligibility of the articles to be included in the study. The selection of articles was achieved by using the search string keywords of databases as shown in **Table 1** and identify the relevant articles through the inclusion and exclusion criterion. The articles were then undergone further screening through

TABLE 1 | Search string of databases (Scopus and Web of Science).

Database	Search string
Scopus	(TITLE-ABS-KEY (*"air quality"*) AND TITLE-ABS-KEY (*"machine learning"*) AND TITLE-ABS-KEY (*"health"*))
Web of science	(*"air quality"*) AND TITLE-ABS-KEY (*"machine learning"*) AND TITLE-ABS-KEY (*"health"*)

TABLE 2 | Inclusion and exclusion criteria for the searching in databases.

Criterion	Inclusion	Exclusion
Literature type	Journal (research article)	Journal (review articles), conference proceeding, book series, book chapter, book, encyclopedia
Language	English	Non-English
Timeline	2010–2021	< 2010
Area	Engineering, Environmental Science, Health Science, Artificial Intelligence	Other than Engineering, Environmental Science, Health Science, Artificial Intelligence

the title, keywords and abstract of the articles. Relevant papers were also selected by the field of research such as engineering, environmental science, artificial intelligence and health science. Lastly, it will be screened for the eligibility of the article by revieing the full-text of the articles.

Identification

The identification and selection of articles relevant to the study begin with the selection of keywords of the subject area. Appropriate keywords are crucial to achieve only the relevant articles accurately. Often, in constructing the appropriate keywords, thesaurus and previous research were referred to and considered. Once the keywords have been constructed, the search strings were developed for advanced searching. **Table 1** illustrates the search string of databases (Scopus and Web of Science). In this stage, data analysis is performed to analyze and summarize the content of the selected articles by extracting important techniques, parameters, and deliverables. The is crucial to identify the scientific research gap in this research. The outcomes of the analysis will be discussed in the section of results and discussion.

Moreover, during retrieving the articles from the databases, criteria such as inclusion and exclusion should be considered for appropriate searching, minimizing the chance of retrieving irrelevant articles. Setting the criteria were significant to narrow the searching of subject areas for the latest research relevant to the study. **Table 2** described the inclusion and exclusion criteria that applied in advanced search of the databases. The journal type and timeline are limited to research article within 2010 to 2022, to ensure the articles and resources content are comprehensive and up to date. This is crucial to produce a more specific research and optimized outcomes. From the keywords searching, 2,417 articles from Scopus and 265 articles from Web of Science were retrieved from the search. In addition, from the additional databases, there were a total of 14,442 articles retrieved from the other 5 databases, namely Science Direct, SAGE Journal, Emerald, IEEE Xplore and Dimensions as shown in **Table 3**. Concurrently, other methods such as searching from websites, organizations and citations were carried out to identify relevant studies. From this method, 86 references were identified using the same keywords. In total, 17,210 references were identified including articles and reports via database and other methods.

Equations Screening

From the 17,210 references, 17,124 references were retrieved via databases and registers and 86 references were identified via databases and other methods as shown in **Figure 1**. The references retrieved were divided into two categories namely duplicated reference and irrelevant subject fields. From this process, 13,746 articles were found to be duplicated in the databases and 2 references in the other methods. After the duplicated references were removed, the number of remaining articles were 3,378 and 84 for databases and other methods respectively. After the duplicated references were removed, the remaining references were further screened, by examining the title, keywords and abstract thoroughly. The terms involved were air pollution or air quality and machine learning techniques in the title and keywords.

On the other hand, in the abstract, artificial intelligence or machine learning techniques as well as the impact of air pollution on health were depicted. From the 3,378 articles from databases, 3,298 articles were excluded due to their irrelevant content to the subject areas, resulting in 80 articles that were relevant to the study. However, 16 out of 80 articles were excluded due to unretrievable full-text articles from databases and 11 out of 84 from other methods. Hence, there were only 64 articles from databases and 73 reports were found via other methods. These references were chosen for the further steps of article selections.

Eligibility

Eligibility screening filters the references by reviewing the full text of the articles to ensure the contents is eligible for the study. From the previous steps, full text of 64 articles and 73 references were involved in reviewing the eligibility. The contents of these articles such as the objective, methodology, input features, research outcomes, research contributions were reviewed and examined to ensure the inclusion and exclusion criteria were fulfilled. As a result, only 13 articles were selected from the database and 4 references were selected from other methods. 50 articles and 69 references were excluded from the screening on eligibility due to their irrelevant content. They were not implementing machine learning techniques on predicting the air pollution and irrelevant to the health hazards caused by air pollution. Thus, the total number of articles selected for this study was 18, as illustrated in **Figure 1**.

Quality Assessment and Data Extraction

The quality assessment of the articles selected was performed by the authors to ensure the usefulness of the articles to the

TABLE 3 | Search strings for 7 databases.

Searching texts	Science direct	IEEE Xplore	Web of science	SAGE	Emerald	Dimensions	Scopus
Air pollution AND telehealth	12	0	7	0	0	395	50
Air quality AND telehealth	11	0	2	2	0	335	41
Air pollution AND digital health	9	0	6	0	10	364	2
Air quality AND digital health	10	0	0	1	9	310	71
Sustainable health AND Air quality	51	0	1	1	8	282	77
Sustainable health AND Air pollution	35	0	7	1	6	350	82
Air quality AND Machine learning AND Health	1407	14	168	18	60	7390	2000
Air quality AND Deep Learning AND Health	451	8	74	5	23	2864	94
Total including duplicates	1986	22	265	28	116	12290	2417
Sub-total including duplicates				17124			
Total selected				18			

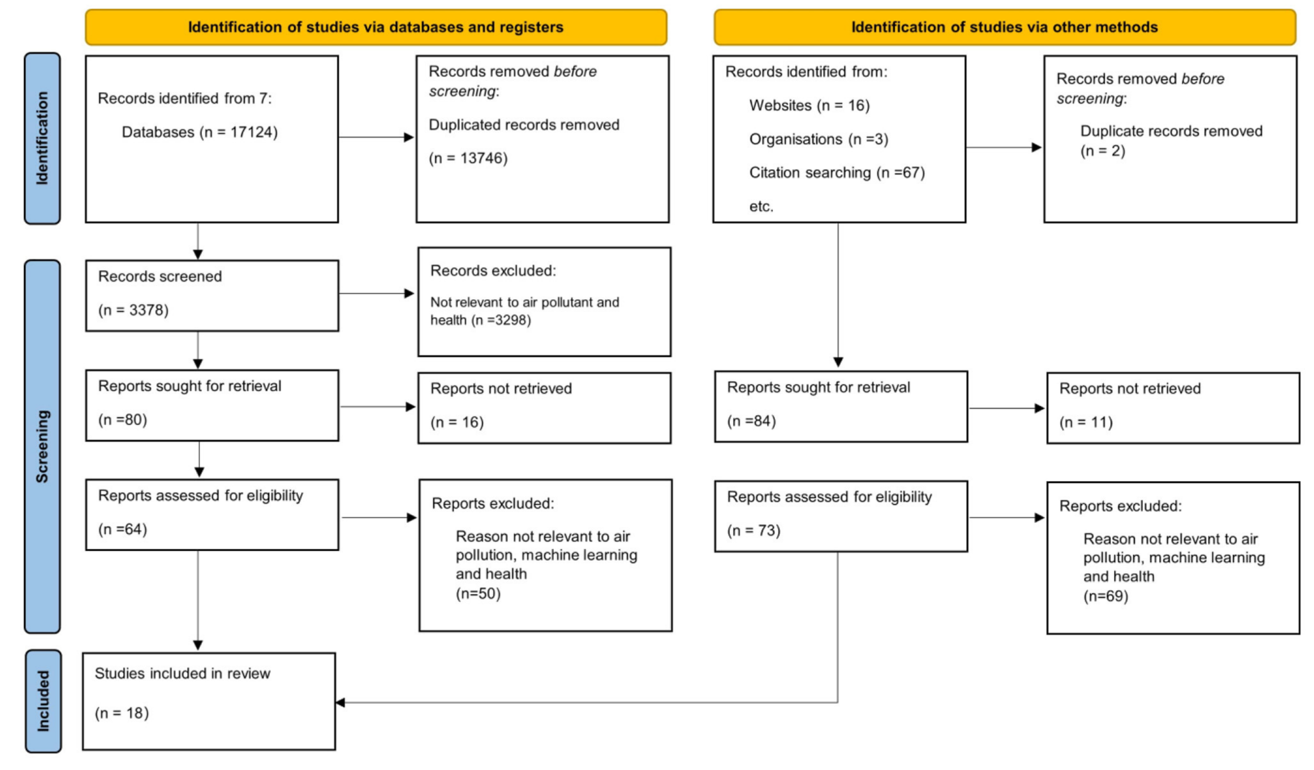

FIGURE 1 | PRISMA flow chart of the review adopted from the PRISMA 2020 statement: an updated guideline for reporting systematic reviews (25).

research. The articles were assessed through the elements such as research aim, research methodology, contribution and highlights from the articles. In addition, the information extracted from the articles was performed for further synthesis and analysis by the authors. The information was compiled in a well-organized summary table. With the tabulation of the information, the crucial parameters and features were extracted and examined thoroughly among the authors.

RESULTS

In this section, the results of the article reviews will be discussed. The general outcomes and contributions from the reviewed articles will be elaborated in the sub-section of background and studies finding. The similarities and research gaps identified from the reviews will be illustrated in a table under the sub-section of the main findings. The analysis is crucial in determining the novelty and the worthiness of the search direction.

Main Studies Findings

The analysis involved 18 articles in the study. From the analysis, we can conclude that the studies showed the significant impacts of air pollution on the health of different regions worldwide. Health hazards identified from the studies were categorized into 3 categories: i) cardiorespiratory diseases, ii) premature and birth death and iii) cancers. In addition, from the analysis, the pollution markers were identified which significantly contributed to the health hazard. The pollution markers were particulate matters (PM), ozone (O_3), carbon oxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and other suspended materials such as volatile organic compounds (26).

According to WHO, these contaminants were potentially harmful to human health as well as to the environment and ecosystem. **Table 4** shows the summary of the general overview of the findings from the review.

Based on the review performed, the most significant and dominant pollutant marker was the particulate matter particles ($PM_{2.5}$). The majority of the studies conducted had analyzed the impact of particulate matter ($PM_{2.5}$, PM_{10}, $PM_{<2.5}$) on human health (3, 5–18, 28). Pollution markers such as ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) are among other important contaminants that were studied by (2–4, 6, 7, 10–15). Chemicals such as nitrogen oxides (NO_x) also played crucial roles in causing adverse health effects in humans, for instance, cardiorespiratory diseases and cancers.

To identify the health hazard contributed by poor air quality, a predictive monitoring system shall be established to trace the hidden interaction and effects of air pollution on health. Predictive or monitoring systems are often developed using artificial intelligence (AI) techniques such as machine learning and deep learning. Machine learning techniques that are commonly utilized are regression, random forest (RF), multilayer perceptron (MLP), support vector machine (SVM) etc while deep learning techniques involved namely deep neural network (DNN), long short-term memory (LSTM) have emerged as new predictive tool in anticipating air pollutions occurrences. On the other hand, aside from the artificial intelligence-based model, there are some models such as mathematical or statistical models being used to assess the association of air pollutants and health hazards. From the review, a few authors implemented predictive models to estimate the health hazards associated with air pollution. Studies by (5, 10–12, 14, 15, 18) determine the potential relationship and the impact of air pollution to health using the artificial intelligence-based model. Among the authors, there are only studies by (10, 15) that discuss the health hazard hospitalization and emergency department visitation due to air pollution. The techniques used by the authors have enhanced long short-term memory (LSTM), neural network and random forest. By using these techniques, the authors, able to predict the hospitalization of cardiorespiratory and chronic respiratory disease due to long term exposure to pollutants (PMs, ozone, CO, NO, NO_x, NO_2, and SO_2). Meanwhile, studies by (3–6, 12, 14, 16, 18, 28) analyzed the impact of air pollution on health and their association using machine learning techniques such as MLP, random forest, neural network, regression, etc. The contribution of these studies enables to predict and forecast the health hazards contributed by air pollution.

A few other researchers study the association between health hazards and air pollution. To assess the association, researchers developed models using mathematical and statistical knowledge (2, 3, 7, 8, 14, 17). These authors performed the association assessment using modeling of Poison's regression, quasi-Poison distribution, generalized additive model (GAM), etc. These models are useful in helping to identify the association of the health hazards due to pollutants such as $PM_{2.5}$, SO_2, NO_2, O_3, and VOC. From the reviews, often the pollutants mentioned associated with maternal complications and birth defects, premature deaths, mortality and morbidity on Covid-19, cancers, etc. The models are useful in examining the association between the air pollutant and health implications due to air pollution. Hence, prediction of pollution and its impact on health could be performed by developing predictive and monitoring models.

In different studies conducted by Cazzolla Gatti, Velichevskaya (6), Sethi and Mittal (12), Tusnio, Fichna (14), a chemical substance such as benzene (C_6H_6) enhanced the effect of air pollution on the human health such as cancers and even increase mortality risk for Covid-19 especially during air pollution. In addition, from the study completed by (12), toluene and ammonia (NH_3) are important parameters in determining the effect of air pollution on the mortality of Covid-19 during air pollution seasons. On the other hand, (4) have explored a new perspective in predicting chemical compounds such as methane (CH_4), formaldehyde (CH_2O), aerosol and their association to Covid-19 mortality during air pollution.

In the study performed by (14), chemical compounds such as benzene (C_6H_6), heavy metals such as lead (Pb), Arsenic (As), Cadmium (Cd), and Nickel (Ni) which are in PM10, and aromatic hydrocarbon, benzo-alpha-pyrene (BaP) can caused various types of cancers. From the review, it is proven that these chemical compounds and heavy metals significantly causing cancers in the human body. It is reported that NOx caused intestines and colorectal cancer, $PM_{2.5}$ contributed to lung cancer formation while Arsenic, benzopyrene and nitrogen dioxide trigger large intestine diseases after long-term exposure.

From the review summarized above, we can conclude the health hazard of air pollutions were diverse. From the recent findings of Amoroso et al. (4), Cazzolla Gatti et al. (6), Hadei et al. (7), Sethi et al. (12), air pollution brings impacts on human health as well as to the Covid-19 related hazards. The studies showed that the air pollution affected the mortality and fatalities of the Covid-19 patients, as well as the infected rate or morbidity of Covid-19 with the presence of pollutants in the air. Among the common pollutants extracted from these studies are $PM_{2.5}$, PM_{10}, NO_2, O_3, and VOC. Besides that, factors such as temperature and meteorological factors are also considered in the studies.

On the other hand, according to Peng et al. (10), Reid et al. (11), Usmani et al. (15), Wang et al. (16) air pollution brings impact to the respiratory system, causing cardiovascular disease. The cardiovascular and respiratory diseases often involved asthma, respiratory infection, chronic obstructive pulmonary diseases (COPD). Besides, air pollution also affects heart rate

TABLE 4 | Summary and overview of the review findings.

Authors	Air pollution markers	Health hazard impact from air pollution	Techniques	
			Prediction/ monitoring model	Association assessment
Reid et al. (11) *(United States (US))*	Particulate Matter ($PM_{2.5}$), Ozone (O_3)	Respiratory diseases	Generalized additive model (GAM), generalized boosting model (GBM), k-nearest neighbor model regression, lasso regression,	Poisson generalized estimating equations
Usmani et al. (15) *(Malaysia)*	Particulate Matters (PM_{10}), Ozone (O_3), carbon monoxide (CO), nitrogen oxides (NO_x), nitrogen dioxides (NO_2), nitrogen monoxide (NO), sulfur dioxide (SO_2)	Cardiorespiratory diseases	Enhanced long short-term memory (ELSTM)	-
Tusnio et al. (14) *(Poland)*	Sulfur dioxide (SO_2), nitrogen dioxides (NO_2), nitrogen oxides (NO_x), carbon monoxide (CO),Ozone (O_3), Particulate Matters ($PM_{2.5}$,PM_{10}), benzene (C_6H_6), Lead (Pb), Arsenic (As), Cadmium (Cd), Nickel (Ni), Benzo(a)pyrene (BaP) in PM_{10} size	Various types of cancers	Random forest	Pearson correlation coefficient
Wang et al. (17) *(China)*	Particulate Matters ($PM_{2.5}$, and PM_1)	Blood cell counts for pregnancy preparation	-	Generalized additive mixed model (GAMM)
Achebak et al. (2) *(Spanish)*	Ozone (O_3), nitrogen monoxide (NO),	Premature mortality	-	Quasi-Poison regression model
Wang et al. (16) *(China)*	Particulate Matters ($PM_{2.5}$, and PM_1)	Blood pressure	Random forest model	Generalized additive mixed model (GAMM)
Zani et al. (4) *(Equatorial Asia)*	Particulate Matters ($PM_{2.5}$, and PM_{10})	Premature mortality	Deep neural network (DNN)	Generalized exposure mortality mixed model
Zou et al. (18) (*Western U.S, Pacific Northwest (PNW)*)	Particulate Matters ($PM_{2.5}$)	Mortality	Ordinary multi-linear regression, generalized boosting method, random forest	-
Cazzolla Gatti et al. (6) *(Italy)*	Particulate Matters ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), Benzene (C6H6), ozone (O_3)	Mortality and infectivity of COVID-19	Random forest regression, Pearson's correlation coefficient	-
Sethi et al. (12) *(India, Delhi)*	Carbon monoxide (CO), sulfur dioxide (SO_2), particulate matters ($PM_{2.5}$), Ozone (O_3), nitrogen dioxide (NO_2), ammonia (NH_3), toluene (C_7H_8), benzene (C_6H_6)	Covid-19 fatalities	Decision tree, linear regression, random forest	-
Peng et al. (10) *(China)*	Carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), particulate matters ($PM_{<2.5}$)	Respiratory disease	Bagging, adaptive boosting, and random forest	-
Shen et al. (13) *(South Korea)*	Particulate matter ($PM_{2.5}$ and PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2)	-	Prophet forecasting model (PFM)	-
Al Noaimi et al. (3) (*Lebanese Republic*)	Particulate Matters ($PM_{2.5}$), sulfur dioxide (SO_2), nitrogen dioxide (NO_2)	Prenatal and birth defect	Multivariate regression models	-
Li et al. (9) *(China)*	Particulate Matters ($PM_{2.5}$)	Esophageal cancer	-	quasi-Poisson generalized linear model
Amoroso et al. (27) (*European Countries*)	carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), methane (CH_4), formaldehyde (CH_2O), aerosol	Covid-19 mortality	Random forest	-
Hadei et al. (7) *(Iran)*	Particulate Matters ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), ozone (O_3),	Covid-19 mortality and morbidity	Distributed-lag non-linear model (DLNM), generalized additive model (GAM)	-
Li et al. (8) *(China)*	Particulate Matters ($PM_{2.5}$)	Esophageal cancer	-	Geographic weighted Poisson Regression
Ren et al. (28) *(China)*	Particulate Matters (PM_{10})	Congenital heart defects	Random forest (RF) and gradient boosting (GB)	-

and blood pressure as mentioned by Wang et al. (16). The study shows that the systolic and diastolic blood pressure increases after experiencing long-term exposure to particulate matter particles. In addition, air pollution exposure tends to increase the visits and admission to the emergency department and eventually admission to the hospital. This can be observed from the study of Peng et al. (10), Usmani et al. (15), which related to the chronic respiratory and cardiorespiratory diseases. It could also lend to fatality for long term effects.

Moreover, the analyses from the review concluded that air pollution hazard to health by causing various types of cancer, namely esophageal cancer, lung cancer, malignant neoplasm, or tumor formation in various parts of the body such as the large and small intestine, etc. Cancer formation occurs often due to long term exposure to harmful pollution markers such as $PM_{2.5}$, NO_2, and compounds such as arsenic and benzo-alpha-pyrene (BaP) in the dust (14). These harmful components are carcinogenic which bring chronic impacts to the health, and worse, it could result in mortality. Last but not least, from the review, exposure to air pollution could lead to adverse pregnancy outcomes, in both infant and pregnant women proven by Achebak, Petetin et al. (2), Al Noaimi et al. (3), Bruni Zani et al. (5), Wang et al. (17).

According to Al Noaimi et al. (3), exposure to $PM_{2.5}$ during the pregnancy, especially first trimester causes higher risk of birth defect in infants and genitourinary defect in pregnant women, while according to Bruni Zani, Lonati (5) long term impact of $PM_{2.5}$ exposure increases the premature deaths in babies. Aside from $PM_{2.5}$, NO_2, and O_3 also contributed to premature mortality, proven by Achebak, Petetin et al. (2). From the study, it is concluded that the premature mortality rate decreases with the NO_2 reduction. Besides, exposure to air pollutants such as PMs contributes to complications to women preparing for pregnancy and laboring as mentioned in the studies done by Wang et al. (17). In the same research, it was found that white blood cells (WBC), upon long period of exposure to PMs, is greatly reduced and at the same time, red blood cells (RBC) and thrombocytes increased. These turns of events could lead to complications such as immunocompromised due to decrement of WBC and cardiopulmonary diseases (29) such as stroke and myocardial infarction due to increment of RBC (30, 31). In addition, it could also contribute to longer Disability-Adjusted Life Years (DALY) in pregnant women and infants. In addition, maternal exposure to PM_{10} also increase the susceptibility to congenital heart diseases especially during the weeks 3 to 8 in pregnancy, which is the prenatal cardiac development window (28).

Impact of Air Pollution Markers on Human Health

Previous studies demonstrated the relationships and the association between air pollutants and their impact on health, as well as techniques to predict air pollution events. From the review, we found that the pollution markers vary on the events of accidents. For instance, pollution markers of $PM_{2.5}$ and O_3 are found in wildfires. This can be supported by the hypothesis of the presence of air pollution markers present in the air are determined by socioeconomic and human activities. Different activities and events produce different air pollutants which lead to various health effects on the human body. Predictive systems such as random forest, long short-term memory and neural network are capable to predict the potential air pollution and its adverse health effect. In the following subsections, we will discuss the health hazards due to pollutants and provide recommendations on the new techniques to predict the health impact due to pollution in future research. There are various pollution markers such as particulate matter particles, ozone, carbon monoxide, nitrogen oxides etc. In this section, we are interested to discuss the formation of pollutants and how do they impact human health.

Air Quality Index (AQI)

Air quality index (AQI) refers to an index on the degree of air contamination associated with its health implications which are made available to the public employed by the government. As the AQI grows, so do the public health dangers. The AQI was renamed and amended by the United States Environmental Protection Agency (U.S. EPA) in 1999 from the Pollution Standard Index (33). The AQI varies in all the countries around the world according to the air quality standard established in the country. To assess the air quality level, there are 6 levels of pollution, labeled with different colors symbolizing the levels of concern, namely, good (green), moderate (34), unhealthy for sensitive groups (orange), red (unhealthy), purple (very unhealthy), maroon (hazardous). The levels of pollution are categorized according to the index values, which is computed from the equation as shown below. **Table 5** present the classifications of AQI recommended by U.S. EPA.

$$I_P = \frac{I_{Hi} - I_{Low}}{BP_{Hi} - BP_{Low}} \left(C_p - BP_{Low} \right) + I_{Low}$$

I_p = Index of pollutant P
C_p = Concentration of pollutant P
I_{Hi} = AQI corresponding to Index of BP_{Hi}
I_{Low} = AQI corresponding to Index of BP_{Low}
BP_{Hi} = Breakpoint that is higher than or equal to C_P
BP_{Low} = Breakpoint that is lesser than or equal to C_P

To determine the pollution level of the air, EPA has established National Ambient Air Quality Standards (NAAQS) based on the Clean Air Act. The NAAQS is developed for the primary pollutant, which is hazardous to public health and the environment, namely carbon monoxide, lead, nitrogen dioxide, ozone, PM particulate, and sulfur dioxide. **Table 6** present the NAAQS table and illustrate the recommended threshold of the concentration of the pollutant in assessing the air quality.

To standardize the quality standard, WHO (1) had established the air quality guidelines in 2005 and published them in 2006, namely Air quality guidelines – global update 2005. The purposes of the guidelines are specific to provide evidence-based recommendations in form of air quality guidelines (AQG) levels, as well as an indication of the shape of concentration-response function (CRF) in connection to adverse health outcomes for pollutants such as particulate matters (PM). Nitrogen dioxide

TABLE 5 | Recommendation of Air Quality Index (AQI) classification by U.S. EPA (32).

AQI color	Index value	Pollution level of concern	AQI description
Green	0–50	Good	Air pollution and satisfactory air quality pose little or no harm.
Yellow	51–100	Moderate	Air quality is adequate. Some people, however, may be at danger, particularly those who are highly sensitive to air pollution.
Orange	101–150	Unhealthy for sensitivity groups	Members of the sensitive group may suffer health consequences. Less liked to have an impact on the broader populace.
Red	151–200	Unhealthy	Some members of the general population may suffer from health consequences, while members of sensitive groups may suffer from more significant health problems.
Purple	201–300	Very unhealthy	Health warning: Everyone is at elevated risk of adverse health impacts.
Maroon	≥301	Hazardous	Everyone is most likely to be impacted by emergency situations, according to a health warning.

TABLE 6 | Recommendation of pollutant concentrations by National Ambient Air Quality Standards (NAAQS) by U.S. EPA (35).

Pollutant		Average time of exposure	Level of exposure
Carbon Monoxide (CO)		8 h	9 ppm*
		1 h	35 ppm*
Lead		3 months average	0.15 ug/m^3***
Nitrogen Dioxide (NO_2)		1 h	100 ppb**
		1 year	53 ppb**
Ozone (O_3)		8 h	0.070 ppm*
Particulate matters / particles pollutions	$PM_{2.5}$	1 year	12.0 ug/m^3***
		1 year	15.0 ug/m^3***
		24 h	35.0 ug/m^3***
	PM_{10}	24 h	150.0 ug/m^3***

*ppm = parts per million by volume.
**ppb = part per billion by volume.
***ug/m^3 = micrograms per cubic meter or air.

(NO_2), ozone (O_3), sulfur dioxide (SO_2), and carbon monoxide (CO). It is useful for both long- and short-term pollutant exposure. The established guidelines are important to meet the air quality guidelines by providing interim targets, which to direct the reduce-effort activities. In addition, the guidelines play an important role in providing good practice statements in particular types of particulate matter management where there is insufficiency of evidence in deriving quantitative air quality guidelines threshold but emphasizes the health significance. According to the guidelines, recommendations such as air quality guideline (AQG) and the interim targets are given for the primary pollutants mentioned above as illustrated in **Table 7**.

However, in Malaysia, Department of Environment, Ministry of Environment and Water has established its own ambient air quality measurement which is closely referred to the PSI prepared by U.S. EPA. The air quality measurement in Malaysia is presented as Air Pollutant Index (API). The pollutants were monitored at varied average times in accordance with the standards given by WHO, based on the requirements of the Malaysian Ambient Air Quality Standard (MAAQS) in terms of human health consequences (37). In Malaysia, API are categorized into 5 categories as presented in **Table 8**.

To compute the API, the New Ambient Air Quality Standard was developed in accordance to standardize the air pollutant concentration threshold. The pollutants involved are particulate matters (PM_{10} and $PM_{2.5}$), ozone (O_3), sulfur dioxide (SO_2), carbon monoxide (CO), and nitrogen dioxide (NO_2). **Table 9** shows the air pollutants concentration levels adopted by the New Ambient Air Quality Standard.

Particulate Matters

Particulate matters (PM), which are common airborne particles, is a complicated mixture of solids and aerosol made up of minute liquid droplets, solid fragments and solid cores coated in liquid (39). PM has been categorized into 3 categories based on the particle sizes, namely coarse particulate matter (PM_{10}), fine particulate matter ($PM_{2.5}$), and ultrafine particulate matter ($PM_{0.1}$). The difference between PM_{10} and $PM_{2.5}$ is the aerodynamic diameter where PM_{10} has a diameter of 10 µm while $PM_{2.5}$ has a diameter of 2.5 µm. Diameter in ultrafine particles is the smallest, which is smaller than 0.1 µm.

$PM_{2.5}$ particles are often composed of substances such as sulfate (SO_2). Nitrate (NO), ammonium (NH^+), organic compounds, and metal such as lead (Pb), Cadmium (Cd), vanadium (V), nickel (Ni), Copper (Cu), and Zinc (Zn), and hydrocarbons (40). The sources of the fine particles, $PM_{2.5}$ normally can be found in the combustion of coal, oil, and gasoline. It is also produced from the transformation of NO_x and SO_2. High temperature processes such as smelters and steel mills tend to produce the PM_2.5. Based on (41), the presence of $PM_{2.5}$ in the air or the lifetime of $PM_{2.5}$ can be last from days to weeks, meanwhile, PM_{10} only lasts for minutes to hours. Fine particles ($PM_{2.5}$) have a travel distance of 100 to 1000 kilometers, while the travel distance is limited to only 1 to 10 km (42). Coarse particles (PM_{10}) composed of dust such as soil dust, resuspended dust, street dust and oil fly ash. Metal oxides such as silicon (Si), aluminum (Al), Titanium (Ti), calcium carbonate ($CaCO_3$) etc. and substances such as pollen and mold spores are categorized

TABLE 7 | Summary of Air Quality Guidelines (AQG) levels and interim targets recommendations by WHO (36).

Pollutant	Average time	Interim Target 1 (IT-1) $\mu g/m^3$	Interim Target 2 (IT-2) $\mu g/m^3$	Interim Target 3 (IT-3) $\mu g/m^3$	Interim Target 4 (IT-4) $\mu g/m^3$	Air Quality Guidelines Levels $\mu g/m^3$
$PM_{2.5}$	Annual	35	25	15	10	5
	24-h	75	50	37.5	25	15
PM_{10}	Annual	70	50	30	20	15
	24-h	150	100	75	50	45
O_3	Peak Season	100	70	-	-	60
	8-h	160	120	-	-	100
NO_2	Annual	40	30	20	-	10
	24-h	120	50	-	-	25
SO_2	24-h	125	50	-	-	40
CO*	24-h	7	-	-	-	4

*In mg/m^3.

TABLE 8 | Air Pollution Index classification recommended by Department of Environment (DoE), Malaysia (37).

Air Pollution Index (API)	API status	Color	API description
0–50	Good	Blue	There is little pollution, and these are no harmful health effects.
51–100	Moderate	Green	It has no harmful effects on health.
101–200	Unhealthy	Yellow	Sensitive folks should avoid. Health conditions for the elderly, pregnant women, children, and persons with heart and lung issues deteriorate.
201–300	Very Unhealthy	Orange	Unhealthy for the public. Worsening health and a reduced tolerance for physical activity might lead to lungs and heart issues.
>301	Hazardous	Red	Emergency

TABLE 9 | Ambient air quality standard in Malaysia by Department of Environment (DoE), Malaysia (38).

Pollutant	Averaging time	Ambient air quality standard
PM_{10}	Annually	40 $\mu g/m^3$
	24 h	100 $\mu g/m^3$
$PM_{2.5}$	Annually	15 $\mu g/m^3$
	24 h	35 $\mu g/m^3$
SO_2	1 h	250 $\mu g/m^3$
	24 h	80 $\mu g/m^3$
NO_2	1 h	280 $\mu g/m^3$
	24 h	70 $\mu g/m^3$
O_3	1 h	180 $\mu g/m^3$
	24 h	100 $\mu g/m^3$
CO	1 h	30 mg/m^3
	24 h	10 mg/m^3

under coarse particles. Particles which are having course size often produce from soil track, roads and streets, suspension from soils and industrial dusts. Coal and oil combustion also play an important role in the coarse particle formation (42). High concentration of particulate matters distribution often happens in the area or nearby sources such as industrial area, agricultural activities, and fuel combustions.

High levels of PM pollution are well-known in causing adverse health in humans, no matter whether under short-term or long-term exposures. The most common and major health effects reported are cardiovascular and respiratory morbidity and mortality. Other effects such as adverse fatal development and infancy, induction or exacerbation of diabetes mellitus and cancer have been linked to the consequences of PM exposure (43–48). The impact of PM exposure to cardiovascular and respiratory systems should not be underestimated. In respiratory system, pollution has become the key contributor to the Global Burden of Diseases (GBD) (49, 50). Based on the GBD 2015, PM, specifically $PM_{2.5,}$was the fifth leading cause of death, contributed to 4.2 million of death, that represent global deaths of 7.6%, 10.31 million were facing disability-adjusted life-years (DALYs), which is about 4.62% of global DALYs rate (51). According to Cohen, Brauer (51), various studies have been done in proving the effect $PM_{2.5}$ exposure that is closely associated with the variety of respiratory diseases. There has been positively increment in the tendency of respiratory infections, outpatient visits frequency, emergency visit and hospitalization frequency for respiratory infection.

Inhalation of particulate matters increases the exposure and adverse health effect in respiratory system. Fine particles ($PM_{2.5}$) possess the greatest risk to human health where the particle size fine enough to penetrate deep into human respiratory tracts and lungs, as well as the bloodstream while PM_{10} has a lower risk in causing human health effect due to its coarse size. Although PM_{10} can cause irritation to eyes, nose and throat, due to the bigger size particle, it is unable to penetrate into bloodstream and lungs (52). Based on (53), particles size between 5 µm to 10 µm tends to be deposited in tracheobronchial tree whereas particles with diameter of smaller than 5 µm is more susceptible to enter the respiratory bronchioles and alveoli, where gaseous exchange takes place. Fine particles with diameter smaller than $1\,\mu m$ has a similar characteristic and as gas molecules, they able to diffuse into the bloodstream, subsequently translocate into cell tissue and/or circulatory system (54). According to (40), studies concluded that PM particles also tend to trigger airway injury and inflammation which increased the production of reactive oxygen species (ROS) in vivo, consequently damage in cellular and tissue. Besides, PM particles also contributed to high impact on lungs and cardiovascular system diseases by inducing the pro-inflammatory cytokinesis production. These genotoxic effects in human lung cells, have majorly caused causing oxidative stress (40).

Many experimental studies have been and successfully proven that the exposure of $PM_{2.5}$ potentially makes the body more vulnerable to pathogens by weakening the respiratory host defense. Impairment of respiratory host defense included defective airway epithelial host defense functions, alterations in respiratory microecology and insufficiency and dysfunction of immune cells (55). A healthy and normal airway epithelial is free from pathogens, protected by a barrier function of epithelium, namely mucociliary clearance. (55) and (56), claims that fine particles ($PM_{2.5}$) exposure impairs the bronchial mucociliary system, which reduces bacterial clearance. The exposure of $PM_{2.5}$ has disrupted the defense function of the mucociliary system, as well as the secretion of antimicrobial peptides, hence, increase the vulnerability of the body to pathogens.

In addition, studies found that upper airway in human consisted of bacterial flora, which is a crucial natural immune defense mechanism. The bacterial flora established a biological barrier against foreign materials and harmful germs by a space-occupying effect, nutritional competition and release of bacteriostatic or bactericidal chemicals (57–59). Moreover, $PM_{2.5}$ contributed to insufficiency and dysfunction of immune cells, causing adverse health impact in humans. $PM_{2.5}$ exposure has reduced the phagocytic phagocytosis and increased the chance of pneumonia, by getting *S.aureus* infection (48). Besides, $PM_{2.5}$ reduced the immune system by declining the phagocytic capacity of macrophages, diminishing the production of antimicrobial oxidants in response to *L. monocytogenes* in macrophages. This is crucial as low production of antimicrobial oxidants increased the chance of respiratory infections. *L. monocytogenes* infection, bacterial infections often lead to meningitis, as well as spontaneous abortions in pregnant women. Not forgetting the impact of $PM_{2.5}$ on metabolic activation, it is frequently found in laminar organelles. $PM_{2.5}$ will have a variety of harmful consequences on the targeted cells. This can be occurred due to the metabolically activation of organic chemicals in $PM_{2.5}$ by xenobiotic-metabolism enzyme system. The aryl hydrocarbon receptor (AhR) is activated by the release of organic molecules (VOCs and PAHs) from $PM_{2.5}$. Subsequently, enhanced the AhR-regulated gene expression which forms the xenobiotic-metabolism enzyme system (60).

Furthermore, exposure to PM particles induce cardiovascular diseases such as ischemic heart disease, heart failure, as well as cerebrovascular diseases (61). Studies proved that the risk of myocardial infraction, fatal and non-fatal ischemic heart diseases and heart failure incident are associated with the ambient exposure no matter in acute or chronic exposure (31, 62–67). According to WHO (1), 3.7 millions of death are caused by the outdoor ambient pollution, 80% of deaths are resulted from heart diseases and stroke. As mentioned earlier, fine particles and ultrafine particles are small in sizes, and due to their chemical composition and charge, the particles are able penetrate through the bloodstream, and move to the other parts of the body.

A low concentration of PM exposure in the blood stream has a high possibility in cumulating toxicity (68). According to (69), PM exposure has both direct and indirect actions onto the cardiovascular system. These include the deposition of the particles onto the vascular endothelium, an inner layer of blood vessels that contact the blood, could result in the local oxidative stress and inflammation. Subsequently, resulting the instability of atherosclerotic plaque and thrombus formation (70). In addition, according to (71), PM causes elevation of ejection fraction and premature ventricular beats. These events often lead to adverse impact onto cardiac especially patients with coronary heart disease by increasing the unhealthy cardiac oxygen needs and exacerbate the ischemia condition. Besides, the indirect effect of PM is also crucial in contributing burden to cardiovascular system. The indirect event often caused by the inflammation in lungs, lead to atherosclerosis progression and blood coagulability and endothelial dysfunction, finally exacerbate myocardial ischemia (69). In addition, exposure of PM is hypothesized to activated the autonomic nervous system (ANS), causing autonomic balance to be disrupted and sympathetic tone to be favored (72, 73). (73) claimed that an elevated risk of cardiovascular disease is linked to the overactive sympathetic tone, by inducing prohypertensive vasoconstriction and proclivity for arrhythmias. In investigating the impact of PM exposure on the cardiac, the modulation of microRNAs (miRNAs) has become one of the risk factors to be investigated on. This is especially critical when involved in systemic inflammation, endothelial dysfunction and atherosclerosis (74, 75).

Often, PM pollution is concerned among the public and researchers due to its adverse impact on human health and climate. According to WHO suggestion, the concentration of $PM_{2.5}$ should not exceed 10 $\mu m/m^3$ annually and 25 $\mu m/m^3$ daily to ensure the cleanliness of the air while the concentration of PM_{10} should be controlled within 20 $\mu m/m^3$ annually and 50 $\mu m/m^3$ daily. This is to ensure the concentration of the particles in the atmosphere is within the healthy level and has a low health impact on humans. Due to the various sources of PM particles, it is not an easy task to determine the peak concentration, or the trend of PM particles released in the atmosphere daily and annually. To monitor the concentration of PM particles, Air Quality Index (AQI) plays an important role in determining the air quality. AQI in Malaysia is adopted from the guidelines provided by U.S. EPA. To assess the air quality, the PM concentration often referred to the AQI as a baseline to determine the concentration level and its impact on humans. Therefore, it is important to establish a system in forecasting the

PM concentration, concurrently, predict the peak concentration of PM particle daily and annually according to the AQI.

Carbon Monoxide

Carbon monoxide (CO), a colorless and odorless gas that is produced from incomplete combustion (76). Carbon monoxide (CO) is often produced during combustion with low oxygen level or low mixing, which often happens in motor vehicles, power stations, waste incinerators, domestic gas boilers and cookers. Although CO is not poisonous, it possesses an adverse temporary effect on the human respiratory system by inhibiting the oxygen uptake in hemoglobin. This is due to the nature of CO, which has a far higher affinity to hemoglobin than oxygen, which leads to severe poisoning in case of long-term CO exposure (77). Ones inhaling excessive CO will experience symptoms such as dizziness, headache and nausea, while experience disorientation, unconsciousness and death (78).

Sulfur Dioxide

Sulfur dioxide (SO_2), a colorless gas in physical characteristic, alongside a choking and suffocating odor. SO_2 is primarily produced by human activities for instance, combustion of coal and oil, often happening in power plants, or from copper smelting. Meanwhile, it can also be produced or released naturally into the air by volcanic eruptions (79). According to WHO, SO_2 shows adverse effect on sensitive cohort such as asthmatics patients with respiratory diseases (36). This is due to its ability to penetrate the body, mainly through the respiratory system. Exposure to SO_2 often contributed to daily death number and hospital admissions for respiratory or cardiovascular causes such as asthma and chronic obstructive pulmonary disease (COPD). In long-term exposure to SO_2, studies proved that SO_2 plays an important role in the frequency and possibility of wheeze and symptoms such as cough and phlegm (80–82). Chronic effects of SO_2 exposure included decrement in lung function or changes in the lung function. SO_2 tends to cause inflammation on the respiratory tract and raises the risk of infection. Moreover, excessive SO_2 exposure could induce coughing and mucus flow, aggravates asthma and chronic bronchitis.

Nitrogen Oxide

Nitrogen oxides (NO_x) is a big umbrella that indicated a group pollutants gases produced by the reaction between nitrogen (N_2) and oxygen (O_2) (83). NO_x is a colorless and odorless gas which is also formed by fuel combustion at high temperature. NO_x is formed when the "fixation" of nitrogen in the dilution air into NO_x under a high temperature (84). The pollutant gases under the umbrella of NO_x are NO, NO_2, N_2O, NO_3, N_2O_3, N_2O_4, and N_2O_5(85). The main sources of NO_x are mobile and stationary sources such as motor vehicles or transportation fuel combustion, and power or heating generation. Often, the major or predominant nitrogen oxides involved in the air pollution are nitrogen dioxide (NO_2) and nitric oxide (NO) (86). NO_2, which is visible in reddish brown, along with particles in the air. In urban areas, when the pollution of NO_2 occurs, a layer of reddish-brown color can be seen over the air. Meanwhile, nitric oxide is formed from the oxidation of nitrogen dioxide. Although the gases are colorless and odorless, it causes an adverse and harmful effect to the health when penetrates the body through inhalation. Excessive inhalation of the NOx will irritate the respiratory system, and induce diseases such as coughing, wheezing, dyspnea, bronchospasm, and pulmonary edema (77). According to U.S. EPA (87), NO_2 plays an important role in increasing inflammation of airways and asthma attacks, especially in children, reducing lung function, as well as increasing the possibility of emergency and hospitals admission. Long-term exposure of NO_x tends to impact health by causing chronic lung diseases, increase the chance of impairing the smelling sense in human. It also causes irritation symptoms to eyes, throat and nose. Based on (88, 89), NO_2 concentration often shows the highest reading in urban regions, especially in urban areas where the roadways or traffic are busy.

Ozone

Ozone (O_3), a gas molecule that is made up of three oxygen atoms in the presence of a third-body molecule capable of absorbing the reaction's heat. The stratosphere, a layer high in the upper atmosphere which protects humans from the UV radiation produced by the sun. However, when the ozone air pollution happens in the troposphere, which is at the ground level, it is harmful to humans when inhaling, caused major health concerns (90). The upper respiratory tract absorbs most of the ozone after inhalation, which is carried into the intrathoracic airways. Often, oral inhalation also allows ozone absorption into the body, a relatively lower rate. However, higher penetration of ozone into the lung is possible to occur when carrying out an aggressive activity (91). (92) and (77) claims ozone-induced toxic consequences have been documented in metropolitan areas all over the world, raising issues in biochemical, morphologic and functional and immunological aspects. According to (91), ozone causes adverse health effects by dissolving in a thin layer of epithelial lining fluid in the lower respiratory tract after inhalation. Due to its characteristic of low solubility in water, ozone is unable to be removed effectively from the body by upper respiratory tract. It can only be removed as secondary oxidation products that caused oxidative stress, contributed to cellular injury and altered cell signaling in respiratory tract, inflammation as well as chemokines and cytokines, vascular endothelial adhesion molecules. Besides, the ozone contributed to acute and chronic health effect such as mortality, pulmonary system effect caused by ozone exposure relative to respiratory health, cardiovascular diseases such as vascular oxidative stress, elevated heart rate and diastolic pressure, inflammation, and decreased heart rate (93, 94). Meanwhile, in chronic health effects, asthma, life expectancy reduction and lung function effects as well as atherosclerosis are often linked to the consequences of long-term exposure of ozone (O_3) (91).

Heavy Metals

In air pollution, heavy metals play an important role in causing irreversible effects on human health. Not only to human health, but heavy metal contamination is also threatening the environment and ecosystem. There are various heavy metals such as lead (Pb), arsenic (As), copper (Cu), mercury (Hg), Cadmium (Cd), Vanadium (V), Titanium (Ti) and etc. Due to the emergence of anthropogenic activity and increase of the use of heavy metals, mining, smelting, foundries as well as leaching of metals occurred. These activities are important in contributing to heavy metal pollutions (95). Hence, it has impacted the terrestrial and aquatic. Exposure to heavy metals is often related to adverse health effects such as DNA damage, causing carcinogenic effects, cell or cell membrane damage, cellular function reduction as well as neurotoxicity where the nervous system is damaged. Among the heavy metals that contributed majorly to pollution are lead (Pb), arsenic (As), copper (Cu), mercury (Hg), Cadmium (Cd), and nickel (Ni). Lead (Pb) exposure often occurs through inhalation of dust particles or aerosols contaminated with Pb, as well as through consumption of polluted sources of food (96). According to (97), high exposure or poisoning of Pb has a likelihood of damaging the kid ney, liver, heart, brain, skeleton and nervous system. It also causes auditory impairment, gastrointestinal damage and cognitive skills and health. Cancers and diseases such as Alzheimer's have a higher possible in the exposure of Pb (98). Meanwhile in Cadmium (Cd), according to (96), studies show that excessive exposure to Cd can damage respiratory, cardiovascular, renal, skeletal system and cancer development. Workers from metal industries are the major cohort to expose to Cd (99). On the other hand, exposure to mercury can be caused by consumption of agricultural products and dental care-amalgams (100). The effect of ingestion of mercury includes gastrointestinal toxicity, neurotoxicity, and nephrotoxicity as the mercury exposure are being aggregated in kidneys liver and neurological tissues (101). According to WHO, arsenic, a highly toxic metal which often exposed to human by eating, drinking, and preparation of food and irrigating crops using contaminated water as well as industrial processes (102). Chronic health effects due to long-term exposure of arsenic included skin lesions, patches on limbs (palms and soles), cancers such as skin cancer, lung cancer and bladder cancer. Besides, long-term exposure of arsenic also causes adverse pregnancy outcomes such as infant mortality, development defects and cognitive health. It could also cause irreversible effects such as pulmonary disease, cardiovascular disease, and myocardial infraction. And worst, it could cause mortality (103, 104).

Other Pollutants (VOCs and PAHs)

Pollutants such as volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs) have toxicology potential which is harmful to human health. Volatile organic compounds are known as a crucial pollutant that existed in variety of industrial fields (105). VOCs presented in the emission of fossil fuels and motor vehicles in the ambient air (106). However, it is more common to find VOCs in indoor pollution, which is produced from paints, photocopy machines and air fresheners and disinfectant. Compounds such as toluene, benzene, and xylene are under the big umbrella of VOCs, which have been linked to the development of cancers in humans (77). Exposure to VOCs contributed to both short term and long-term health effects such as hazardous and toxic reactions, irritation of the eyes, nose, throat and mucosal membranes (107). Besides, exposure to high levels of VOCs can lead to cancers and central nervous system damage as chronic exposure effect.

Polycyclic aromatic hydrocarbons (PAHs) are a group of organic compounds that are composed of two or more fused aromatic rings. Compound such as naphthalene, benzo[a]pyrene, pyrene, fluorene, acenaphthylene and etc are under the umbrella of PAHs and these compounds are labeled as high priority pollutants (108). PAHs often produced by incomplete combustion of fuels and organic materials such as coal, petrol, oil and wood. It can also be found in the food, water, soil and plant (106, 109). Due to its presence in the food and water, especially in barbecue, it could cause cancer due to the carcinogens present in the food. PAHs can also be found in indoor pollution sources such as tobacco smoke and wood stove (106). According to (77) PAH compounds are recognized as an crucial risk factor for lung cancer which they is toxic and contains mutagenic and carcinogenic substances. Exposure of PAHs can occur through ingestion, inhalation, and dermal contacts (110). The most significant exposure of PAHs is through the inhalation of PAHs into the human body. Exposure of PAHs contributed to adverse health effects such as the risk of lung cancer (111). Acute excessive exposure to PAHs possesses symptoms such as irritation of eyes, nausea, vomiting and diarrhea (15). Chronic health effects such as immunity declined, organ damage, cataracts, respiratory issues such as breathing problems and asthma-like symptoms, as well as lung function abnormalities. Ones may also experience inflammation on skin after repeated contact (110).

DISCUSSION

Therefore, realizing the impact of air pollution on health, we propose a new framework of an integrated environmental and health impact assessment system through the development of federated learning network architecture. This is important to assess the potential risk contributed by air pollutants to human health. The output of the impact assessment is critical in healthcare management and monitoring, and to enhance the quality of healthcare services. In this section, we will also highlight our proposed contributions to the techniques applying in the integrated system, namely federated learning.

Integrated Environmental and Health Impact Assessment

Air pollution is among the primary contributors to climate change, and currently it is the most significant environmental challenge (112). Air pollution contributed to irreversible effects to human health. As presented in the previous section, urban air pollution particularly has become a global threat to human welfare and health. This situation has been affecting more than half of the world's population and it is growing and will continue to grow reaching 70% by the year 2050 (113–115). Hence, it is crucial to establish an artificial intelligence (AI) based integrated environmental and health decision system to assess the risk of environmental pollution to the health particularly on the air pollution. AI has been widely used in a variety of fields in improving effectiveness of automation and analyze data at a much faster rate than humans. From (116), AI has extended its application to environmental management problems, including in modeling water quality, fish stock prediction and other environmental engineering applications.

In the twenty-first century, AI is widely applied in various fields. AI and its subsets machine learning and deep learning has been the backbone of decision support system, monitoring and predictive tools, often involved in engineering, medical, analytics etc. As from the review performed, it is clearly presented that AI has been extensively used in monitoring the environmental issues associated with the health impacts. The AI techniques helped in assessing the relationships between environmental pollution and health impacts, subsequently study the trend of the associations without human interventions. The AI techniques that commonly applied are machine learning such as random forest, decision tree, Naïve Bayes, SVM, regression models etc, while the deep learning techniques such as ANN, long short-term memory (LSTM), DNN etc. In addition, assessment of the association between pollution and health impacts has been performed using techniques such as quasi- poison generalized linear regression, generalized additive mixed model (GAMM), geographic weighted poison regression etc. These are the common models used in the previous studies.

However, there are limitations from previous studies. According to the performed review as shown in **Table 3**, where the techniques used are almost similar. Generally, techniques such as decision tree, random forest and regression models are the most common techniques used by scientists in prediction of air pollution and the association between its impact to human health. Although these are well-known and powerful techniques, their accuracy prediction is depended on the data being processed. Besides, the major limitations such as insufficient data on pollutant information and insufficient monitoring stations also present as the research gap of the studies. Moreover, insufficient variables also directed as the study limitations. In addition, there is lacking studies and evidence in air pollution predictive system in Malaysia. This review paper aims to propose an AI integrated environmental and health impact assessment.

The integrated environmental and health impact assessment is an integrated system which acts as a means for monitoring the environmental pollution and its impact to human health, concurrently, assesses the health impact on human after the pollution. This is to provide and support a more comprehensive decision-making. This system has handful approaches in establishing the integrated system, which are system dynamics, Bayesian networks, coupled component models, agent-based models and expert systems (117). In this study, the construction of the integrated system is developed according to a structured framework (118). A good, structured framework allows simultaneous monitoring and interpretation, and provides a systematic way in discovering linkages or correlations between the environment and human health (119). According to the (119), a robust framework should have 4 elements, namely i) conceptual clarity and scope, ii) flexibility, iii) balance, and iv) usability. INTRASE project completed by author (120) developed an integrated environmental and health impact assessment framework which assess the health-related problem derived from the impact of policies related to environment and health, as well as other factors and interventions that affecting the environment (118). The framework considers the complexities, interdependencies and uncertainties in reality (119, 121). The framework comprised of 4 stages namely, (i) issue framing to define the problem and aim for the assessment, concentrates, restricts the scope of evaluation and management alternative. (50) Design stage with the goal to transform conceptual model developed during issue framing into a comprehensive evaluation process. (iii) Execution stage which is the heart of the evaluation procedure. (iv) Appraisal which the outcome synthesis and interpretation (118).

In this study, the proposed conceptual framework of the integrated assessment system is constructed as **Figure 2**. The integrated system is feed with input parameters, related to data such as meteorological data, wind speed, wind direction, weather, humidity, atmospheric pollutant data of particulate matter, ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide and volatile organic compounds (VOCs); data of health impacts of air pollution; geographical and socio-economic activities. Missing and incomplete dataset can be solved based on the predictive models using the parameters retrospective data. The data input into the models is significant for the correlational studies between air pollutant and health impacts, based on socio-economics activities. The significant outputs of the model will serve as the input variables of the air quality index predictive models. The AQI predictive models are crucial in generating the measurement of air quality, monitoring the trend of the pollution. The AQI model is the core model to identify the pollution threshold concentration of the ambient pollutant. It is critical for air quality standard monitoring and policy making. In addition, the impact assessment environmental pollution and health can be carried out with the output information of AQI predictive model. The impact assessment is crucial in determining the potential impact of pollution to the human health, hence, aids in hospital and health care services planning and management, which is the main research gap in the study. The planning and management of hospital and healthcare services is critical in early preparation of services to accommodate the needs and ensure the sustainability of public health.

Federated Learning: Towards Integrated AQI Monitoring Solution

The proposed integrated system will be developed using federated learning (FL) techniques as the foundation of the predictive models. Federated learning is an evolving machine learning approach aimed at addressing the problem of data island while protecting data privacy (122), proposed by Google (123–125). Federated learning is named on its characteristic which the learning task is performed by multiple clients, or an informal network of participating devices for instance mobile devices (126). It is coordinated by a central server for decentralized machine learning settings. According to author (122), FL closely associated with distributed learning. It connects numerous computers in various places over a communication

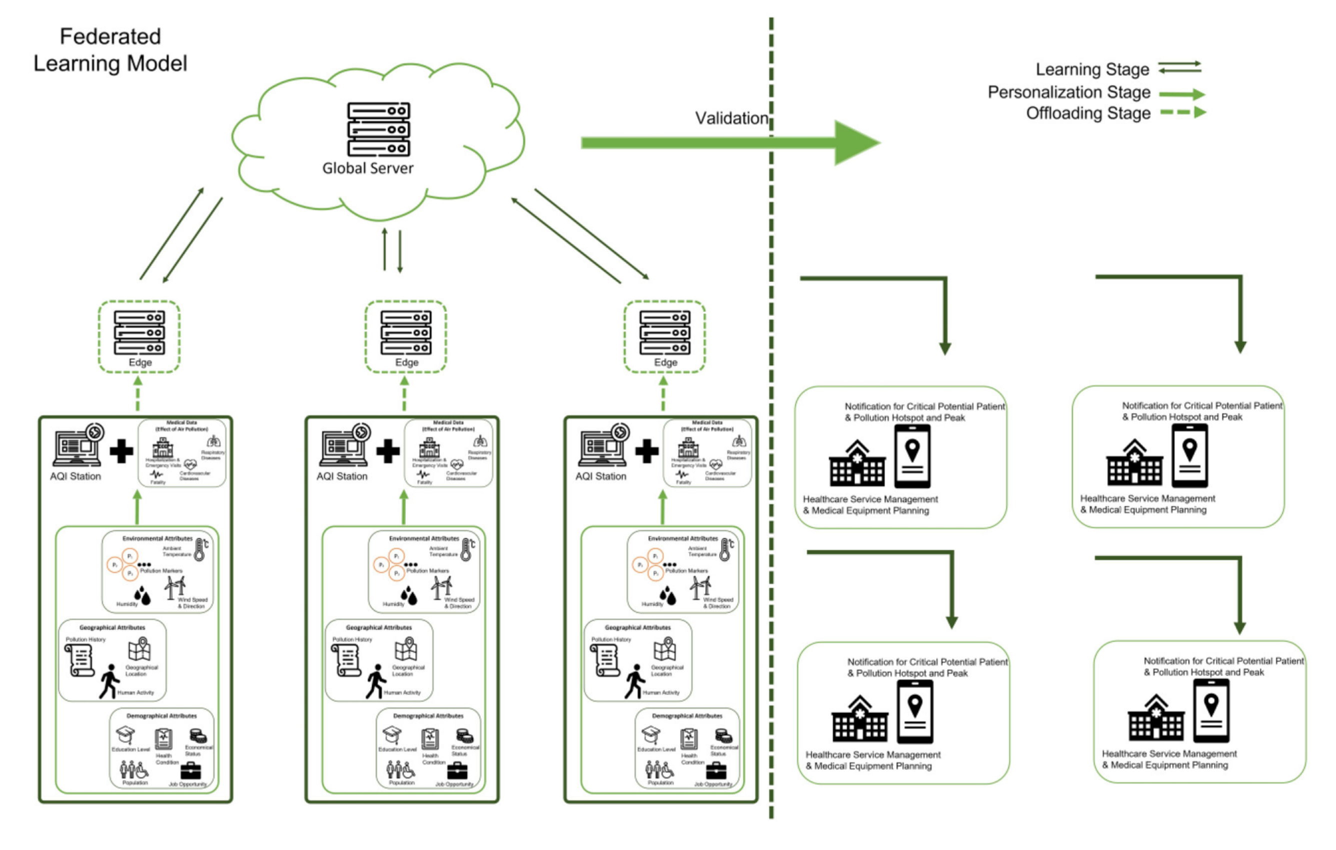

FIGURE 2 | Framework of integrated environmental and health impact assessment.

network under the management of central server, so that each computer completes different sections of the same operation. This proved that distributed processing is concerned with the n accelerating processing stage whereas FL is primarily concerned with developing a collaborative approach that does not compromise privacy. With its novel architecture, FL permits multiple participants to build a machine learning model jointly while keeping their private training data private. FL is thought of as privacy-preserving, decentralized collaborative machine learning. It has also been seen as an operating system for edge computing since it offers a learning protocol for coordination and security (127).

Federated learning, as an innovative modeling that can train a single model on data from multiple sources without jeopardizing the privacy and security of those data, has promised its application in industries such as sales, finance, healthcare etc. Due to intellectual property rights, privacy protection and data security, these data cannot be directly aggregated for training machine learning models (127). Looking at this study, to address the privacy concern in AQI prediction and impact assessment, FL is implemented as the environmental data and medical data are very sensitive and private. This is critical when the environmental agencies and medical services collaborate in monitoring and defeating the issues of pollution and its impact on health. Several research have implemented FL in their studies. For example, authors (128–130) have implemented FL in monitoring air quality and forecasting. FL is implemented in these studies as FL contributed to protect the data when monitoring without sharing the raw data, for instance the data images from unmanned aerial vehicles (UAV). Besides, the reason of implementing FL includes its flexibility, which FL learning can be performed when the devices are in charging mode, on or not on the internet or WiFi connection [135]. Besides, FL also enables real time prediction. There is no need to be concerned about any time lag while sending information to and from the server. Also, FL only requires a minimal infrastructure, it does not require intensive hardware. These advantages are promising to be applied in air quality monitoring contact especially in the developing countries as Malaysia. Since the air quality monitoring stations are scattered throughout the country, the feasibility of processing air quality attributes using decentralized collaborative machine learning in FL will enable faster diagnosis and thus rapid environmental decision making can be made. Since the FL does not require intensive hardware, the FL architecture can be easily embedded with the existing sensor networks at air quality monitoring stations.

Overall, FL has various promising potential to be utilized in predictive models. Although there is no research proven the feasibility of implementation of FL in the construction of integrated environmental and health impact assessment, there are studies proven that federated learning is famous particularly in data security as discussed above. The aim of this paper is to propose the implementation of FL in the integrated impact assessment system as it involved environmental and medical data.

CONCLUSION

Air pollution has become a major environmental issue around the globe. Poor air quality affects human health by exposing to the poisonous air pollutants such as particulate matters, carbon monoxide, ozone, Sulfur dioxide, heavy metals, VOCs etc. Both short-term and long-term exposures are significant in contributing to adverse health effects such as respiratory diseases, cardiorespiratory diseases, irritation to eyes, nose and throat and worst, it can cause cancers to human. Hence, it is important to monitor air quality as different pollutants possess different threshold concentration of impurities. Prediction of air pollutant can reduce the health impacts caused by air pollution, especially to the sensitive groups of publics by forecasting the potential pollution. Besides, the impact assessment is also crucial to understand the potential adverse health effect contributed by air pollution. With the aid of the assessment, hospital management is able to provide effective and efficient medical services to the patients. Therefore, an integrated system of environmental and health impact assessment is proposed. In this context, AI is expected to serve as a predictive model technique in air quality index and integrated environmental and health impact assessment. This is due to the capability and feasibility of AI to identify trends and patterns from big data, open previously unimagined avenues for addressing complicated environmental issues.

From the study above, research on air pollution and its impact on human health revealed a fundamental comprehension of the relationships and association between air pollution and health hazards to humans. The study also provided insight on the prediction of human health due to air pollution and air pollution prediction using machine learning techniques. The ultimate benefits gained from this study is the need of a highly capable integrated impact assessment system to understand the effect on the health caused by environmental issues, which is air pollution in this context. This is critical in medical services preparation and prioritizing the critical patients affected by the air pollution.

According to the reviews and findings, it is found that there are insufficient studies performed on the prediction of impact of health caused by air pollution in Malaysia. In addition, there is also lacking research on the prediction of potential hospitalization and emergency visits associated with the impact of air pollution in Malaysia, which is mainly concerned to accommodate the healthcare services that prioritize the potential patients affected by air pollution. Hence, it is essential and critical for us to propose the integrated environmental and health impact assessment to curb the current issue and fill in the research gap. Therefore, this study provides recommendations that will be useful in future research:

Feasibility of developing an integrated system on environmental and health impact assessment to monitor the trend and pattern of the relationships of the pollutant sources, markers and effects on health, as an effort to solve complex interaction and serve as a pre-requisite for AQI predictive model.

AQI prediction in monitoring pollution markers levels based on socio-economic activities and geographical area. AQI serves as an indicator of health quality monitoring referral in sensitive groups. It is also critical in providing guidelines and reference in standards making.

Imposing a framework on integrated environmental and health impact assessment systems based on the information from environmental, health, and AQI prediction. The capability of AI and FL in learning and predicting the big data. It is also critical in hospital monitoring in the context of prediction of early health care services preparation and hospital management, for effective medical services.

Considering evidence, the review provided a new insight on prediction of air pollution and its impact to health, by adopting AI and FL. Concurrently, an integrated environmental and health impact assessment development aids in reducing future threats to human health and lifted the healthcare service quality and management.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

EN and KH designed and developed the study protocol as well as major contribution to the article writing. MM and KL performed the identification, screening, eligibility, quality assessment, and information extraction of the articles. MA, SR, and HH checked all the synthesized data and approved the final version to be submitted for publication. All authors have substantially contributed to the article.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.851553/full#supplementary-material

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Impact of Particulate Matter on Hospitalizations for Respiratory Diseases and Related Economic Losses in Wuhan, China

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Background: Prior studies have reported the effects of particulate matter (PM) on respiratory disease (RD) hospitalizations, but few have quantified PM-related economic loss in the central region of China. This investigation aimed to assess the impacts of PM pollution on the risk burden and economic loss of patients admitted with RD.

Methods: Daily cases of RD admitted to the hospital from 1 January 2015 to 31 December 2020 were collected from two class-A tertiary hospitals in Wuhan, China. Time series analysis incorporated with a generalized additive model (GAM) was adopted to assess the impacts of fine particulate matter ($PM_{2.5}$) and inhalable particulate matter (PM_{10}) exposures on patients hospitalized with RD. Stratified analyses were performed to investigate underlying effect modification of RD risk by sex, age, and season. The cost of illness (COI) approach was applied to evaluate the related economic losses caused by PM.

Results: A total of 51,676 inpatients with a primary diagnosis of RD were included for the analysis. $PM_{2.5}$ and PM_{10} exposures were associated with increased risks of hospitalizations for RD. Subgroup analysis demonstrated that men and children in the 0–14 years age group were more vulnerable to PM, and the adverse effects were promoted by low temperature in the cold season. A 152.4 million China Yuan (CNY) economic loss could be avoided if concentrations of $PM_{2.5}$ and PM_{10} declined to 10 and 20 $\mu g/m^3$, respectively.

Conclusions: $PM_{2.5}$ and PM_{10} concentrations were positively associated with RD hospitalization. Men and children were more vulnerable to PM. Effective air pollution control measures can reduce hospitalizations significantly and save economic loss substantially.

Keywords: ambient particulate matter, respiratory diseases, hospitalization, economic loss, generalized additive model

INTRODUCTION

According to the Global Burden of Disease (GBD) Study 2019, particulate matter (PM) was one of the largest increased risk exposures worldwide between 2010 and 2019, the percentage of disability-adjusted life-years (DALYs) attributable to PM increased from 2.7% in 1990 to 4.7% in 2019 (1). PM pollution contributed to approximately global 2.49 million deaths and 83 million DALYs in 2017 (2). A province-level disease burden study in China reported that PM was one of the top four risk factors for a number of deaths and accounted for more than 5% of DALYs in 2017 (3).

PM can cause damage to the respiratory system by absorbing toxic metals, carcinogens, and pathogenic bacteria (4); on the other hand, PM deposited in the lung can lead to lung damage by mediating inflammatory response and oxidative stress (5, 6). Population-based epidemiological evidence suggests that PM was associated with respiratory disease (RD) morbidity and mortality (7, 8). Fine particulate matter ($PM_{2.5}$) and inhalable particulate matter (PM_{10}) were affirmed to be associated with increased emergency (9, 10) or hospital admissions (11, 12) for asthma (4, 11), pneumonia (13), chronic obstructive pulmonary disease (COPD) (11, 14), and bronchiectasis (11). Some studies also demonstrated the effect of PM on mortality in COPD (14), pneumonia (15), and lung cancer (15, 16). PM was the second-highest risk factor for respiratory tract cancer (tracheal, bronchus, and lung cancers) in 2019, contributing to 15.1% of deaths for these cancers (16). In the past few decades, China has experienced dramatic increases in industrialization and urbanization, accompanied by deterioration of air quality and population health. A study covering 338 Chinese cities revealed that $PM_{2.5}$ caused 1.35 million all-cause premature mortalities, which were equivalent to 17.2% of reported deaths in China in 2017 (17).

Air pollution caused a heavy disease burden, at the same time the economic loss could not be ignored. Air pollution resulted in illness and in turn reduced productivity, decreased working hours and labor supply, and lost welfare (18, 19). An economic study forecasted that the global economic costs of outdoor air pollution gradually increased to 1% of global gross domestic product (GDP) by 2060, with the highest GDP losses in China (20), which mainly reaches to relatively high pollution-related health expenditures and aging population. In China, air pollutants caused economic loss attributable to hospital admission, and premature mortality was 2,065.54 billion China Yuan (CNY), accounting for 2.5% of the national GDP in 2017 (21). A lot of domestic studies analyzed medical costs or economic loss in the northern area like Shanxi (22) and Hebei (23) or economically developed regions like Beijing (24, 25) and the Pearl River Delta (26, 27). However, few studies focused on the central region. Wuhan is the only sub-provincial city in central China. The objective of this study is to provide the risk assessment for RD hospitalization followed by the economic loss evaluation of PM in Wuhan.

METHODS

Description of the Study Area

Wuhan is the capital of Hubei province. In 2020, Wuhan had a 12.32 million permanent resident population (28). Wuhan is a nationally important industrial base and a comprehensive transportation hub. Vehicle sources and manufacturing emissions were the main air pollution sources in Wuhan (29). Meanwhile, Wuhan is located in the Jianghan Plain, which is one of the largest commercial grain production bases in China (30). Biomass burning also caused heavy pollution in Wuhan (31). The annual average concentration of $PM_{2.5}$ and PM_{10} were 45 and 71 $\mu g/m^3$, respectively in 2019, exceeding the national air quality secondary standard ($PM_{2.5}$: 35 $\mu g/m^3$; PM_{10}: 70 $\mu g/m^3$).

Data Collection

Records of Hospitalization

Hospitalization data were obtained from the hospital information system (HIS) of two class-A tertiary hospitals in Wuhan from 1 January 2015 to 31 December 2020. The data consisted of age, gender, principal disease diagnosis, admission date, discharge date, length of stay (LOS), and hospitalization expenses. The diagnosis of the disease was coded according to the International Classification of Disease Tenth Revision (ICD-10). Hospitalization due to all RDs (ICD-10: J00-J99), COPD (ICD-10: J40–J44), and pneumonia (ICD-10: J12-J18) was analyzed in this study. Hospitalization cost was adjusted according to the consumer price index (CPI) to eliminate the impact of price fluctuations.

Daily Air Pollutants and Meteorological Data

In recent years, the air pollutant concentrations obtained from ground monitoring networks have been used in many studies to evaluate the health effects associated with air pollution in China (21). Daily mean concentrations of $PM_{2.5}$ and PM_{10} from 1 January 2015 to 31 December 2020 in Wuhan were collected from the Hubei Environmental Protection Bureau (https://sthjt.hubei.gov.cn/), and contemporary meteorological data, such as daily mean temperature and relative humidity, were obtained from China Meteorological Data Network (http://data.cma.cn/).

Statistical Analysis

A three-stage analysis was applied to assess the impact of $PM_{2.5}$ and PM_{10} exposures on RD hospitalizations and related economic losses.

Time Series Decomposition

In the first stage, we decomposed the time-series data of all hospitalizations for RDs, pneumonia, and COPD to detect potential long-term trends and seasonality. The time series data were split into three components (32):

$$Y_t = T_t + S_t + R_t,\ t = 1, 2, \ldots, n,$$

where Y is the number of RD hospitalizations, T_t is the long-term trend, and S_t is seasonality and R_t is residual.

Impact on Hospitalization

In the second stage, the Spearman rank correlation was applied to measure the association between air pollutants and meteorological data. A generalized additive model (GAM) with quasi-Poisson regression was used to fit the association between PM and RD hospitalization, adjusting for a set of covariates:

$$\log\ (E_i) = \beta_i\ (C_i) + ns\ \left(Time, df\right) + ns\ \left(Mt, df\right) \\ + ns\ \left(Rh, df\right) + DOW + Holiday + \ \alpha,$$

where E_i is the expected value of the hospitalization count for RD on day i; β_i is the regression coefficient; C_i is mean concentrations of air pollutants on day i; *Time* is the days of calendar time on day i and *DOW* and *Holiday* are dummy variables that represent the day of the week and a public holiday, respectively (12); *ns* represents a natural spline smoothing function (12); *Mt* is the mean temperature; *Rh* is the relative humidity; and α is the intercept. The degree of freedom (*df*) of each variable was chosen referred to the previous study. We initialized the *df* as 4 *df*/year for *Time*, 3 *df* for *Mt* and *Rh* (33).

We calculated the percent change (PC) of hospitalization count for RD attributable per 10 $\mu g/m^3$ addition of PM:

$$PC = \left[exp\ \ (\beta_i \times 10) - 1\right] \times\ 100,$$

where β_i refers to the regression coefficient of air pollutants derived from the GAM analysis.

Given that air pollutant exposure had a significant delayed effect on health, this study examined the effect with different lag structures of single-day lag (from lag0 to lag7), where lag0 corresponds to the current day. In addition, we estimated the association between PM and RD hospitalization count for subgroups stratified by gender (male and female), age (0–14, 15–64, and 65+ years), season (warm and cold season), and specific disease (pneumonia and COPD). The warm season was defined as the month of admission date between April and October, and the cold season was the month of admission date between November and March (34).

Economic Losses Analysis

In the third stage, we applied the cost-of-illness (COI) approach to estimate the economic loss due to hospital admissions for RD (21). Attributable number (AN) and attributable fraction (AF) are indicators of attributable risk. AN is the number of RD hospitalizations attributed to air pollution. AF represents the proportion of hospital admission contributed to air pollution in total hospitalization:

$$AF = \sum\nolimits_{i=0}^{n} \left\{1 - \frac{1}{\exp\left[\beta \times (C_i - C_0)\right]}\right\},$$

where β refers to the regression coefficient obtained from the GAM analysis; C_i is the mean concentration of PM on day i; C_0 is the threshold concentration of PM, which was assumed to be 0 in this study (21).

$$AN = AF \times \sum\nolimits_{j=1}^{n} (Pop_j \times\ Pro_j),$$

where Pop_j represents the permanent population of Wuhan, which was 10.61, 10.77, 10.89, 11.08, 12.21, and 12.45 million in 2015, 2016, 2017, 2018, 2019 and 2020, respectively. Pro_j is the hospitalization rate of RD. We used the annual RD hospitalization rate of China in 2017 to replace it due to data unavailability, which was 810.22 per 10^5 population (21).

The economic loss attributable to RD hospitalization related to PM was estimated with the COI method:

$$ECO_{loss} = COST_{mean} + Day_{mean} \times PGDP_{day} \\ TECO_{loss} = AN \times\ ECO_{loss},$$

where ECO_{loss} is the average economic loss for RD hospitalization for each case; $COST_{mean}$ is the average hospitalization cost for RD of each case; Day_{mean} is the average LOS for inpatients of RD; $PGDP_{day}$ is the GDP per capita per day in Wuhan. $TECO_{loss}$ is the total economic loss for RD hospitalization attributable to PM.

Sensitivity Analysis

To test the robustness of the model, we performed a sensitivity analysis by: (1) changing *df* for *Time* ($df = 3$ or $df = 5$) and (2) establishing two-pollutants models (SO_2, NO_2, O_3, CO).

All analyses were performed in R programming language (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). The values of $p < 0.05$ were considered to be statistically significant.

RESULTS

A total of 51,676 RD hospitalization cases were included in this study, of which 60.68% were men. **Table 1** presents the descriptive statistics of daily hospitalization counts, air pollutant concentration, and meteorological factors. Daily mean hospitalization counts for all RDs were 23.57. More daily hospitalization counts were observed in men than women. In addition, daily hospitalization counts of the group aged 65+ were higher than that of the 0–14 and the 15–64 age groups.

Figure 1 shows the result of the time series decomposition analysis of the hospitalization count of all RDs, pneumonia, and COPD from 2015 to 2020. The daily hospitalization counts showed an increasing trend between 2015 and 2019 but reduced notably in 2020. The obvious seasonal fluctuations existed in daily hospitalization counts, which were higher in spring and winter than that in summer and autumn.

The median of all RD hospitalization costs between 2015 and 2020 was 8,938.16 CNY, and the average LOS of all RDs was 9.33 days. More details are shown in **Supplementary Tables S1**, **S2**. **Figure 2** illustrates the trend of average hospitalization costs and LOS by disease, gender, and age group from 2015 to 2020. The average hospitalization cost of patients with all RDs and COPD showed a fluctuating trend between 2015 and 2019, then increased in 2020. While the average hospitalization cost of patients with pneumonia showed an increasing trend, exceeding that of all patients with RDs and COPD, and then increased dramatically in 2020. The hospitalization cost of male patients with RD was higher than that of female patients. The age group

TABLE 1 | Descriptive statistics of daily hospitalization counts of RD, air pollutant concentration, and meteorological factors in Wuhan, China, 2015–2020.

Variable	$\bar{X} \pm s$	Min	P_{25}	P_{50}	P_{75}	Max
Daily hospitalization counts						
All RD	23.57 ±12.60	0	15	23	32	77
Pneumonia	5.48 ±3.94	0	3	5	8	23
COPD	5.68 ±3.68	0	3	5	8	30
Male	14.31 ±8.00	0	9	14	19	49
Female	9.27 ±5.59	0	5	9	13	39
0–14 years	4.34 ±3.30	0	2	4	6	21
15–64 years	8.76 ±5.43	0	5	8	12	32
65+ years	10.48 ±6.22	0	6	10	14	53
Warm season	23.52 ±11.17	0	15	23	31	67
Cold season	23.65 ±14.39	0	13	23	34	77
Air pollutants (μg/m^3)						
$PM_{2.5}$	51.05 ±34.50	4	27	43	64	281
PM_{10}	81.86 ±47.40	3	48	73	107	618
Meteorological factors						
Mean temperature (°C)	17.25 ±9.20	−3.8	9.0	18.0	25.1	33.9
Relative humidity (%)	79.26 ±10.37	41.3	73.0	80.5	87.2	100.0

Min, minimum; P_{25}, the 25th percentiles; P_{50}, the 50th percentiles; P_{75}, the 75th percentiles; Max, maximum.

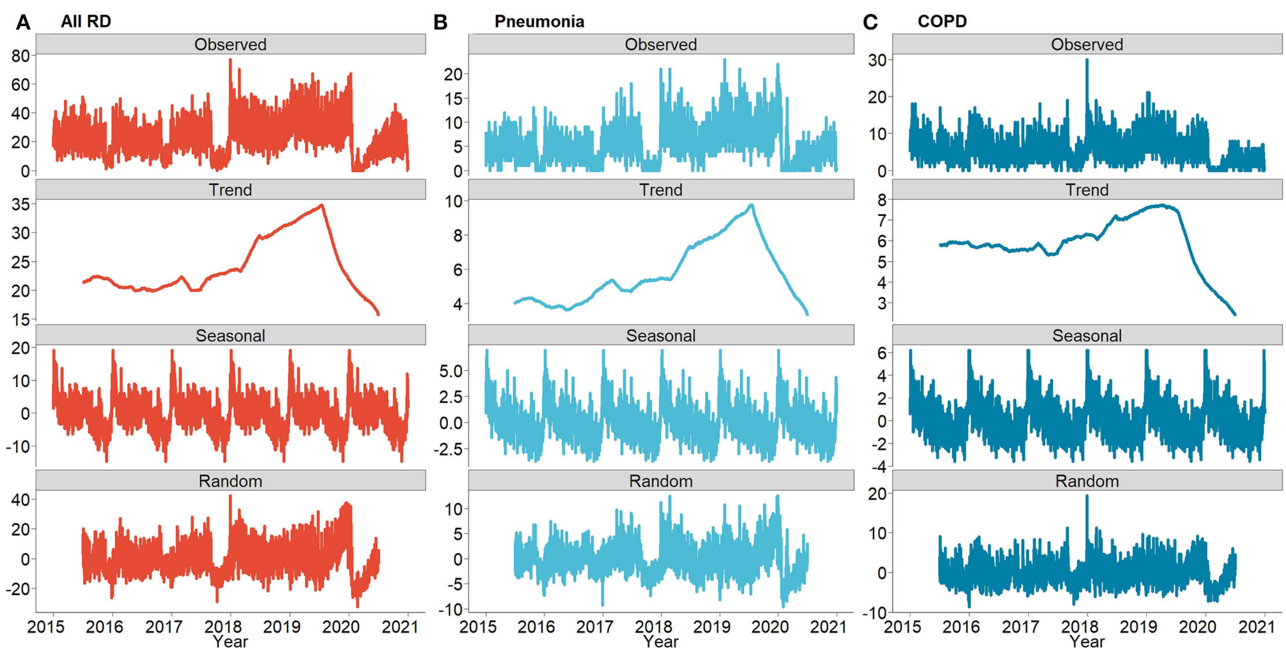

FIGURE 1 | The decomposed distributions for the daily number of hospitalizations due to all RDs, Pneumonia and COPD in Wuhan, China from 2015 to 2020: **(A)** daily number of hospitalizations of all RDs, **(B)** daily number of hospitalizations of Pneumonia, and **(C)** daily number of hospitalizations of COPD.

of 65+ years old had the highest hospitalization cost in all age groups. The average LOS of patients with RD showed a decreasing trend from 10.14 days in 2015 to 8.41 days in 2019 and increased to 9.92 days in 2020. The LOS of patients with COPD was relatively consistent with the trend of all RDs, whereas the LOS of patients with pneumonia increased markedly in 2020 and exceeded all RDs and COPD.

The Spearman rank correlation results are shown in **Supplementary Table S3**. Briefly, we observed positive correlations between $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO but a negative correlation between these pollutants and O_3. The results of GAM are presented in **Figure 3**. When $PM_{2.5}$ concentration increased by 10 μg/m^3, the number of hospitalizations for all RDs increased by 1.23% (95% CI: 0.31, 2.15), 1.60% (0.68, 2.52),

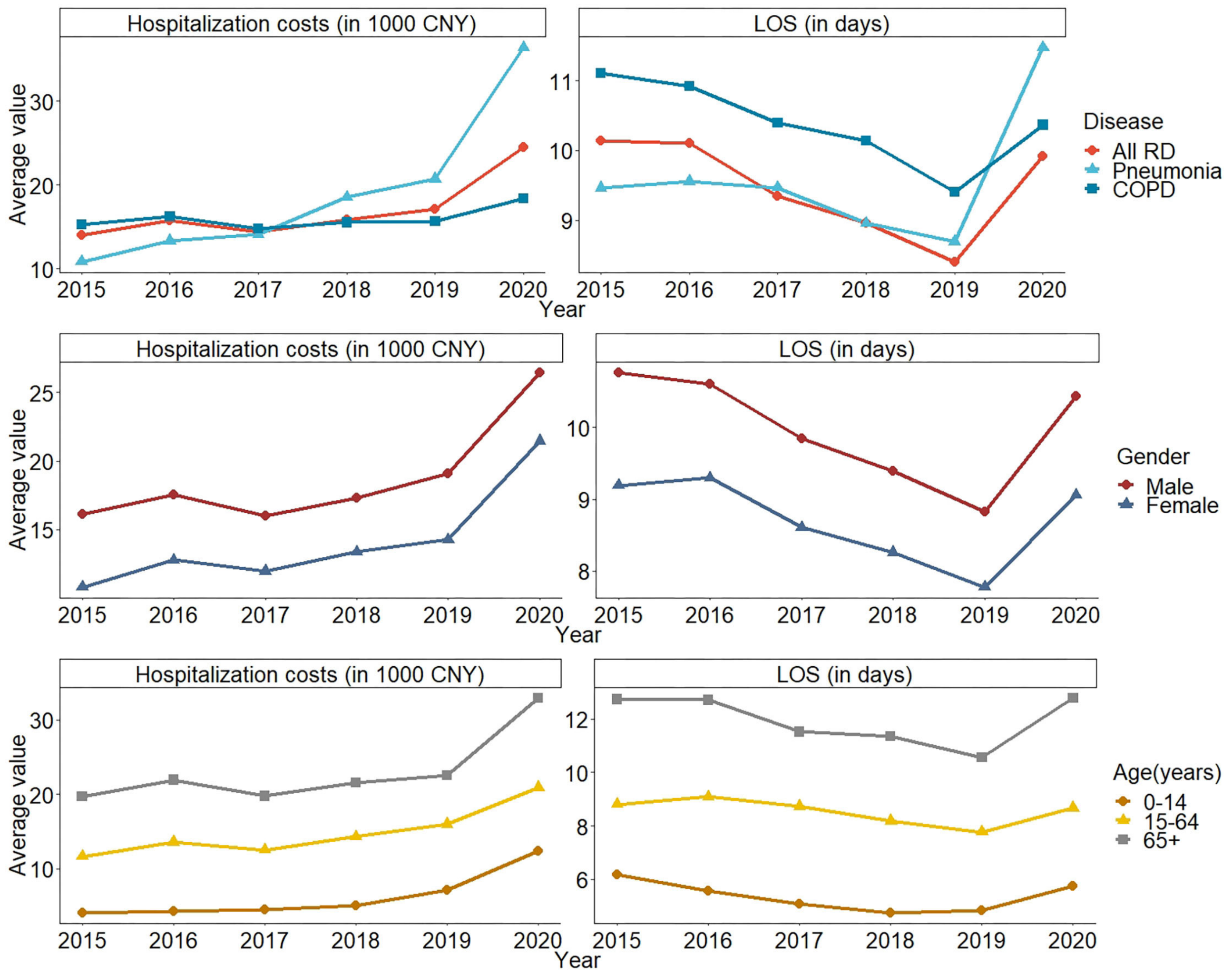

FIGURE 2 | The trend of average hospitalization costs and LOS due to RD in Wuhan, China from 2015–2020 by disease, gender, and age group.

and 2.34% (1.42, 3.27) on lag5, lag6, and lag7, respectively. The number of pneumonia hospitalizations significantly increased on lag5, lag6, and lag7, by 1.28% (0.49, 2.07), 1.50% (0.71, 2.30), and 1.75% (0.95, 2.55), respectively. Although no statistical significance was found, we observed a negative association between increasing $PM_{2.5}$ concentration and the number of all RD and pneumonia hospitalizations on lag0–lag4. $PM_{2.5}$ increased COPD hospitalization on lag0 and lag7, by 0.9% (0.17, 1.63) and 1.75% (1.03, 2.48), respectively. Every 10 $\mu g/m^3$ increase of PM_{10} concentration only caused hospitalization increase for all RDs and pneumonia on lag7; the PC was 0.77% (0.20, 1.33) and 0.73% (0.24, 1.23), respectively. Similarly, the increase of PM_{10} showed a decreased effect in the number of hospitalizations on lag0. Also, PM_{10} had no significant effect on COPD.

Figure 4 shows the PC of hospitalizations attributable to the increase in $PM_{2.5}$ and PM_{10} concentrations at different lag days by gender, age group, and season. The 10 $\mu g/m^3$ increment in $PM_{2.5}$ caused distinct hospitalization count rise on lag0, lag1, lag3, lag6, and lag7 for men and on lag0, lag1, and lag7 for women; both highest increases occurred on lag7 with 1.76% (1.27, 2.25) and 0.74% (0.14, 1.35). The effect of PM_{10} concentration increase was demonstrated on lag7 with 0.88% (0.57, 1.18) rise for men, and PM_{10} had no significant effect on women. In age-specific analyses, we found that increasing $PM_{2.5}$ and PM_{10} concentration had the greatest effect on the 0–14-year age group, which resulted in 2.34% (1.42, 3.27) and 0.77% (0.20, 1.33) hospitalization increase on lag7. For the 15–64-year age group, the greatest effect associated with $PM_{2.5}$ exposure on the number of hospitalizations appeared on lag7 with 1.08% (0.45, 1.72). For the age group of 65+, the highest PC of hospitalization with a 10 $\mu g/m^3$ increment in $PM_{2.5}$ was found on lag7 with 1.25% (0.70, 1.81). The effects of $PM_{2.5}$ and PM_{10} concentration rise in the cold season were greater than those in the warm season. The largest effect of $PM_{2.5}$ in the cold season was observed on lag7 with 0.76% (0.29, 1.23). The results of

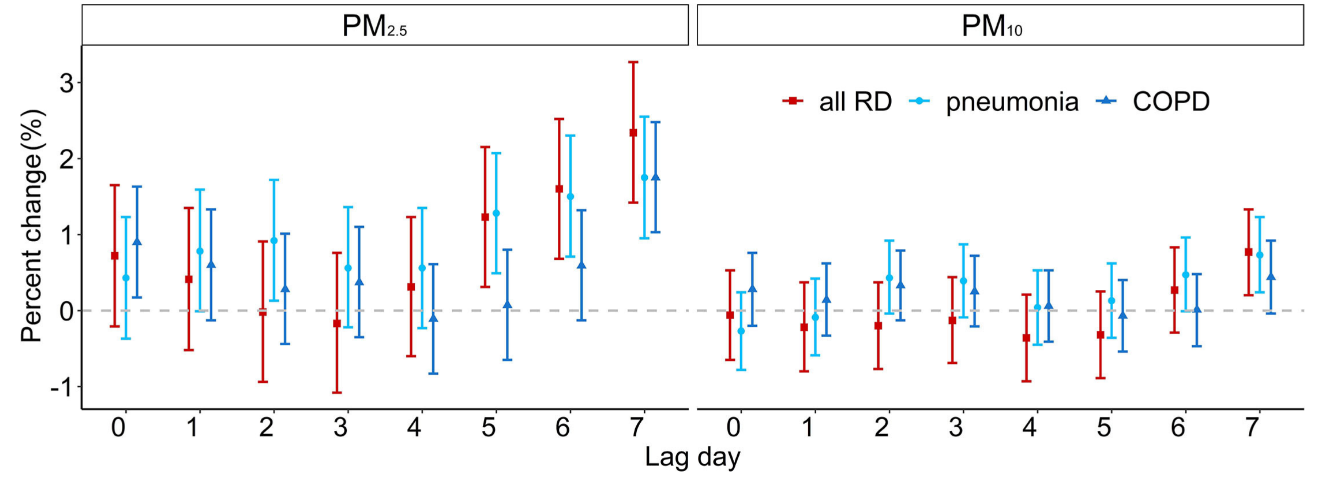

FIGURE 3 | The estimated PC of RD hospitalizations per 10 μg/m^3 increase in $PM_{2.5}$ and PM_{10} concentrations.

disease-specific analysis (pneumonia and COPD) are exhibited in **Supplementary Tables S4**, **S5**. On the whole, under the influence of the PM concentration increase, the number of hospitalizations of subgroup showed a trend of first rise, then decline and rise again, which was especially obvious in the influence of $PM_{2.5}$ on women and on the 0–14-year age group.

The result of sensitivity analyses is shown in **Supplementary Table S6**. After changing *df* for *Time* and establishing two-pollutant models, the effect of PM on hospitalizations remained stable, suggesting that the main model is stable and meaningful.

The lag days with the greatest impact of PM on RD hospitalization were selected for attribution analysis; the results of the RD hospitalization count and economic losses due to $PM_{2.5}$ and PM_{10} are demonstrated in **Table 2**. The number of RD hospitalizations attributable to $PM_{2.5}$ and PM_{10} was 59.40 thousand and 32.60 thousand, respectively. The economic losses attributed to $PM_{2.5}$ and PM_{10} were 1,304.92 million CNY and 716.29 million CNY. Higher hospitalization count and economic losses were found in men and 65+ year-old age group.

In the WHO 2020 global air quality guidelines, 4 interim target recommendations were proposed for annual concentrations of $PM_{2.5}$ (35, 25, 15, and 10 μg/m^3) and PM_{10} (70, 50, 30, and 20 μg/m^3). Assuming that the concentrations of $PM_{2.5}$ and PM_{10} from 2015 to 2020 can reach the WHO guidelines, the annual avoidable hospitalizations and the savable economic losses are displayed in **Figures 5**, **6**. If the annual concentration of $PM_{2.5}$ could reach 10 μg/m^3, 4,580 hospitalizations and 100.57 million CNY economic losses could be avoided. If the annual concentration of $PM_{2.5}$ could reach 20 μg/m^3, 2,360 hospitalizations could be avoided for all RDs, and the corresponding cost reduction could be 51.77 million CNY.

DISCUSSION

In this research, we used comprehensive data to examine the RD hospitalization risk attributable to PM exposure and evaluate the accompanying economic losses. $PM_{2.5}$ and PM_{10} were demonstrated to increase hospitalization for RD, and this influence had a delay effect. Men and 0–14-year-old age group were most vulnerable. PM caused huge RD hospitalization costs; if the concentration of $PM_{2.5}$ and PM_{10} could reach the guideline values recommended by WHO, enormous economic losses could be avoided.

From 2015 to 2019, hospitalizations for all RDs, pneumonia, and COPD showed a fluctuating upward trend, which is consistent with previous findings. In 2020, the number of hospitalizations decreased notably. In early 2020, the global outbreak of coronavirus disease 2019 (COVID-19) pandemic extremely affected people's behavior in work, outdoor activities, and medical treatment. Fears of COVID-19 and tightening hospital admission standards lead to a significant reduction in hospital admissions in 2020. The LOS of discharged patients is an important indicator of hospital performance evaluation (35). In this study, LOS showed a downward trend between 2015 and 2019, which may be related to the hospital actively improving the level of diagnosis and treatment and strengthening the management of hospitalization (36). The influencing factors of hospitalization cost mainly include the LOS, the age of the patient, complications, surgery or not, and intensive care vs. no intensive care (37). In this study, LOS decreased between 2015 and 2019, whereas the hospitalization cost increased at the same time. The increase in the elderly population and the aggravation of the disease may be one of the reasons. In 2020, the LOS and the hospitalization costs increased markedly, and pneumonia exceeded all RDs and COPD, which might have resulted from the COVID-19 pandemic.

The risk estimated in this study was generally higher than those observed in previous studies, especially for $PM_{2.5}$. For

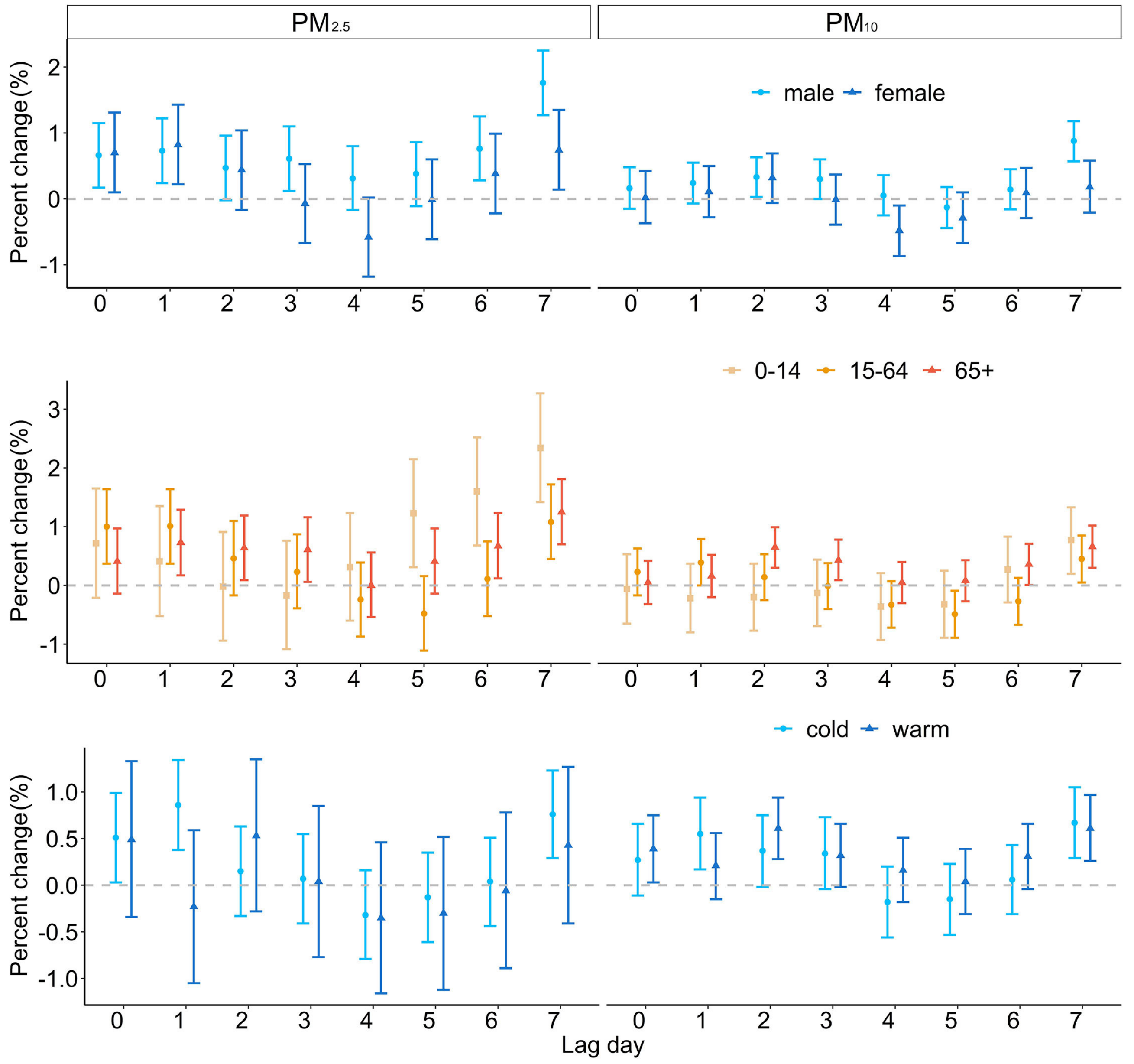

FIGURE 4 | The estimated PC of RD hospitalizations per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and PM_{10} concentrations by gender, age group, and season.

every 10 $\mu g/m^3$ increase of $PM_{2.5}$ and PM_{10}, we estimated a 2.34% and 0.77% increase in all RD hospitalizations. A study in Nanjing city concluded that every 10 $\mu g/m^3$ increase of $PM_{2.5}$ and PM_{10} concentrations was associated with 0.36% and 0.33% increase in hospital outpatient visits for RD (38). A Chinese national-level study covered 26 cites and concluded that a 10 $\mu g/m^3$ increase of $PM_{2.5}$ was associated with 0.26% increase in RD hospitalization (39). However, studies in New Mexico (40) and Arkansas (41) found no association between air pollution and emergency room visit for RD. PM concentrations and compositions varied substantially over geographical regions in China (42). The difference in the composition of PM, weather conditions, age structure, and population susceptibility may be responsible for the different associations.

Meanwhile, we also found a diverse delay effect model. A study in Nanjing demonstrated the acute response of RD hospital outpatients to PM exposure (38). In this case, the highest effect of $PM_{2.5}$ and PM_{10} appeared on the current day (lag0). In this research, PM decreased RD hospitalization on lag0, and the highest risk appeared on lag7. This study is based on hospitalization date rather than the time of symptoms onset, and the gap may explain the diverse highest risk lag pattern. Although not statistically significant, PM_{10} exhibited a "protective effect" on pneumonia and COPD on lag0, and

TABLE 2 | The number of RD hospitalizations and economic losses attributable to $PM_{2.5}$ and PM_{10} in Wuhan, China, from 2015 to 2020.

Variable	Attributable number of hospitalizations (in thousand)		Attributable economic losses (CNY, in million)	
	$PM_{2.5}$	PM_{10}	$PM_{2.5}$	PM_{10}
All RD	59.40	32.60	1304.92	716.29
Pneumonia	13.81	7.58	303.45	166.57
COPD	14.30	7.85	314.21	172.48
Male	36.04	19.78	791.83	434.65
Female	23.35	12.82	513.09	281.65
0–14 years	10.95	6.01	240.47	132.00
15–64 years	22.06	12.11	484.61	266.01
65+ years	26.39	14.49	579.84	318.28

decreased hospitalizations of all RDs and pneumonia. The "protective effect" may result from the conscious behavior of the study population. The proportion of 65+ year age group was 44.43% in this study. Elderly people with underlying diseases may be more cautious about air pollution. When PM concentrations increase, they may choose to reduce outdoor activities during the day, which may lead to a decrease in hospitalizations on the days of pollution and even in the first 3 days (43). In subgroup analysis, the PC of hospitalization showed a trend of increase, then decrease and increase again, especially for women and 0–14 age groups. These two groups may have lower immunity but less attention to air quality in their daily activities (44). When the PM concentration increases significantly, the exposure on the current day/lag0 has acute effects, such as asthma and pneumonia, and has the greatest impact on chronic RDs, such as COPD, after a lag of 5–7 days.

In this study, we found that the estimated risk of $PM_{2.5}$ was higher than PM_{10} on all lag days. PM_{10} is different from $PM_{2.5}$ in sources, composition, and lung deposition patterns. $PM_{2.5}$ can reach the bronchioles and deposit in the alveoli (13). In addition, $PM_{2.5}$ has a larger surface area than PM_{10}, so it can absorb more toxic substances per unit mass (13, 45). For specific diseases, $PM_{2.5}$ exposure had a higher effect on pneumonia (2.11%) than COPD (1.90%), and PM_{10} only had an effect on pneumonia hospitalizations (0.82%). Pneumonia is an acute inflammation of the lower respiratory tract (46). PM caused emergency room visits for pneumonia, and hospitalization increase had been confirmed in the previous study (13, 47). COPD is a chronic RD, and acute exacerbations were the main cause of medical visits and hospitalizations for COPD (48). PM can damage the airway epithelium and can weaken the immune system by oxidative stress and then cause exacerbation of COPD (49).

The subgroup analysis demonstrated that men had a higher increase in PC of hospital admissions for RD than women. A possible explanation could be that men were more inclined to smoking and drinking and that behavioral factors had synergistic effects with air environmental factors (50). A study in Taiwan (51) also indicated that men were more sensitive to PM_{10} exposure. Age differences also existed. In our study, 65+ year age group had the longest LOS and the highest hospitalization cost, which may result in their weakened immune function. However, the 0–14-year age group had a greater increase of RD hospitalization than the older group. Children's respiratory systems are not fully developed, and they are more sensitive to pollutants than middle-aged and elderly people. Moreover, children's outdoor activities increase their exposure to outdoor air pollutants (44). PM had greater effect on RD hospitalization increase in cold season than in warm season, which was consistent with previous studies (41, 52).

Previous studies have found that PM is a risk factor for respiratory infection by carrying microorganisms and affecting body's immunity. The association between PM and COVID-19 pandemic drew attention. $PM_{2.5}$ accelerated COVID-19 spread and its lethality (53), and significantly positive associations were observed in PM with newly COVID-19 confirmed cases (54). Meanwhile, the pandemic may have a different influence on other RDs such as COPD and asthma. Lockdown had a significant impact on the environment and air quality due to reduced industrial activity and traffic, which decreased PM concentration (55). Quarantines and wearing masks reduced PM exposure (56). Taking these factors into consideration, the increase of PM concentrations still leads to an addition in hospitalizations overall, further illustrating the significant impact of PM on RDs and the need for air quality intervention.

PM causes not only RD hospitalization rise but also substantial economic loss. According to our results, $PM_{2.5}$ and PM_{10} exposure led to 92,000 hospitalizations and 2,021.21 million CNY economic loss from 2015 to 2020 in Wuhan. From another perspective, the economic benefits of air pollution control are also considerable. An economic modeling study in Beijing concluded that an incremental monetary benefit from cardiovascular disease decline can offset over two-thirds of the air pollution-control spending if the $PM_{2.5}$ concentration can be reduced to 35 $\mu g/m^3$ and offsets the total spending if the $PM_{2.5}$ concentration can be reduced to 15 $\mu g/m^3$ (24). The same significant effect can be achieved in RDs. A value assessment study calculated that avoided economic loss for RD mortality was 103.5 million dollars when $PM_{2.5}$ dropped to 10 $\mu g/m^3$ in 2017, accounting for 7.31% of all-cause deaths (57). In our study, when the concentration of $PM_{2.5}$ dropped to 10 $\mu g/m^3$, the annual avoidable hospitalization and the annual savable economic losses were 4,580 and 100.57

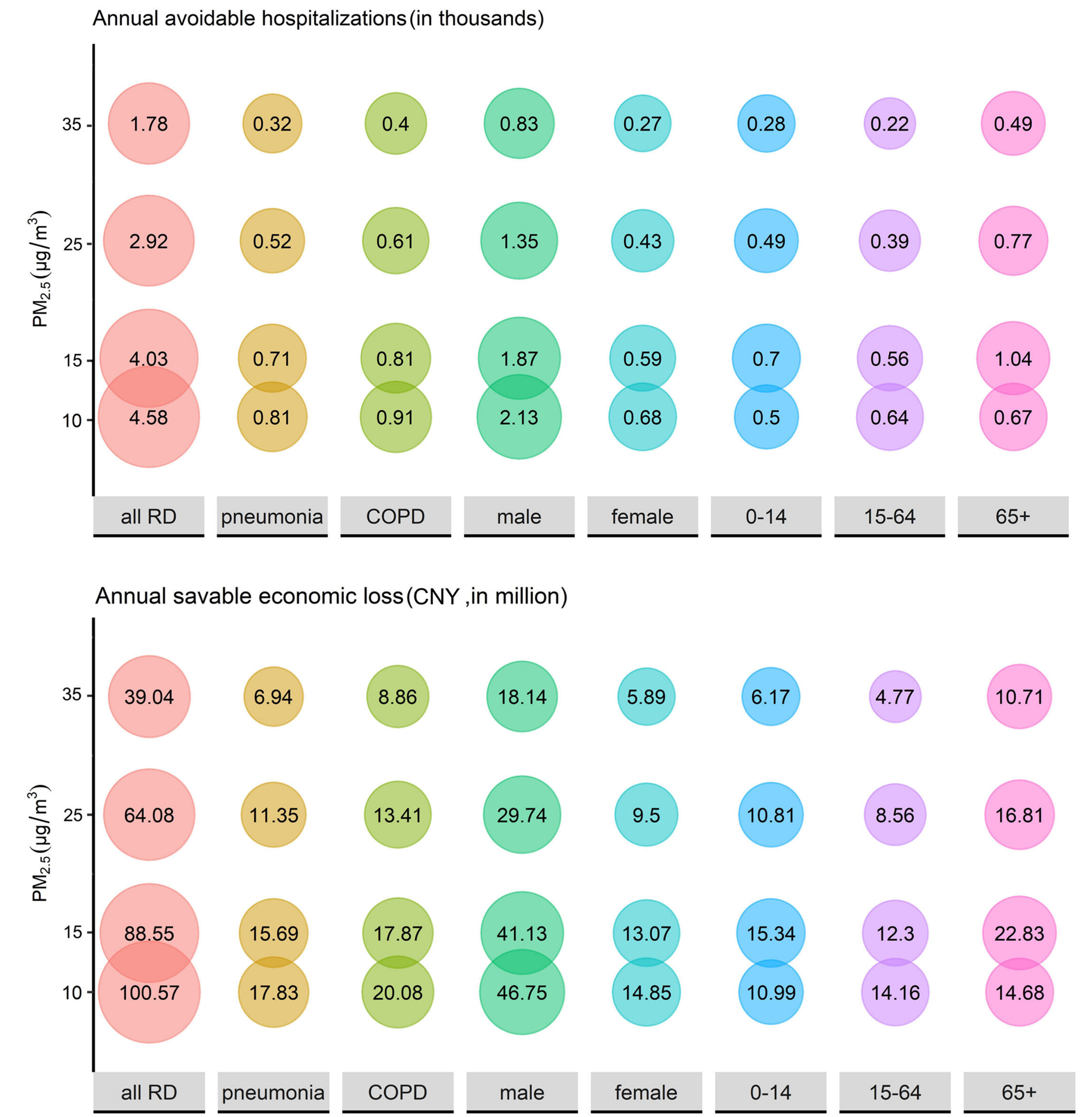

FIGURE 5 | The estimated annual avoidable hospitalizations and savable economic losses if the historical concentration of $PM_{2.5}$ could be maintained at relatively low levels.

million CNY, respectively, equating to a 7.71% reduction in both hospital admissions and financial losses. In the same way, when the PM_{10} concentration reached 20 $\mu g/m^3$, the annual avoidable hospitalization and economic losses were 2,360 and 51.77 million CNY, respectively, reducing for 7.24% hospitalization and 7.23% economic loss. Therefore, air pollution control investment can produce enormous monetary benefits, but effective measures should be taken to control PM pollution.

Nevertheless, our study had several limitations. The main limitation of the present study was the unavailability of data on individual exposure to PM pollution. Using monitoring data to represent individual exposure levels may cause measuring errors and underestimate exposure. Patients' information, such as

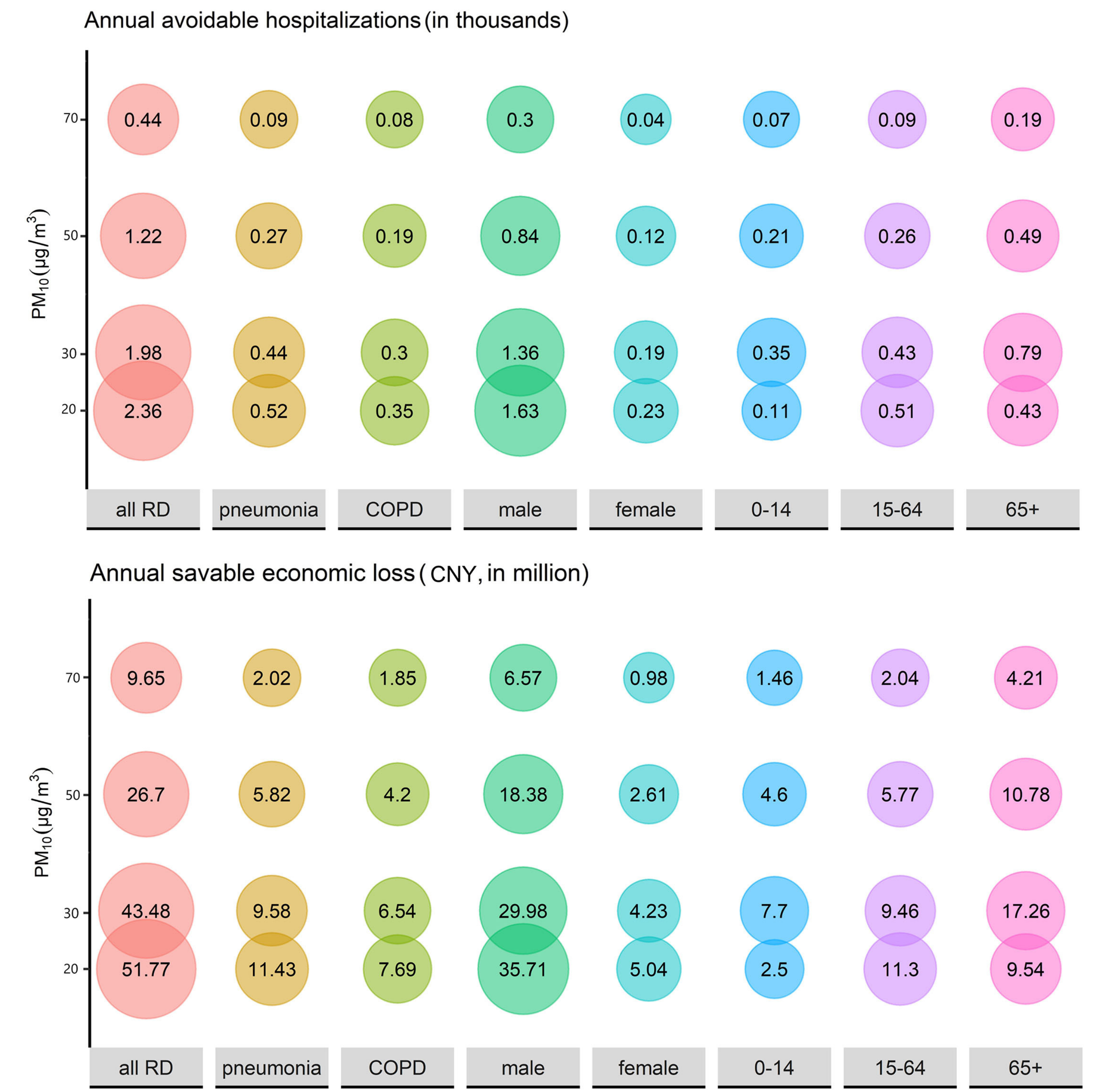

FIGURE 6 | The estimated annual avoidable hospitalizations and savable economic losses if the historical concentration of PM_{10} could be maintained at relatively low levels.

smoke and case history, was unknown, which limited the ability to identify potentially vulnerable people. On the other hand, a combined effect may exist between PM and other air pollutants. Deeper researches are necessary to explore the independent effect of PM on RD. We used hospitalization data of two hospitals to estimate the situation of Wuhan due to data unavailability, and this leads to a certain lack of representativeness in our results, so more comprehensive data are needed in future research.

CONCLUSIONS

In summary, we assessed RD hospitalization and relevant economic loss contributed to PM during 2015–2020 in Wuhan, China. We observed that $PM_{2.5}$ and PM_{10} concentrations at different lag days were positively associated with hospitalization for all patients with RD, pneumonia, and COPD. Men and children were more vulnerable to PM. Effective air pollution control measures can reduce hospitalizations significantly and save economic loss substantially.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

CY, XW, and GQ: design of study. GQ, TW, LH, and CY: data collection, analysis, and visualization. XW, GQ, and DN: writing the original manuscript. CY, YLi, YLiu, and HW: reviewing and editing the manuscript. CY: funding acquisition. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.797296/full#supplementary-material

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Effects of the COVID-19 Lockdown on Air Pollutant Levels and Associated Reductions in Ischemic Stroke Incidence in Shandong Province, China

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Background: Local governments in China took restrictive measures after the outbreak of COVID-19 to control its spread, which unintentionally resulted in reduced anthropogenic emission sources of air pollutants. In this study, we intended to examine the effects of the COVID-19 lockdown policy on the concentration levels of particulate matter with aerodynamic diameters of $\leq$1 μm (PM_1), $\leq$2.5 μm ($PM_{2.5}$), and $\leq$10 μm (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO) and the potential subsequent reductions in the incidence of ischemic and hemorrhagic stroke in Shandong Province, China.

Methods: A difference-in-difference model combining the daily incidence data for ischemic and hemorrhagic stroke and air pollutant data in 126 counties was used to estimate the effect of the COVID-19 lockdown on the air pollutant levels and ischemic and hemorrhagic stroke incident counts. The avoided ischemic stroke cases related to the changes in air pollutant exposure levels were further estimated using concentration-response functions from previous studies.

Results: The PM_1, $PM_{2.5}$, PM_{10}, NO_2, and CO levels significantly decreased by −30.2, −20.9, −13.5, −46.3, and −13.1%, respectively. The O_3 level increased by 11.5% during the lockdown compared with that in the counterfactual lockdown phase of the past 2 years. There was a significant reduction in population-weighted ischemic stroke cases (−15,315, 95% confidence interval [*CI*]: −27,689, −2,942), representing a reduction of 27.6% (95% *CI*: −49.9%, −5.3%). The change in the number of hemorrhagic stroke cases was not statistically significant. The total avoided PM_1-, $PM_{2.5}$-, PM_{10}-, NO_2-, and CO–related ischemic stroke cases were 739 (95% *CI*: 641, 833), 509 (95% *CI*: 440, 575), 355 (95% *CI*: 304, 405), 1,132 (95% *CI*: 1,024, 1,240), and 289 (95% *CI*: 236, 340), respectively.

Conclusion: The COVID-19 lockdown indirectly reduced the concentration levels of PM_1, $PM_{2.5}$, PM_{10}, NO_2, and CO and subsequently reduced the associated ischemic stroke incidence. The health benefits due to the lockdown are temporary, and long-term measures should be implemented to increase air quality and related health benefits in the post-COVID-19 period.

Keywords: lockdown, air pollution, ischemic stroke, COVID-19, incidence

INTRODUCTION

COVID-19 broke out in China in December 2019. Within a few months, this disease spread around the world, becoming a global pandemic (1). The governments of most countries adopted lockdowns to retard the spread of COVID-19 (2). Chinese provincial governments took the Level I major public health emergency response action on 24 January 2020, and all cities implemented lockdowns. Thus, many industrial and human activities were restricted only to the essentials or a bare minimum (3–6).

Although the cost of implementing nationwide restrictions is undoubtedly enormous, the lockdowns contributed markedly to successfully controlling the spread of the pandemic. Moreover, they generated a range of unintended environmental and health benefits (7). Extensive studies have been conducted to evaluate the impacts of the COVID-19 lockdowns on air quality, as there were substantial reductions in the industrial and vehicle emissions of air pollutants due to the reduced anthropogenic sources (8–10). Most studies suggest that the lockdowns had positive effects on the improvement of regional air quality, especially in areas with severe air pollution (e.g., the Middle East, India, and China) (4, 9–12). Furthermore, some studies focused on the health benefits attributable to the COVID-19 lockdowns (13–18). For example, significant reductions in mortality and hospitalizations for cardiovascular diseases, such as atrial fibrillation, acute coronary syndrome, myocardial infarction, and ischemic stroke, were observed in both developed and developing countries (13–18).

In China, there were approximately 29 million prevalent stroke cases in 2019, and stroke has become the leading cause of death and disability-adjusted life-years (19). Accumulating evidence suggests that short-term exposure to air pollutants is associated with increased risks of stroke incidence and mortality (20). Therefore, the lowered air pollution levels due to the lockdowns may have reduced stroke-associated events. Several studies confirmed the causal effects of the COVID-19 lockdown on improved air quality and its subsequent health benefits. However, most of them focused on stroke mortality, and using mortality as the outcome of interest may underestimate the number of people affected by the lockdowns (3, 5, 17). In contrast, using stroke incidence as an outcome may greatly outnumber mortality events, and the estimated number of stroke incidence cases avoided because of the reduced air pollution levels due to the lockdowns may be greater than that of mortality, thus providing greater statistical power for examining the health benefits generated by the COVID-19 lockdowns.

To the best of our knowledge, no study has yet examined the reduction effect of the COVID-19 lockdowns on ischemic and hemorrhagic stroke incidence in China to date. In addition, most previous studies focused on the changes in commonly monitored air pollutants (i.e., $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO), and only limited studies (from Croatia, France, India, Italy, and the western Mediterranean) examined the effect of the COVID-19 lockdowns on the PM_1 level and relevant literature is scarce in China (21–25). In this study, we investigated the impacts of a COVID-19 lockdown on the concentrations of PM_1 and other air pollutants ($PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO) and the potential subsequent reductions in ischemic and hemorrhagic stroke incidence in 126 counties in Shandong Province, China. We collected stroke incidence data from a stroke registry system, which covered all stroke case records from every medical institution (e.g., private clinics, community health service centers, and public hospitals) in the included counties.

MATERIALS AND METHODS

Stroke Registry Data

Data on the county-specific daily incidence of stroke were obtained from the stroke registry system operated by the Shandong Center for Disease Control and Prevention (CDC). Patient admissions to all medical institutions with a stroke diagnosis in each county must be reported to this registry system. From 2017 to 2020, the system covered 126 of the 136 counties in Shandong, and the total population of these counties was 91 million, equivalent to 6.4% of the whole population of China.

In this stroke registry system, registry certificates were filled in by the attending physician who diagnoses patients according to their symptoms, inquiries, complaints, and medical inspection results. The diagnosis was then categorized according to the International Classification of Diseases version 10 (ICD-10). In addition, each patient was asked to report when clinical symptoms occurred, which was then recorded as the incidence date. Then, the registry certificates were reported to the registry system in real-time. The information on each certificate was validated by professionals in the CDC of each county within 7 days, who also checked for completeness and coding. In this study, we focused on ischemic stroke (ICD-10 code: I63) and hemorrhagic stroke (ICD-10 codes: I60-I61). Ethical approval was obtained from the Ethics Review Committee of Public Health, Shandong University (No. LL20211203).

Air Pollution Data

Daily ambient PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, and CO data were collected from ChinaHighAirPollutants (CHAP, available at https://weijing-rs.github.io/product.html) datasets for Shandong province from 2017 to 2020 at a spatial resolution of 0.1° (≈10 km). These data were estimated using a developed space-time extremely randomized trees model, which integrates satellite remote sensing products, atmospheric reanalysis, and ground-based measurements to accomplish model simulations (26–32). The data on the predicted air pollutants levels were compared validly with ground-level measurements. The cross-validation coefficients of determination (CV-R^2) were 0.82, 0.91, 0.86, 0.84, 0.84, 0.87, and 0.80, and the root-mean-square errors (RMSEs) were 10.86, 12.67, 24.34, 7.99, 10.07, 17.10, and 0.29 mg/m^3 for daily concentrations of PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, and CO, respectively. The CHAP datasets have been widely applied in recent epidemiological studies evaluating the impact of exposure to ambient air pollutants on population health in China (33–35). For our analysis, the daily mean concentrations of PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, and CO for each county were estimated by calculating the average of the pixel values weighted by the proportion of the area of the county covered by the pixel, which enhanced the spatial representativeness of air pollution for each county.

Statistical Analysis

In this study, we first calculated the changes in the levels of each air pollutant and the ischemic and hemorrhagic stroke counts. Then, we calculated the estimated avoided stroke incident cases attributable to these air pollution changes by county. We employed a quasi-experiment design and used a difference-in-difference (DID) approach to estimate the effect of the COVID-19 lockdown on air pollutant levels (PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO) and ischemic and hemorrhagic stroke incident counts. Using this approach, we compared the same period in the past 2 years before the COVID-19 lockdown with a certain period in the year of the lockdown. Then, the net treatment effect of the lockdown on the air pollutant levels and stroke incident counts can be estimated. The detailed procedure is illustrated in **Figure 1**.

The government of Shandong province announced the Level I major public health emergency response on 24 January and lifted the Level I response on 7 March. In this context, the lockdown phase was defined as the period between 24 January and 7 March, which lasted for a sum of 44 days. We set the period between 11 December 2019, and 23 January 2020, as the baseline phase to make the time length of the baseline phase equal to that of the lockdown phase. Then, we created a DID model to quantify the change level of each air pollutant for each county. Taking PM_1 as an example, we first selected four corresponding phases (C_{B1}, C_{L1}, C_{B2}, and C_{L2}) from 2017 to 2019, with C_{B1} denoting the mean daily PM_1 concentration level from 11 December 2017 to 23 January 2018, C_{L1} the mean daily PM_1 concentration level from 24 January 2018 to 8 March 2018, C_{B2} the mean daily PM_1 concentration level from 11 December 2018 to 23 January 2019, and C_{L2} the mean daily PM_1 concentration level from 24 January 2019 to 8 March 2019. Next, the means of C_{B1} and C_{B2} (i.e., C_B) and C_{L1} and C_{L2} (i.e., C_L) were calculated to form a PM_1 concentration at the baseline and lockdown phases, respectively, as the counterfactual control groups. Then, we calculated the difference in the PM_1 concentration levels of the treatment group and the control group during the lockdown phase ($T_L - C_L$) and the difference between the two groups during the baseline phase ($T_B - C_B$). The changes in the PM_1 concentration level for each county related to the lockdown policy beyond background trends can be estimated using the above two differences: $(T_L - C_L) - (T_B - C_B)$.

Three key assumptions of DID should be satisfied (36). First, the event shock should be completely exogenous. In this study, the COVID-19 lockdown in Shandong province is used as a quasi-experiment, and no one could have predicted the COVID-19 outbreak or the unprecedented nationwide lockdown in late 2019, which can be regarded as a "black swan." Thus, the DID model used in this study meets the exogeneity assumption. Second, the exogenous shock should affect only the treatment units and not the potential control units. In this study, the 44 days before and after the day of the announcement of the lockdown policy (24 January 2020) were selected as the treatment group, and the same period in the past 2 years was selected as the control group. The COVID-19 outbreak in 2020 cannot affect the air quality levels in 2018 or 2019. Third, the outcome of interest between the treatment and control groups must have similar fits before the exogenous event occurs, otherwise known as the parallel trend assumption. If this assumption is satisfied, we can reasonably assume that the parallel trends of air pollutant concentrations over time would be the same for both groups. This assumption was examined using a regression model, which included the interaction term between time and the baseline period (18). We found that the coefficient for the interaction term is not statistically significant for each of the outcomes, indicating the parallel trend assumption for the DID model is plausible (**Supplementary Table 1**) (18).

Our preliminary analyses showed a statistically significant change in ischemic stroke cases. Thus, the following formula was used to estimate the counts of the avoided ischemic stroke cases related to changes in the air pollutant exposure levels, which was adopted from recent studies evaluating the impact of ambient air pollutants exposure on population health (3, 37, 38):

$$\Delta C_m = B_m \times (e^{\beta \times \Delta ap_m} - 1)$$

ΔC_m indicates the avoided ischemic stroke incident cases for county m, B_m is the baseline counts (i.e., the average of the counts from 24 January to 7 March in 2018 and 2019) for ischemic stroke for county m, β represents the exposure-response effect estimates extracted from two previous studies (**Supplementary Table 2**) (39, 40), and Δap_m is the change in one specific air pollutant for county m.

All the above analyses were weighted by the population in each county. We conducted a sensitivity analysis by estimating the change of the sex- and age-adjusted incidence rates of ischemic stroke and hemorrhagic stroke during the lockdown phase in the DID model to further check the robustness of using the

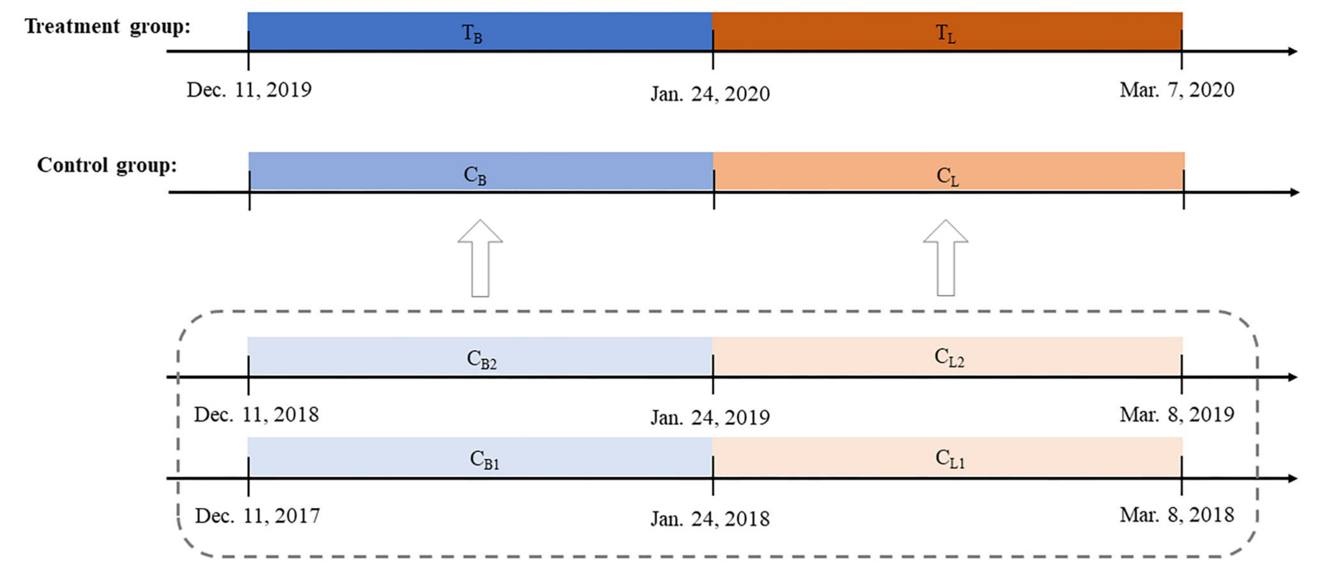

FIGURE 1 | Settings of the difference-in-difference (DID) model.

incident count of stroke as the outcome. The sex- and age-adjusted incidence rates were calculated using the population data for each county, which were collected from China's 2010 census survey.

The statistical analysis was carried out using R 4.0.3 (The R Project for Statistical Computing, Vienna, Austria), and two-sided values of $p < 0.05$ were considered statistically significant.

RESULT

During the lockdown phase in 2020, the mean [standard deviation (SD)] population-weighted PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, and CO concentration levels were 45.1 (7.6) μg/m^3, 58.5 (8.9) μg/m^3, 79.5 (10.0) μg/m^3, 23.9 (3.0) μg/m^3, 13.9 (2.5) μg/m^3, 83.6 (3.5) μg/m^3, and 0.95 (0.07) mg/m^3, respectively, and the total ischemic and hemorrhagic stroke cases were 44,043 and 9,434, respectively (**Table 1**).

Figure 2 shows the changes in population-weighted average air pollutant levels and stroke cases between the lockdown phase in 2020 and the counterfactual lockdown phase of the past 2 years for each county using the DID model. All 126 counties (100.0%) showed reductions in PM_1 and NO_2 levels, 122 counties (96.8%) showed reductions in $PM_{2.5}$ level, 120 counties (95.2%) showed reductions in PM_{10} level, 110 counties (87.3%) showed reductions in CO levels, while 94 counties (74.6%) showed increases in SO_2 levels, and 123 counties (97.6%) showed increases in O_3 levels. The average changes in the population-weighted PM_1, $PM_{2.5}$, PM_{10}, NO_2, O_3, and CO levels across the 126 counties were statistically significant (**Table 2**), and the respective estimates were −14.3 (95% confidence interval [*CI*]: −17.9, −10.8) μg/m^3, −15.9 (95% *CI*: −20.5, −11.4) μg/m^3, −16.9 (95% *CI*: −22.8, −11.0) μg/m^3, −11.1 (95% *CI*: −13.1, −9.0) μg/m^3, 8.4 (95% *CI*: 7.0, 9.9) mg/m^3, and −0.16 (95% *CI*: −0.20, −0.11) μg/m^3, representing a change of −30.2% (95% *CI*: −37.6%, −22.8%), −20.9% (95% *CI*: −26.9%, −15.0%), −13.5% (95% *CI*: −18.2%, −8.8%), −46.3% (95% *CI*: −54.7%, −37.8%), 11.5% (95% *CI*: 9.5%, 13.4%), and −13.1% (95% *CI*: −17.0%, −9.3%) relative to the counterfactual lockdown phase of the past 2 years, respectively. The average change in the SO_2 level was 0.9 (95% *CI*: −1.0, 2.9) μg/m^3, corresponding to a change of 2.3% (95% *CI*: −2.5%, 7.1%), which was not statistically significant.

In total, 110 counties (87.3%) showed a reduction in ischemic stroke cases, whereas 80 counties (63.5%) showed a reduction in hemorrhagic stroke cases. The population-weighted ischemic stroke cases were significantly reduced across the 126 counties (−15,315, 95% *CI*: −27,689, −2,942), representing a 27.6% reduction (95% *CI*: −49.9%, −5.3%) compared with that of the counterfactual lockdown phase. Furthermore, the reductions in the population-weighted ischemic stroke cases in both male and female subgroups, and all three age subgroups (18–64, 65–74, and ≥75 years) were also statistically significant. The total change in the hemorrhagic stroke cases was −1,265 (95% *CI*: −4,778, 2,249), which was not statistically significant. In addition, the changes in the hemorrhagic stroke cases were also not statistically significant in the sex or age subgroups. The sensitivity analysis revealed similar results, showing that the sex- and age-adjusted incidence rate for ischemic stroke decreased by 144 per 100,000 (95% *CI*: −257, −30, $p = 0.013$), and the sex- and age-adjusted incidence rate for hemorrhagic stroke increased by 5 per 100,000 (95% *CI*: −22, 32, P=0.730) during the lockdown for each county.

Since there were no statistically significant changes in the SO_2 level and hemorrhagic stroke cases, we estimated the changes in the ischemic stroke cases attributed to the changes in the PM_1, $PM_{2.5}$, PM_{10}, NO_2, CO, and O_3 levels across the 126 counties using the concentration–response function from previous studies

TABLE 1 | Means and standard deviations (SD) for air pollutant concentration levels and counts of stroke cases for the four phases.

Phase	PM_1	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	CO	Counts of ischemic stroke cases	Counts of hemorrhagic stroke cases
Lockdown phase in 2020	45.1 ± 7.6	58.5 ± 8.9	79.5 ± 10.0	23.9 ± 3.0	13.9 ± 2.5	83.6 ± 3.5	0.95 ± 0.07	44,043	9,434
Baseline phase	65.0 ± 14.2	90.4 ± 17.4	123.4 ± 20.0	51.1 ± 7.3	19.1 ± 4.1	47.2 ± 3.7	1.42 ± 0.18	54,244	9,868
Counterfactual lockdown phase	47.5 ± 7.9	76.2 ± 11.7	125.3 ± 15.8	40.3 ± 4.9	23.9 ± 5.3	73.4 ± 4.0	1.20 ± 0.12	55,442	10,615
Counterfactual baseline phase	53.4 ± 10.1	91.6 ± 18.0	151.3 ± 25.6	56.0 ± 8.3	30.0 ± 6.8	45.3 ± 4.4	1.50 ± 0.16	52,163	10,091

The unit for PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 is $\mu g/m^3$, whereas that for CO is mg/m^3.

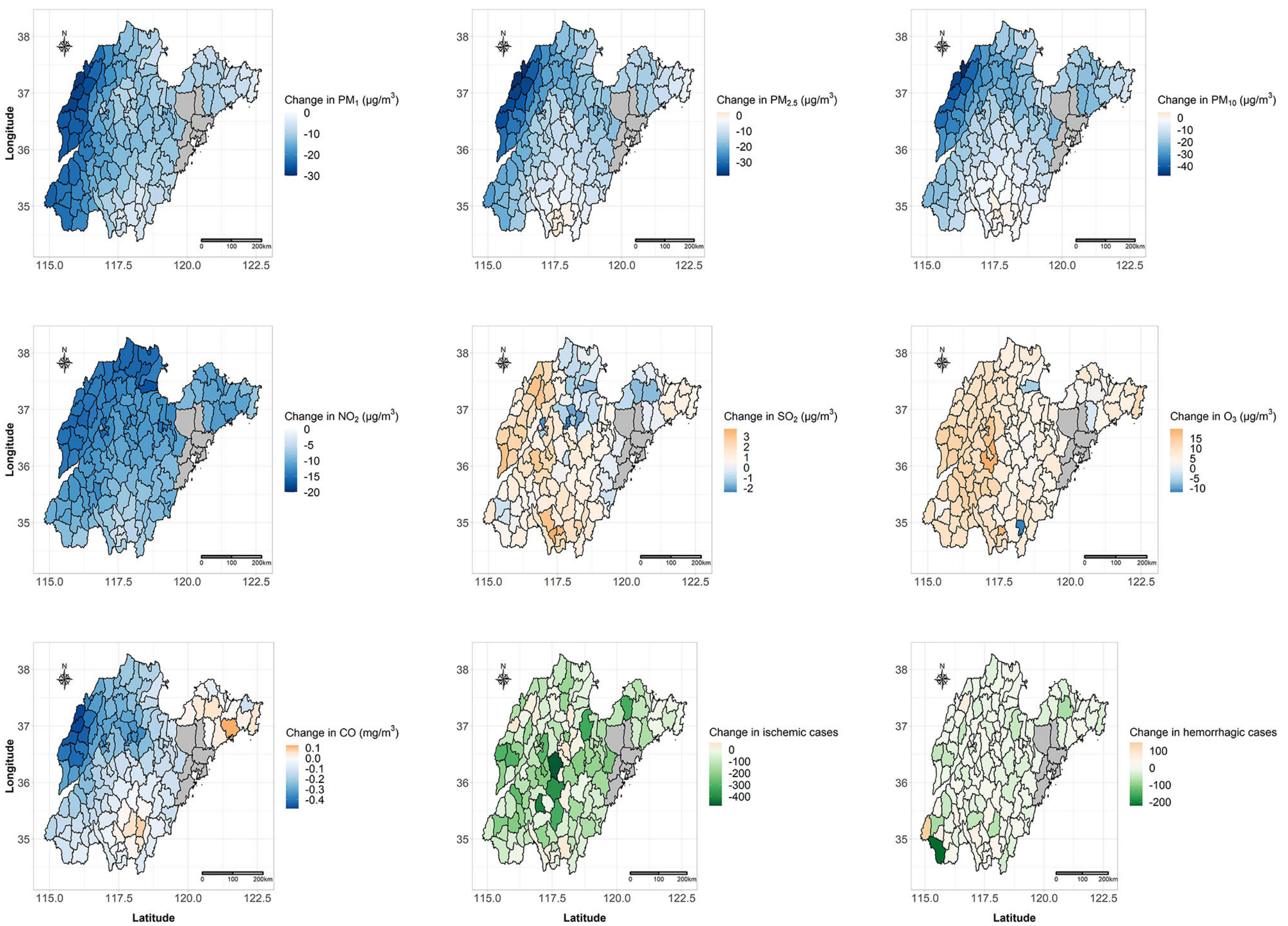

FIGURE 2 | Changes in population-weighted average air pollutant levels and stroke cases between the lockdown phase in 2020 and the counterfactual lockdown phase of the past 2 years for each of the 126 included counties using the DID model.

(**Table 3**). The total avoided PM_1-, $PM_{2.5}$-, PM_{10}-, NO_2-, and CO–related ischemic stroke cases were 739 (95% *CI*: 641, 833), 509 (95% *CI*: 440, 575), 355 (95% *CI*: 304, 405), 1,132 (95% *CI*: 1,024, 1,240), and 289 (95% *CI*: 236, 340), respectively. The corresponding percentages of the avoided ischemic stroke cases were 4.8% (95% *CI*: 4.2%, 5.4%), 3.3% (95% *CI*: 2.9%, 3.8%), 2.3% (95% *CI*: 2.0%, 2.6%), 7.4% (95% *CI*: 6.7%, 8.1%), and 1.9% (95% *CI*: 1.5%, 2.2%), respectively. The increased O_3 concentration levels across the 126 counties during the lockdown phase led to the increased counts of O_3-related ischemic stroke cases at 48 (95% *CI*: 41, 54), corresponding to an increase of 0.3% (95% *CI*: 0.3%, 0.4%).

TABLE 2 | Changes in average air pollutant concentration levels and total counts of stroke cases in the lockdown phase relative to the counterfactual lockdown phase of the past 2 years.

Outcome	Change in the lockdown phase	Proportion (%)	*P*-value
Air pollutants			
PM_1 (μg/m^3)	−14.3 (−17.9, −10.8)	−30.2 (−37.6, −22.8)	<0.001
$PM_{2.5}$ (μg/m^3)	−15.9 (−20.5, −11.4)	−20.9 (−26.9, −15.0)	<0.001
PM_{10} (μg/m^3)	−16.9 (−22.8, −11.0)	−13.5 (−18.2, −8.8)	<0.001
SO_2 (μg/m^3)	0.9 (−1.0, 2.9)	2.3 (−2.5, 7.1)	0.357
NO_2 (μg/m^3)	−11.1 (−13.1, −9.0)	−46.3 (−54.7, −37.8)	<0.001
O_3 (μg/m^3)	8.4 (7.0, 9.9)	11.5 (9.5, 13.4)	<0.001
CO (mg/m^3)	−0.16 (−0.20, −0.11)	−13.1 (−17.0, −9.3)	<0.001
Ischemic stroke			
Total	−15,315 (−27,689, −2,942)	−27.6 (−49.9, −5.3)	0.015
Age group			
18–64 years	−5,782 (−10,362, −1,203)	−29.0 (−51.9, −6.0)	0.013
65–74 years	−5,283 (−9,458, −1,108)	−28.4 (−50.8, −6.0)	0.013
≥75 years	−4,250 (−8,411, −90)	−25.2 (−49.8, −0.5)	0.045
Sex			
Male	−7,740 (−14,196, −1,285)	−26.0 (−47.7, −4.3)	0.019
Female	−7575 (−13,496, −1,654)	−29.5 (−52.5, −6.4)	0.012
Hemorrhagic stroke			
Total	−1,265 (−4,778, 2,249)	−11.9 (−45.0, 21.2)	0.490
Age group			
18–64 years	−744 (−1,857, 370)	−16.7 (−41.8, 8.3)	0.192
65–74 years	−259 (−1,586, 1,068)	−8.7 (−53.0, 35.7)	0.715
≥75 years	−262 (−1,529, 1,005)	−8.2 (−48.1, 31.6)	0.698
Sex			
Male	−520 (−2,208, 1,168)	−8.8 (−37.6, 19.9)	0.558
Female	−745 (−2,519, 1,029)	−15.7 (−53.2, 21.7)	0.418

Ninety-five percent confidence intervals are presented in parentheses.

TABLE 3 | Estimated counts of ischemic stroke cases related to the change in air pollutants in the lockdown phase relative to the counterfactual lockdown phase of the past 2 years.

Air pollutants	Counts related to change in air pollutants	Percentage (%)
PM_1 (μg/m^3)	−739 (−833, −641)	−4.8 (−5.4, −4.2)
$PM_{2.5}$ (μg/m^3)	−509 (−575, −440)	−3.3 (−3.8, −2.9)
PM_{10} (μg/m^3)	−355 (−405, −304)	−2.3 (−2.6, −2.0)
NO_2 (μg/m^3)	−1,132 (−1,240, −1,024)	−7.4 (−8.1, −6.7)
CO (mg/m^3)	−289 (−340, −236)	−1.9 (−2.2, −1.5)
O_3 (μg/m^3)	48 (41, 54)	0.3 (0.3, 0.4)

DISCUSSION

With the spread of COVID-19 worldwide, varying degrees of lockdown policies were implemented by the government to control this pandemic in most countries, and almost all aspects of life were affected during this period (2). The government of Shandong province imposed strict restrictions to lower the intensity of population outdoor activities (e.g., industry, traffic, construction, and entertainment), and the whole province was thrown into an unprecedented state of shutdown for about 6 weeks. This pandemic allowed us to estimate the changes in air pollutants and stroke cases relative to those during the same period in previous years using a quasi-experiment design.

The DID model indicated that if no lockdown occurred, the average concentrations of PM_1, $PM_{2.5}$, PM_{10}, NO_2, and CO across the 126 counties would increase by 30.2, 20.9, 13.5, 46.3, and 13.1%, respectively, whereas the average concentration of O_3 would decrease by 11.5%. Most previous studies focused on the changes in commonly monitored air pollutants, and no study has quantified the change in PM_1 levels during the lockdown in China (21–25). Our findings added to the growing literature evaluating the role of the COVID-19 lockdowns on ambient particulate matter, as we found substantial reductions in PM_1, $PM_{2.5}$, and PM_{10} levels during the COVID-19 lockdown phase. Moreover, the PM_1 concentration level seemed to decrease more precipitously than those of $PM_{2.5}$ and PM_{10}. The detailed reason for the heterogeneity of the reduction effect of the lockdown on the particulate matter of different sizes is unclear and requires further exploration in future studies.

For other gaseous air pollutants, many studies from China and other countries (e.g., France, India, Italy, and Mexico) also found that the concentration of NO_2 showed the most significant decrease and that of O_3 showed an increase during the lockdowns (6, 12, 22, 23, 41, 42). A previous study based on 597 major cities worldwide reported similar findings (43). As nitrogen oxide is mainly related to emissions from motor vehicles, the remarkable reduction in the NO_2 level may be due to the restriction of human traffic activities during the lockdowns (12, 42). Then, the reductions in the nitrogen oxide emissions because of the depressed anthropogenic activities may explain the observed increases in O_3 during the lockdowns, as the drop in nitric oxide (NO) may slow down its interaction with O_3 ($NO + O_3 = NO_2 + O_2$). Thus, the O_3 concentration may increase (7, 42).

Our results indicated that the COVID-19 lockdown did not result in significant changes in SO_2 concentrations, which was consistent with several previous studies in northern and eastern China (44, 45). However, some studies also suggested that the levels of SO_2 significantly decreased during the lockdowns in other regions of China (3, 6, 11). A possible interpretation for the limited influence of the lockdown on the SO_2 levels in this area is that the additional emissions from coal-burning for residential heating because of the people staying at home during the relatively cold season may counterbalance the reduction in other emissions, such as those from factories (44, 45).

Several studies suggested significant drops in mortality or hospital admissions during the COVID-19 lockdowns, but only limited studies used stroke-related events as the outcome of interest (17, 46–48). For instance, in France, a significant drop in hospitalization related to stroke was observed only in the area most affected by COVID-19 compared with those in previous years. In contrast, no significant change in hospitalization for stroke was observed in the least affected area (17). Another study collected data from a hospital in Spain and reported that relative to March 2019, the number of stroke admissions declined by about 23% in March 2020 (46). Similarly, Zhao et al. reported that hospital admissions for stroke reduced by $\sim$40% in February 2020 compared with that in the same period in 2019 in 227 hospitals across China (47). Kansagra et al. used the number of patients with stroke who underwent imaging as a surrogate for the number of cases of acute ischemic stroke in more than 800 hospitals in the United States, and they found that the number decreased by 39% during the early days of the pandemic (48). In this study, we estimated that the lockdown resulted in a drop of 27.6% in ischemic stroke cases compared with average values for the same periods of the previous 2 years. The reductions in PM_1, $PM_{2.5}$, PM_{10}, NO_2, and CO concentrations could have prevented as many as 4.8, 3.3, 2.3, 7.4, and 1.9% of the total ischemic stroke cases, respectively. The count of hemorrhagic stroke cases fell by a much smaller number ($n = -1{,}265$), which was not statistically significant. This finding is partly in line with previous studies indicating that exposure to air pollutants may exclusively increase ischemic stroke risks and not those of hemorrhagic stroke (20).

We noticed that not all avoided ischemic stroke cases could be attributed to the improved air quality during the COVID-19 lockdowns. Several other potential reasons may contribute to the observed decrease in the counts of ischemic stroke cases. First, the chance of family members and friends recognizing that a patient was having stroke symptoms may have been decreased because of the increased social isolation due to the lockdown (47). Second, most hospitals canceled their courses on stroke awareness education because of the imposition of social distancing (47). Third, patients with suspected acute stroke may have been worried about being infected with COVID-19 at hospitals (17). Fourth, some patients with severe stroke might have died at home (17). Fifth, evidence from other countries suggests that the reduced capacity of emergency services due to the burden of patients with COVID-19 may have limited the number of patients with stroke seeking essential medical services (49). However, only a total of no more than 800 COVID-19 cases were diagnosed across Shandong province during the lockdown, and this has limited influence on hospitals providing medical services for patients with stroke (50). Moreover, a recent study revealed that the onset-to-door time became even shorter during the lockdowns in Beijing, China, which might have benefited from the better traffic situation (51).

Our results imply that substantial health benefits could be achieved if stringent and effective control measures are implemented to tackle air pollution. Lockdowns are not appropriate for improving air quality in the long run, and persistent efforts are needed to reduce air pollution through a series of abatement measures for anthropogenic emissions (52). For example, policymakers could consider comprehensive strategies to upgrade local power and steel industries, provide more subsidies for public or electric transportation, and encourage households to transition from coal to cleaner energy sources (such as gas and electricity) (4).

Our study has several limitations. First, this is a quasi-experiment based on stroke count data at the population level. Thus, confounding factors at the individual level (e.g., tobacco smoking, hypertension, physical activity, and diet) (19, 53) could not be fully excluded, although the reductions in ischemic stroke cases were significant in all sex and age subgroups. However, we expect that the individual changes in the confounding factors did not cause substantial bias in the relation between the lockdown and stroke incidence at a population level (52). Second, the avoided ischemic stroke cases attributed to the changes in the air pollutant concentration levels were estimated using single-pollutant models. The strong correlation between the included air pollutants and the absence of epidemiological dose-response functions that account for the full suite of pollutants did not allow us to estimate the independent effect of each air pollutant. Therefore, some avoided stroke cases might have been counted more than once (52). Third, the method we used could not rule out the influence of meteorological conditions (e.g., air pressure, temperature, and wind field) on air pollutant concentration levels and the effect of extreme cold temperature on ischemic stroke incidence (54). However, a previous study suggested that the adjustment of meteorological variables had little effect on the estimated changes in air pollutant concentration levels during the lockdown in China (7). In addition, all people had to stay at home during the lockdown. Thus, we anticipate that the outdoor extreme cold temperature had a limited influence on the ischemic stroke incidence. Fourth, household air pollution (HAP) is also a risk factor for ischemic stroke (55), and the exposure level of HAP might be increased as most residents had to stay at home for longer durations during the lockdown (56). However, the additional counts of ischemic stroke resulting from HAP could not be estimated because of the lack of relevant data.

CONCLUSION

The life-changing restrictions during the COVID-19 lockdown indirectly reduced the concentration levels of air pollutants (PM_1, $PM_{2.5}$, PM_{10}, NO_2, and CO) and subsequently reduced the associated ischemic stroke incidence. However, the health benefits brought by the lockdown are temporary, and long-term measures should be implemented to decrease air pollution levels and related health loss in the post-COVID-19 period.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Review Committee of Public Health, Shandong University. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

HW: formal analysis, methodology, visualization, and writing the original draft. ZL and BZ: investigation, data curation, writing, reviewing, and editing. JW: methodology, resources, data curation, writing, reviewing, and editing. XL: validation, writing, reviewing, and editing. MZ: formal analysis, validation, and writing the original draft. WL: software, writing, reviewing, and editing. XG: supervision, resources, writing, reviewing, and editing. BX: conceptualization, supervision, funding acquisition, writing, reviewing, and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.876615/full#supplementary-material

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Three Exposure Metrics for Fine Particulate Matter Associated With Outpatient Visits for Acute Lower Respiratory Infection Among Children in Guangzhou, China

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Ambient fine particulate matter ($PM_{2.5}$) is associated with an elevated risk of acute lower respiratory infections (ALRI). However, this association has not been examined using alternative exposure metrics. We collected outpatient data of patients with ALRI aged < 14 years from the administrative database of a large tertiary hospital in Guangzhou, China, from 2013 to 2019. Ambient $PM_{2.5}$ was measured using three metrics: (a) daily mean, (b) daily excessive concentration hours (DECH), and (c) hourly peak. Generalized additive models were fitted to estimate the excess risk (ER) associated with $PM_{2.5}$. A total of 105,639 ALRI (35,310 pneumonia and 68,218 bronchiolitis) outpatient visits were identified during the study period. An interquartile range increment in $PM_{2.5}$ DECH was consistently associated with the highest ER of ALRI-related outpatient visits: 12.30% (95% confidence interval [CI]: 9.49–15.18%), compared with 11.20% (95% CI: 8.34–14.13%) for daily mean and 9.73% (95% CI: 6.97–12.55%) for hourly peak. The associations between the three metrics of $PM_{2.5}$ and ALRI-related outpatient visits were stronger in the cold season than in the warm season. Future studies should consider $PM_{2.5}$ DECH as an alternative method of exposure measurement, in addition to daily mean and hourly peak concentrations of $PM_{2.5}$.

Keywords: PM 2.5, air pollution, acute lower respiratory infection, China, children

INTRODUCTION

Lower respiratory infections, including pneumonia and bronchiolitis, are the leading causes of death in children under the age of 5 years (1–3). In China, an estimated 55.8 million (95% uncertainty interval [UI]: 48.17 to 55.51 million) cases of lower respiratory infections and 1,85,264.33 (95% UI: 157651.46 to 212877.21) deaths due to them were reported in 2019. These infections represented a major health burden and were the leading cause of mortality among children aged < 5 years in China (4).

Ambient particulate matter, especially particulate matter with an aerodynamic diameter of < 2.5 μm ($PM_{2.5}$), is associated with an increased incidence, hospital admission, and mortality of acute lower respiratory infections (ALRI) (5–12). However, these studies used daily mean concentrations almost universally as proxy measurements for ambient $PM_{2.5}$. Although a few alternative measurements of $PM_{2.5}$ concentrations were proposed by researchers (13–17), none have been applied in empirical research to investigate the association between different metrics of $PM_{2.5}$ and the risk of ALRI-related outpatient visits.

In this study, we collected outpatient data from 105,639 patients with ALRI aged 14 years in a large tertiary hospital in Guangzhou, China over a consecutive observational period of seven years. We measured ambient $PM_{2.5}$ concentrations using three different metrics (daily mean, daily excessive concentration hours [DECH], and hourly peak), and further examined the associations between these three metrics of $PM_{2.5}$ and the risk of ALRI-related outpatient visits.

METHODS

Acute Lower Respiratory Infection Data

From February 2013 to December 2019, ALRI outpatient data for patients aged < 14 years were obtained from Guangdong Second Provincial General Hospital, which is one of the largest tertiary hospitals in Guangzhou, China (18). This administrative database set up by the hospital regularly collects data including demographics, medical conditions, and diagnosis codes (19–21). The diagnoses were completed by attending physicians and further validated by trained medical coders. The causes of outpatient visits were defined using the International Classification of Diseases, Tenth Revision (ICD−10) as follows (20, 22): ALRI (J12–J18 and J20–J22), pneumonia (J12–J18), and bronchiolitis (J20–J21).

Air Pollution and Meteorological Data

The daily concentrations of air pollutants, including $PM_{2.5}$, PM_{10}, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3), were retrieved from 11 air monitoring stations in Guangzhou during the study period. The mean concentration of the air pollutants collected by the 11 air monitoring stations was used as the daily concentration of air pollutants. We used a linear interpolation approach (the "na. approx" function in "zoo" package in R) to impute missing data (0.78% of the total observation days). Considering the potential impact of weather on ALRI, we obtained daily meteorological data (mean temperature and relative humidity [RH]) from the National Weather Data Sharing System (http://data.cma.cn/).

Exposure Metric

We compared the associations between $PM_{2.5}$ and daily ALRI-related hospital admissions using three different exposure metrics: $PM_{2.5}$ DECH, hourly peak concentration, and daily mean concentration. The definitions of these three metrics are available elsewhere (13–16). Briefly, DECH was developed by Lin et al. (23) and defined as the daily total concentration hours above a specific concentration level. Based on the reference Air Quality Guidelines (daily mean of 15 $\mu g/m^3$ for $PM_{2.5}$) formulated by the World Health Organization (WHO) (24), we calculated the DECH using the following formula (16):

$$DECH = \sum_{i=0}^{23} C_i$$

$$C_i = \begin{cases} C_i - 15, & C_i \geq 15 \\ 0, & C_i < 15 \end{cases}$$

where i is the hourly time of 1 day, C_i is the concentration of $PM_{2.5}$ at a given time point, and ΔC_i is the difference between C_i and the threshold concentration (15 $\mu g/m^3$).

Another metric, $PM_{2.5}$ hourly peak concentration, was proposed to investigate the adverse effects caused by high levels of $PM_{2.5}$. $PM_{2.5}$ hourly peak concentration was defined as the maximum concentration of $PM_{2.5}$ during a 24-h period on an observation day. The $PM_{2.5}$ daily mean was the most commonly used definition of ambient $PM_{2.5}$ concentration in the literature.

Statistical Models

Following the design of previous time-series studies in the field of air pollution epidemiology research (10, 11, 25–27), the association between $PM_{2.5}$ and ALRI-related hospital outpatient visits was estimated using generalized additive Poisson models. Public holidays, days of the week, and winter and summer vacations for students were controlled as categorical variables in the models. Temporal trends, temperature, and RH were adjusted for as smoothing splines. We also controlled for the number of doctors per day in the models. In line with prior studies (25–27), we chose six degrees of freedom (df) per year for temporal trends, six df for moving average temperature of the current day, and the previous 3 days (Temp03), and RH.

Considering the potentially delayed adverse effects of air pollution, different lag structures were assessed to examine potential lag effects. In the single-lag day models, we begin with the same day (lag0) up to a five-day lag (lag5) based on previous studies (11, 25). In the multi-day lag models, we considered the accumulated effects (moving averages for the current day and the previous one, two, and three days [lag01, lag02, and lag03]).

Stratified Analyses

To investigate whether the health effects of $PM_{2.5}$ on ALRI, differed by sex, age group (age < 5 vs. 5–14 years), and season (warm vs. cold), we performed subgroup analyses stratified by these factors. The warm and cold seasons are defined as the periods from April to September, and from October to March, respectively. In subgroup analyses stratified by season, we chose 3 dfs per year for temporal trends as each season covers only half of the year. We tested whether the differences between strata were significant by calculating the 95% CI, according to previous studies (10, 11).

Sensitivity Analyses

We conducted a set of sensitivity analyses to check the robustness of the main results to alternative modeling strategies for temporal and meteorological factors, as well as multiple two-pollutant models. To consider the potential collinearity caused by the inclusion of two highly correlated variables in the same model, we examined

TABLE 1 | Summary statistics of acute lower respiratory infections outpatient visits, air pollutants, and meteorological variables.

	Mean	SD	Percentile				
			Min	25th	50th	75th	Max
No. of daily outpatient visits							
ALRI	38	18	1	25	35	47	124
Pneumonia	13	10	0	7	11	17	73
Bronchiolitis	25	11	0	16	23	31	70
Air pollution, $\mu g/m^3$							
$PM_{2.5}$ DECH	443.0	409.6	0.0	137.5	327.0	644.0	3143.0
$PM_{2.5}$ hourly peak	49.8	27.2	7.0	30.0	43.0	63.0	236.0
$PM_{2.5}$ daily mean	35.3	19.1	4.6	21.4	30.8	45.1	154.5
PM_{10}	56.6	27.2	10.0	37.2	50.0	71.2	216.2
SO_2	11.0	4.8	2.6	7.6	10.1	13.5	37.7
NO_2	46.0	18.5	8.8	33.3	41.9	54.3	176.7
O_3	49.6	27.8	3.5	27.9	45.9	66.4	189.0
Meteorological variables							
Temperature, °C	22.3	5.8	1.8	18.2	24.0	27.2	30.7
Relative humidity, %	80.3	11.2	34.0	74.4	82.7	88.9	97.0

ALRI, acute lower respiratory infections; SD, standard deviation; DECH, daily excessive concentration hours.

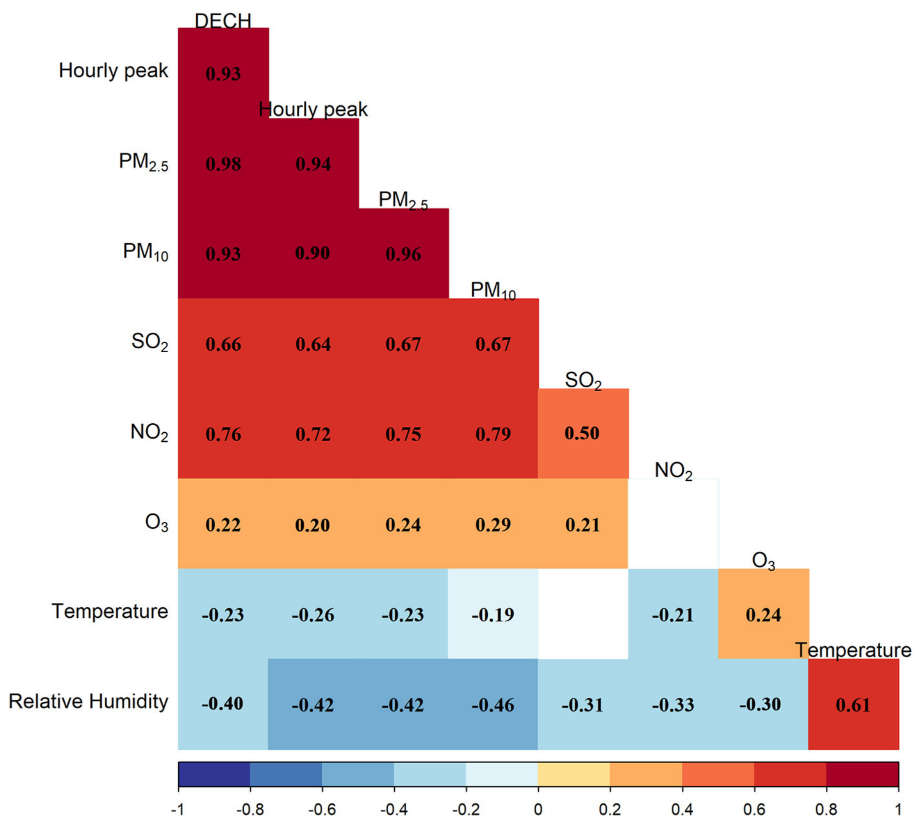

FIGURE 1 | Pearson pairwise correlation plot of ambient air pollutants and meteorological factors.

the correlation between independent variables. If the correlation was > 0.80, they were not included in the same two-pollutant models.

The main results were first estimated by altering the df for the temporal trends and meteorological variables (df alternating from five to eight). Second, gaseous air pollutants (SO_2, NO_2, and

TABLE 2 | Excessive risk (95% confidence intervals) of outpatient visits of acute lower respiratory infection, pneumonia, and bronchiolitis per interquartile range increment in ambient $PM_{2.5}$ (daily mean, daily excessive concentration hours [DECH], and hourly peak) at lag03 using single–pollutant and two–pollutant models.

Pollutants	Models	Excessive risk (95% confidence intervals)		
		ALRI	Pneumonia	Bronchiolitis
$PM_{2.5}$ daily mean, interquartile range: 23.7 $\mu g/m^3$				
	Single–pollutant model	11.20 (8.34, 14.13)	15.60 (11.81, 19.52)	9.50 (6.22, 12.89)
	Two–pollutant models			
	Control for SO_2	9.33 (6.16, 12.59)	12.99 (8.81, 17.32)	7.84 (4.19, 11.62)
	Control for NO_2	7.85 (4.50, 11.31)	12.10 (7.73, 16.65)	5.56 (1.77, 9.50)
	Control for O_3	12.87 (9.80, 16.02)	16.96 (12.95, 21.11)	10.85 (7.38, 14.44)
$PM_{2.5}$ DECH, interquartile range: 506.5 $\mu g/m^3$				
	Single–pollutant model	12.30 (9.49, 15.18)	16.32 (12.68, 20.07)	10.27 (7.09, 13.55)
	Two–pollutant models			
	Control for SO_2	10.47 (7.42, 13.62)	14.15 (10.14, 18.31)	8.95 (5.41, 12.61)
	Control for NO_2	9.28 (6.05, 12.61)	13.48 (9.28, 17.84)	6.96 (3.30, 10.75)
	Control for O_3	13.57 (10.63, 16.60)	17.55 (13.74, 21.50)	11.54 (8.20, 14.99)
$PM_{2.5}$ hourly peak, interquartile range: 33 $\mu g/m^3$				
	Single–pollutant model	9.73 (6.97, 12.55)	13.75 (10.11, 17.50)	8.09 (4.92, 11.36)
	Two–pollutant models			
	Con–rol for SO_2	7.66 (4.64, 10.77)	10.91 (6.95, 15.02)	6.17 (2.68, 9.78)
	Control for NO_2	6.02 (2.79, 9.36)	9.85 (5.67, 14.21)	3.77 (0.11, 7.56)
	Control for O_3	11.13 (8.18, 14.15)	14.84 (11.02, 18.80)	9.18 (5.85, 12.61)

O_3) were further adjusted in addition to PM air pollution using two-pollutant models (28, 29).

All statistical analyses and data visualization were conducted using R version 4.0.5. Statistical significance was set at $P < 0.05$.

RESULTS

Characteristics of the ALRI Outpatient Visits, Air Pollutants, and Meteorological Variables

In 2,058 days of observations, from February 2013 to December 2019, we identified 105,639 outpatient visits of patients with ALRI and aged < 14 years, among which 35,310 (33.4%) and 68,218 (64.6%) were due to pneumonia and bronchiolitis, respectively. **Table 1** presents the descriptive statistics of the daily outpatient visits, concentrations of air pollutants, and meteorological variables analyzed. The mean daily number of ALRI outpatient visits during the study period was 38 (standard deviation [SD]: 18), among which 13 (SD: 10) were pneumonia-related visits and 25 (SD: 11) were bronchiolitis visits. The daily mean of $PM_{2.5}$ during the study period was 35.3 $\mu g/m^3$ (SD: 19.1), the mean of $PM_{2.5}$ hourly peak concentrations was 49.8 $\mu g/m^3$ (SD: 27.2), and the mean of $PM_{2.5}$ DECH in 24 h was 443.0 $\mu g/m^3$ (SD: 409.6).

Figure 1 shows the pairwise Pearson correlation coefficients for the air pollutants and meteorological factors. Ambient particulate matter air pollutants had Pearson correlation coefficients of over 0.9. The associations with SO_2 and NO_2 were moderately strong (Pearson correlation coefficients in the range of 0.6 and 0.8), while the absolute values of Pearson correlation coefficients for particulate matter and O_3, as well as meteorological factors, were < 0.5, indicating a lower strength of linear correlation.

Associations Between the Three Metrics of PM and Risk of ALRI-Related Outpatient Visits

Table 2 and **Figure 2** present the excessive risks (ER) and 95% CIs of ALRI, pneumonia, and bronchiolitis-related outpatient visits per interquartile range (IQR) increment in the three metrics of ambient $PM_{2.5}$ exposure (daily mean, DECH, and hourly peak) at lag03. An IQR increment in $PM_{2.5}$ DECH was consistently associated with the highest risk of outpatient visits for all three diseases [12.30% (95% CI: 9.49% to 15.18%) increase in ALRI, 16.32% (95% CI: 12.68% to 20.07%) increase in pneumonia, and 10.27% (95% CI: 7.09% to 13.55%) increase in bronchiolitis], followed by daily mean [11.20% (95% CI: 8.34% to 14.13%) increase in ALRI, 15.60% (95% CI: 11.81% to 19.52%) increase in pneumonia, and 9.50% (95% CI: 6.22% to 12.89%) increase in bronchiolitis] and hourly peak [9.73% (95% CI: 6.97% to 12.55%) increase in ALRI, 13.75% (95% CI: 10.11% to 17.50%) increase in pneumonia, and 8.09% (95% CI: 4.92% to 11.36%) increase in bronchiolitis].

Sensitivity Analyses

To test the robustness of our findings to alternative models and lag periods of exposure, we conducted two sensitivity analyses. We conducted a series of two-pollutant models by further including gaseous air pollutants (SO_2, NO_2, and O_3), and the results (**Table 2**) were consistent with the main findings that $PM_{2.5}$ DECH was associated with the highest risk of ALRI-related outpatient visits, followed by the daily mean, and hourly peak.

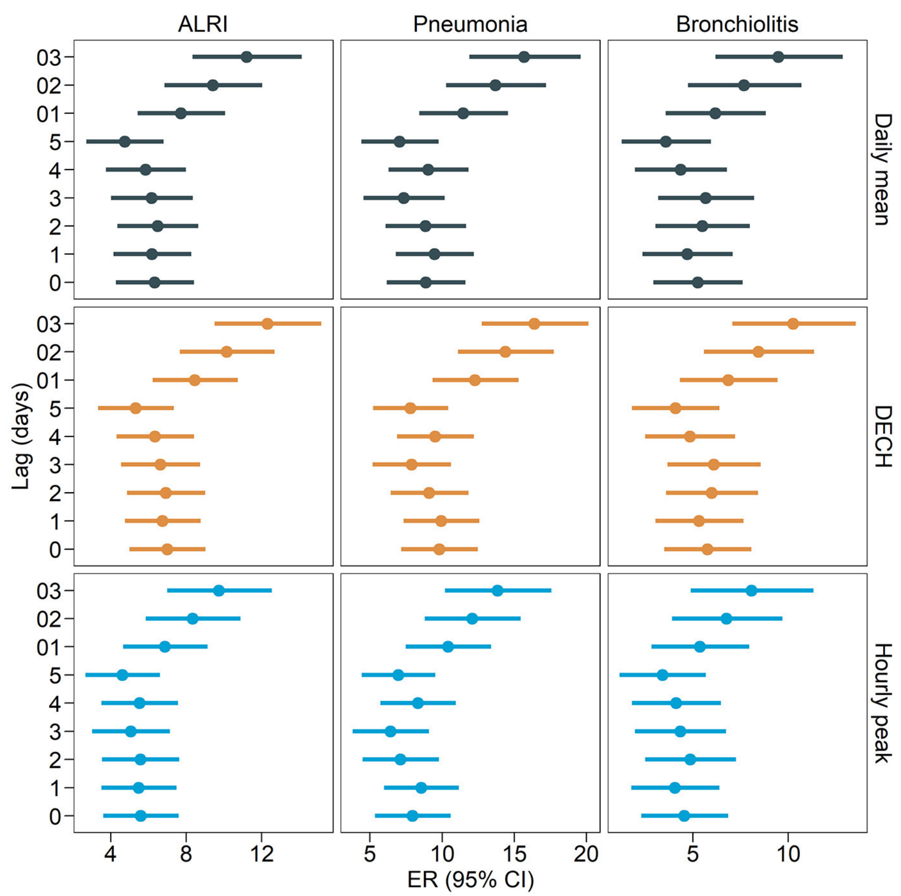

FIGURE 2 | Excess risk (95% confidence intervals) of outpatient visits related to acute lower respiratory infections per interquartile range increment in ambient $PM_{2.5}$ (daily mean, daily excessive concentration hours [DECH], and hourly peak) at different lag periods.

To test the robustness of the results to different lag periods of $PM_{2.5}$, we ran our main models for exposure measured at various lag periods (lag0 to lag5 and lag01 to lag 03). The ERs of ALRI-related outpatient visits were larger when $PM_{2.5}$ was measured as moving averages (lag01, lag02, and lag03). The trend that $PM_{2.5}$ DECH was associated with the highest risk of ALRI outpatient visits was generally consistent at different lag periods. To examine the consistency of the results for different dfs for the spline effects of temporal trends and temperature, we conducted the models using various dfs (**Supplementary Table S1**). The sensitivity analysis results showed that the estimates were larger at larger df, but the results were consistently larger for $PM_{2.5}$ DECH than for daily mean and hourly peak, and all ERs remained statistically significant.

Three Metrics of Ambient $PM_{2.5}$ Associated With ALRI-Related Outpatient Visits in Subgroups

The ERs and 95% CIs of ALRI-related outpatient visits for the three metrics of $PM_{2.5}$ by sex, age group, and season are shown in **Table 3**. We found that the associations between $PM_{2.5}$ and ALRI-related outpatient visits were significantly larger in the cold season (October to March) than in the warm season (April to September), and this trend was consistent among the three metrics. The associations were insignificant during the warm season in several models. Although the ERs of ALRI outpatient visits were higher among men than among women and larger among children aged between five and 14 years than among those under 5 years, the differences across sex and age subgroups were not statistically significant.

DISCUSSION

In this time-series analysis of daily ALRI-related outpatient visits aged < 14 years in Guangzhou, China, we examined the associations of three metrics of ambient $PM_{2.5}$ (daily mean, DECH, and hourly peak) with the risk of ALRI-related outpatient visits. All three metrics of $PM_{2.5}$ were associated with significantly elevated risks of ALRI-, pneumonia-, and bronchiolitis-related outpatient visits. More importantly, $PM_{2.5}$ DECH exhibited consistently larger ER in all models and subgroup analyses than the more commonly used daily mean and

TABLE 3 | Excess risk and 95% confidence intervals of acute lower respiratory infection, pneumonia, and bronchiolitis for per interquartile range increment in ambient $PM_{2.5}$ (daily mean, daily excessive concentration hours [DECH], and hourly peak) stratified by gender, age group, and season.

Pollutants	Stratum	Excessive risk (95% confidence intervals)		
		ALRI	Pneumonia	Bronchiolitis
$PM_{2.5}$ daily mean				
	Sex			
	Male ($N = 47,966$)	13.25 (10.01, 16.59)	18.58 (13.92, 23.43)	10.96 (7.37, 14.67)
	Female ($N = 57,673$)	8.27 (4.93, 11.71)	11.91 (7.17, 16.87)	7.18 (3.09, 11.43)
	Age			
	<5 ($N = 41,799$)	10.47 (7.53, 13.49)	14.39 (10.48, 18.45)	8.62 (5.27, 12.07)
	5–14 ($N = 63,840$)	13.11 (8.34, 18.09)	21.40 (12.60, 30.90)	13.34 (7.89, 19.07)
	Season			
	Warm ($N = 40,922$)	**1.45 (0.32, 2.60)**	**0.61 (−0.82, 2.05)**	2.23 (0.85, 3.62)
	Cold ($N = 64,717$)	**15.05 (10.87, 19.39)**	**24.17 (18.64, 29.97)**	11.28 (6.78, 15.95)
$PM_{2.5}$ DECH				
	Sex			
	Male ($N = 47,966$)	14.00 (10.88, 17.22)	19.02 (14.55, 23.66)	11.75 (8.28, 15.34)
	Female ($N = 57,673$)	9.69 (6.36, 13.12)	12.97 (8.40, 17.72)	7.90 (3.95, 12.00)
	Age			
	<5 ($N = 41,799$)	11.14 (8.30, 14.05)	15.04 (11.28, 18.93)	9.23 (5.99, 12.56)
	5–14 ($N = 63,840$)	16.97 (12.19, 21.96)	22.20 (13.80, 31.23)	14.61 (9.35, 20.12)
	Season			
	Warm ($N = 40,922$)	**1.65 (0.54, 2.76)**	**1.14 (−0.27, 2.56)**	**2.18 (0.84, 3.55)**
	Cold ($N = 64,717$)	**15.68 (11.69, 19.81)**	**24.34 (19.13, 29.79)**	**11.96 (7.65, 16.44)**
$PM_{2.5}$ hourly peak				
	Sex			
	Male ($N = 47,966$)	11.16 (8.05, 14.36)	16.12 (11.68, 20.73)	8.87 (5.42, 12.43)
	Female ($N = 57,673$)	8.27 (4.93, 11.71)	10.73 (6.18, 15.48)	6.91 (2.94, 11.03)
	Age			
	<5 ($N = 41,799$)	9.27 (6.43, 12.18)	12.96 (9.22, 16.84)	7.39 (4.15, 10.73)
	5–14 ($N = 63,840$)	13.11 (8.34, 18.09)	17.12 (8.68, 26.22)	11.22 (6.00, 16.70)
	Season			
	Warm ($N = 40,922$)	**0.30 (−0.68, 1.29)**	**−0.14 (-1.40, 1.15)**	**0.76 (−0.43, 1.97)**
	Cold ($N = 64,717$)	**15.02 (10.77, 19.43)**	**24.47 (18.81, 30.40)**	**11.07 (6.52, 15.81)**

The bold type represents the statistically significant differences ($p < 0.05$).
Warm seasons, April to September; cold seasons, October to March.

hourly peak metrics. The associations of $PM_{2.5}$ with ALRI-related outpatient visits were significantly stronger in the cold season than in the warm season.

Although extensive research has been conducted on the association between ambient $PM_{2.5}$ and the risk of ALRI-related outpatient visits (5–12), investigations are lacking regarding the metrics used (DECH or daily peak). To our knowledge, this is the first study to examine the associations between the three metrics of $PM_{2.5}$ and ALRI-related outpatient visits. Our findings revealed that $PM_{2.5}$ DECH, a metric of total excessive exposure to $PM_{2.5}$ using the WHO guidelines, exhibited the largest risk of ALRI-related (pneumonia and bronchiolitis) outpatient visits. This trend is consistent with that in previous studies that provided evidence that $PM_{2.5}$ DECH exhibited larger effect sizes than the daily mean (11, 16, 23). The larger effect size with $PM_{2.5}$ DECH may be explained by more finessed concentrations of $PM_{2.5}$ measured at different hours in a day; DECH is a summation of excessive $PM_{2.5}$ at each hour, while the hourly peak is the highest hourly concentration in a day and the daily mean does not account for the reference guideline. In addition, previous studies suggested that $PM_{2.5}$ DECH showed a better model fit performance, as measured using the Akaike information criterion (16). $PM_{2.5}$ DECH is also more flexible in terms of the adaptation of the reference concentration and can be computed per guideline concentration in different countries and regions. This is exceptionally helpful in the context of various inconsistent guidelines recommended by different organizations, such as the WHO standard and the United States National Ambient Air Quality Standards (24). Our findings suggest that $PM_{2.5}$ DECH may serve as an alternative measure of ambient $PM_{2.5}$ concentration to the daily mean.

An interesting result of this study is that the associations between ambient $PM_{2.5}$ and the risk of ALRI-related outpatient visits were significantly stronger in the cold season than in the warm season, which is in line with the findings of many previous epidemiological studies conducted in other regions and countries that reported a higher incidence of respiratory diseases attributable to air pollution (5, 11). One possible explanation is that lower temperatures in cold seasons may have synergistic effects on the adverse outcomes of ambient air pollution through mechanisms, such as impaired immunity of the local respiratory tract, poor air circulation, and slow air convection (12). The stronger associations in cold seasons may be partially explained by the influenza epidemic, which usually occurs during winter, but we were not able to control for this in our models owing to data unavailability.

Several biological mechanisms may explain the observed association between ambient particulate matter-related air pollution and elevated risk of ALRI-related outpatient visits in this study. Animal-based experimental studies have suggested that particulate matter induces inflammation in pulmonary cells through oxidant radical generation and further impairs lung function (30, 31). Together, these mechanisms indicate that exposure to ambient particulate matter may exacerbate lung function and prolong the recovery of lung cells from inflammation (5, 32), triggering an increased risk of ALRI within the short period observed in our study.

Previous environmental health studies predominately used daily mean concentration as the metric for ambient air pollution, given its simplicity in data collection and numeric calculation (12, 16, 25). The results of this study have the public health implication that DECH or daily peak can serve as alternative metrics of ambient air pollution and may exhibit larger effect sizes than daily mean concentrations. In addition, the epidemiological results, corroborated by several previous studies (5, 6, 10, 11), also suggest that more care should be provided to children during heavily polluted days to prevent ALRI-related outpatient visits and ameliorate the health outcomes.

This study has some limitations. First, the data used in this study were restricted to a single hospital in Guangdong, China. The limitations of the study sample may limit the generalizability of the findings to other populations. Second, this was a time-series study using the daily counts of ALRI as the outcome variable. The aggregated data make this an ecological study by design and are, therefore, subject to ecological fallacy. Third, because patient addresses were not available to the researchers, the exposure to $PM_{2.5}$ was measured at the city level; ambient air pollution was not measured at an individual level, which may have led to exposure misclassification. Fourth, since we used the secondary administrative database designed by the hospital, a few important variables, such as indoor air pollution, smoking, economic status, and insurance, were missing from the analyses. Fifth, detailed daily data on influenza epidemics are not publicly available and cannot be statistically controlled for in our models; this may have led to residual confounding.

Nonetheless, this is the first study to investigate the association between three metrics of ambient $PM_{2.5}$, and the risk of ALRI-related outpatient visits of patients aged < 14 years. The results of ER and 95% CIs of the three metrics shed light on the adverse effects of ambient $PM_{2.5}$, measured at different scales. Administrative outpatient data of 105,639 patients with ALRI spanning seven consecutive years were collected from a large tertiary hospital in Guangzhou, China, which resulted in relatively large sample size and statistical power.

CONCLUSIONS

This time-series study found that $PM_{2.5}$ DECH manifested larger effect sizes in the associations between ambient $PM_{2.5}$ concentrations and ALRI-related outpatient visits of patients aged <14 years. Future studies may consider using $PM_{2.5}$ DECH as an alternative method of exposure measurement, in addition to daily mean and hourly peak.

DATA AVAILABILITY STATEMENT

The data may be available upon requests to the corresponding author.

AUTHOR CONTRIBUTIONS

DX: conceptualization, investigation, visualization, writing—original draft, and writing—reviewing and editing. WG, DX, and JC: investigation, writing—reviewing and editing. ZL and XZ: investigation, visualization, and supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Assessment of Willingness to Pay for Pollution Prevention, Health and Happiness: A Case Study of Punjab, Pakistan

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Air pollution has been notoriously held accountable for a substantial number of deaths in several countries. Moreover, its negative impact on people's health and well-being has also been witnessed in countries where air pollution is below the recommended national levels. The urban cities of Pakistan are among the worst South Asian areas in terms of air pollution. Because of this problem, the health and well-being of citizens are affected. The present study investigates the impact of air pollution on urban residents' happiness and health. It analyzes their willingness to pay for pollution prevention and its determinants by employing the data obtained through a primary survey. Pakistanis are unaware of air pollution's effect on health and quality of life, therefore only 12.5% consider this problem very serious. The results confirm the significantly negative effect of air pollution on happiness. Concerning the willingness to pay, it is differentiated in the form of tax and social contribution. Pakistanis are willing to pay more in social contribution in return for different environmental attributes. The results show that only 13% of respondents are not willing to pay for income contribution to improve air quality reporting indifferent attitude and insufficient knowledge of the environment. Our findings suggest that their apprehension concerning the environment influences people's willingness to pay. The study concludes that despite Pakistan's underdeveloped economic stature and its poor and flexible budgetary allocation for the betterment of air quality, most Pakistanis showed their willingness to pay for environmental protection. The government and environmental organizations ought to generate consensus among the general population about environmental importance, individual responsibility, and social duties thereby lessening the free-rider problem and reducing air pollution for better social welfare.

Keywords: air pollution, exposure assessment, happiness, tax payment, social contribution

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INTRODUCTION

Air pollution has drawn equal attention of researchers from environmental and economic sciences owing to its multifaceted negative impact on health and the economy (1). Air quality affects a person's utility of public good. An individual's willingness to pay (WTP) taxes for the betterment of air quality can serve as the main factor when an exchange between economic development and environmental regulations takes place (2). In this respect, since 1990s, there has been a growing trend toward studying well-being (or "happiness research" or "quality of life research") theoretically or empirically (3–8). Nevertheless, the life satisfaction valuation approach employed in environmental valuation is considered an unconventional technique that can hardly be found in current standard literature. The life satisfaction method takes into consideration the environmental advantages of decrease in air pollution, which, in turn, can exert a direct impact on individual well-being (experienced utility) in the spheres of physical and psychological health, recreation, and aesthetics (9–12). The majority of countries worldwide have advanced significantly and comprehensively in terms of well-being excepting the natural environment (13). Urban air pollution tops the list of problems emanating from environmental degradation faced by the urban population. Growing empirical evidence categorically suggests that excessive amounts of suspended particulates cause health-related problems creating wide-ranging health hazards particularly affecting lungs and heart. The most harmful among these are the fine particulates of 10 microns or smaller in diameter. $PM_{2.5}$ is a fine air pollution particle that can penetrate deep into the human body. The latest research clearly indicates that exposure to even lower concentrations of $PM_{2.5}$ can raise the chances of critical health issues (14, 15). Pakistan, India, Bangladesh, and China have recorded "increasing trends in $PM_{2.5}$ exposure". While China is known to have improved dealing with pollution, Pakistan, India and Bangladesh "have experienced the steepest increases in air pollution levels since 2010 and now present the highest sustained $PM_{2.5}$ concentrations" (15).

With an alarming figure of estimated 35% of people residing in urban areas, Pakistan is considered the largest urbanized state in the South Asian region (16). Like elsewhere in the developing economies, the urban cities in Pakistan keep on expanding in size and population, providing versatile, unprecedented employment opportunities, convenience, and facilities that are largely unavailable in other parts of the country. However, all that has come at the costs of environmental degradation in the shape of increased amount of pollution, garbage, congestion and the damage to ecosystem. The Pakistani urban area statistics suggest that the PM concentration in urban Pakistan is far greater in comparison to its Bhutanese and Sri Lankan counterparts in the South Asian region. Pakistan has been known to be incapable for systematic monitoring of $PM_{2.5}$. Furthermore, the already poor air quality is further deteriorated when the Punjab, the biggest province of Pakistan in terms of population, is surrounded by toxic smog. Each year, the smog normally occurs for 10–25 days between November and February affecting Southern and Central parts of the Punjab province and significantly decreasing visibility on roads and causing health issues. The regional data recorded in 2016–2019 about air quality names South Asian region to be at the bottom with 30 cities having worst air quality. Lahore, Pakistan's second biggest city with 11 million residents, has been recorded to experience maximum pollution. The quality of air in Lahore has dropped during the last 20 years. Its pollution concentration was 33 $\mu g/m^3$ in 1998, however, by 2016, it reached 64 $\mu g/m^3$—which was six times higher than the WHO standards suggesting a lost life expectancy age of 5.3 years for an average individual when comparing it to the WHO standards. The poor air quality in the third biggest Pakistani city, Faisalabad, causes the loss of an approximate 4.8 years to each individual when comparing it to the WHO standards (15). Smog, in these districts, has become a public health emergency.

Although the Government of Pakistan has taken many measures to address the issues relating to the health hazards caused by environmental pollution, there is still a large room for improvement. A higher ratio of GDP per capita demands effective measures for guaranteeing eco-friendly expansion. In case of weak, impractical policies, the sustainability of economic expansion may be affected (17). According to a new World Bank report (14), the global health cost of air pollution (i.e., $PM_{2.5}$) alone is \$8.1 trillion, or 6.1 percent of global GDP. In China and India, where more than half of the world's fatalities from PM2.5 air pollution occur, costs can reach 12.9 and 10.6 percent of GDP. For Pakistan this is 8.9% of GDP, even though the GDP of China is far > that of Pakistan, the health burden caused by environmental pollution in China and Pakistan is almost similar. Premature death accounts for around 85% of the entire global cost of health losses in 2019, while morbidity accounts for 15% (14). (See **Figure 1**).

In the Pakistani context, air pollution makes up the biggest environmental challenge on account of defectively handled rising motorization and soaring urban industrialization to the air pollution caused by households and farmers. The automobile emissions, industrial discharge and waste, and stubble burning make up the principal sources of air pollution leading to high prevalence of respiratory diseases and premature deaths. In this respect, the statistics, supplied by the Global Burden of Disease (GBD) database, guide about the standing of Pakistan among the South Asian states and also inform about the environmental effect reduction trends in Pakistan. The recent GDB figures indicate approximately 103 deaths per 1,00,000 among Pakistani population caused by $PM_{2.5}$ exposure in 2019 (18) (see **Figure 2**), which is approximately one-third < India, almost similar to Bangladeshi and Chinese contexts; however, it is 41% higher than in Indonesia, and almost double than it is in Turkey and Mexico. The statistics suggest that the states having an extensively lower health burden caused by environmental/occupational hazards possess two to three times greater the per capita GDP in Purchasing Power Parity than Pakistan. These grave consequences are supported by a World Bank (19) study that found 2.5–6.5 percent share of Pakistani GDP to be the cost of air pollution for the year 2016 (19). The improvement in air quality in Pakistan could extend the life expectancy of around 11 million people if the government can work efficiently for decreasing CO_2 emissions (20). The World Bank has dubbed the economy of Pakistan as being "very air polluted intensive". It is estimated that one unit of $PM_{2.5}$ causes the wastage of 18.9 US\$ of GDP per capita. Thus, air pollution in Pakistan makes up a total of 47.8 billion US\$ or 5.88% of GDP as the projected economic burden. To efficiently utilize the overall natural resources, the policymakers and decision makers must consider these environmental costs to attain economic

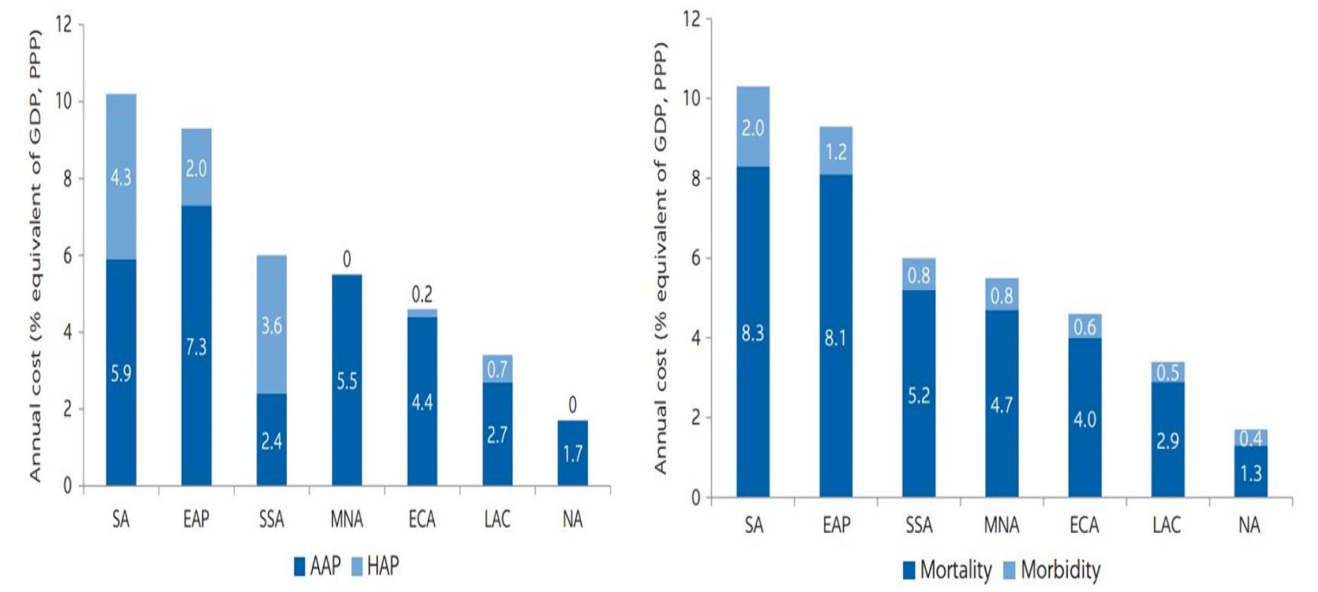

FIGURE 1 | Cost of health damage from $PM_{2.5}$ exposure in 2019 by region, % equivalent of GDP (PPP). Source: World Bank (14). EAP, East Asia and Pacific; ECA, Europe and Central Asia; LAC, Latin America and Caribbean; MNA, Middle East and North Africa, NA, North America; SA, South Asia; SSA, Sub-Saharan Africa. Numbers may not add up due to rounding.

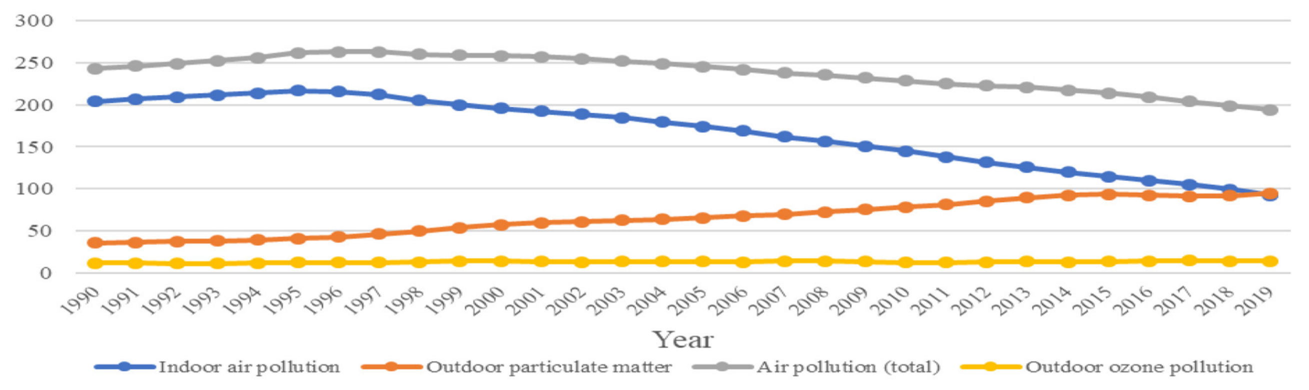

FIGURE 2 | Death rates from pollution in Pakistan (18).

growth. This draws the attention to the pressing need to take steps efficiently in order to minimize air pollution.

The current study aims to highlight the local effects of air pollution, a domain that has drawn considerable attention in recent times. The most important reason for such extraordinary attention is rooted in the multidimensional impact of air pollution, which influences health (13), residential property value (21) and agricultural production (22). Most studies evaluating air quality and employing a life satisfaction approach have used cases of developed economies (23, 24). Silva et al. (25) has provided empirical evidence of air pollution with life satisfaction based on the data obtained from around 50 countries. Investigations carried out in the west have recognized that to prevent pollution, public sensitization and acquaintance about the environment should be increased (26, 27). Several scholars have highlighted other perspectives of environmental concerns in Pakistan. For instance, the study by Ahmed and Shafique (28) investigated the risk perception of households concerning water pollution and its consequent impacts on the health of individuals. Similarly, Khan et al. (29) investigated the long-run and contributing association between air pollution, energy use and water resources in Pakistan by employing CO_2 emissions as a proxy for air pollution.

Their study concluded that energy use and water resources are significantly and positively associated with air pollution in both the short-run and long-run. Hussain et al. (30) discovered the adaptation and mitigation awareness regarding climate change from the general population using Pakistan's case (urban, peri-urban and rural areas).

Researchers must focus on willingness to pay assessments to understand how much better air quality matters to Pakistanis. We presently know very little about how much citizens are willing to pay for cleaner air and how this willingness to pay changes with awareness and across heterogeneous criteria such as income, education, and gender. The current study intends to first test the welfare impact of air pollution and then evaluates the WTP for the betterment of environmental quality and its determinants using the case of developing countries, such as Pakistan. In comparison to existing body of literature, the current study is different in many ways. First, the public WTP in favor of the reduction of environmental pollution and its determinants vary based on many factors: time, air pollution concentration, and yearly income rise. Hence, the current study intends to make a difference by conducting surveys in 2018 and acquires up-to-date data that bestows our results with greater practical and logical shape and artistically divides and regards both the tax payment and social contribution, thus providing the decision makers a clear public perception. Second, our study underscores the direct subjective WTP rather than indirect assessment through income that reveals a more realistic value for supporting pollution reduction at both individual and society levels. Besides the employment of common factors, the current study includes vital determinants associated with knowledge, such as risk perception and attitude for discovering the determinants of public WTP for cutting air pollution amount, thereby offering a fresh evidence for formulating explicit policies in order to deal with air pollution particularly in urban areas. Third, most of the current research on pollution control addresses micro level and policy aspect, while our research is based on microdata and offers a micro foundation for public environmental policymaking.

The rest of this paper is organized in the following way: Sections 2 and 3 supply a concise account of the literature review and key methodical approaches. Section 4 highlights the empirical results and compares them with other similar studies. The last section submits the conclusions of the study.

LITERATURE REVIEW

The environmental valuation method based on life satisfaction takes into consideration indirect objective data from the respondents concerning WTP for air pollution reduction or the environment (10, 31). The sample population is asked about their socio-demographic characteristics and their life satisfaction perception. The air pollution data, deemed an external variable, is obtained from official sources. Therefore, the employment of the environmental valuation method shows the respondents' preferences and their WTP, rendering it a revealed preference method (10, 32). Since many of these techniques, revealed preferences, or stated preferences employ income variable for estimating WTP, the gains out of reduction in issues relating to environment do reveal the income level of the affected areas (33, 34).

Furthermore, employing the life satisfaction method, it is difficult to directly appraise the evaded fatalities by reducing pollution (in the damage function method, this essential value is incorporated) because it considers the perception of well-being of the survey respondents only.

Concerning the data use, two common approaches are employed in air quality valuation through the life satisfaction method (31): a macro approach (aggregate data) and a micro approach (individual data). A number of studies have employed techniques based on the employment of subjective self- reported air pollution level assessment rather than objective monitoring measures or modeling data. In this regard, Rehdanz and Maddison (35) examined the association between self-reported effect of air pollution and SWB data, supplied by the German socio- economic panel (SOEP) survey. On the same line of inquiry, Li et al. (36) carried out a study using the case of Chinese mining area. These two studies offer a careful control of demographic and socio-economic variables influencing SWB and found an inverse association between SWB and air pollution.

The models on air pollution are capable to break down the spatial data into individual level. The study by MacKerron and Mourato (37) created survey tool for collecting data on individual SWB among the Londoners. The study findings suggest that measured air pollution data negatively associate with SWB. The study by Ambrey aimed to examine multi-air pollutants in Queensland, however, out of a number of pollutants, the variable of life satisfaction was discovered to be strongly and negatively associated with PM_{10} only (38). Using the Estonian case, Orru et al. (11) obtained the individual SWB data from ESS. The data of air pollution was acquired from Eulerian air quality dispersion model with 1 x 1 km grid squares covering the entire country. The study discovered SWB to be negatively influenced by PM_{10}. Based on the happiness data obtained from General Social Survey (GSS), the study by Levinson (39) found happiness and air quality to have a significant association on daily and regional levels. The study also found high levels of particulates and well-being in the USA to be inversely associated.

The study of Welsch (31) employed a macro strategy with diverse states and various air pollutants to assess the intensity of air pollution. Menz and Welsch (40) also employed macro strategy on the same footing, but they only did it for the OECD states panel data. The study by Luechinger (41) collected the data on SO_2 concentration for about 20 years obtained from 553 German monitor stations and SWB data from SOEP survey for the same period. Correlations between the two variables were examined based on average yearly German regional data. The study controlled the variables of socio-economic characteristics and particulates and found a significant impact of SO_2 on SWB. The study by Ferreira and Moro (42) valuated PM_{10} using Irish regional data. Based on the locations of respondents, the average yearly pollution data from the nearest monitoring stations were connected to SWB data of the respondents. The individual-level SWB was found influenced by the concentration of PM. The study of Ferreira et al. (43) primarily carried out the cross-sectional examination with spatially disaggregated data of the European region on SO_2 to investigate individual SWB. The study found a robust inverse association of SO_2 concentrations with self-reported life satisfaction. A latest study by Zhang et al. (40) was successful in evaluating air quality employing moment-to-moment happiness data on daily basis and local level, and discovered insignificant negative impact of bad daily air quality on overall life satisfaction, but found that poor daily air quality is likely to reduce subjective well-being and increase the chances of depression. Several authors such as Di Tella et al. (44) and Beja (45) blended microdata (life satisfaction and socio-demographic characteristics) with macro data (income and air pollution) for a number of states. These multi-regional studies offered wide-ranging interactive information between significant indicators, such as the association between air pollution and economic/environment background. Only a few studies used spatially disaggregated air pollution data at individual level.

The CV technique has recently been witnessed for its wide employment in the estimation of the economic value of non-market commodities and services, for instance environmental effect and health economics (26, 27). Clean air is considered to be a non-market commodity, which is without a market price. Therefore, this method may serve as a suitable instrument when assessing the economic worth of air pollution reduction because it can acquire market prices for non-traded commodities. In addition to the most commonly used Contingent Valuation Method (CVM), environmental researchers are increasingly utilizing self-reported "well-being or Life Satisfaction Approach (LSA)" to measure the non-marketed benefits of environmental improvements through response surveys to elicit respondents' behavior in welfare and cost-benefit analysis (46, 47). The life satisfaction method employed for estimating air quality regards the respondents' responses concerning their subjective well-being as the fundamental variable. The assessment model in this method measures experienced utility (perceived hedonic experience) instead of decision utility (associated to preferences) (48). The responses are then connected to the stated income and to the external objective air pollution data, while the demographic and other important variables are controlled. One of the main characteristics of life satisfaction method is its assumption that higher income and low environmental destruction improve the well-being of people regardless of their understanding of these determinants. Therefore, an assessment of the association between the two variables can be made (49) thereby paving way for a possibility of an indirect WTP measurement for air pollution reduction (50). The researcher then estimates the monetary value of an environmental good or service using data constituted of a set of variables. Since then, the results have been similar to those obtained using the CVM. As a result, the LSA appears as a helpful alternative to more established methodologies while also expanding the range of techniques available for environmental-economic assessment (51–55).

THE MODEL

The current study employs the micro-level approach. A robust life satisfaction function for evaluating micro-level data was developed by Welsch and Kühling (50) in the following shape:

$$LS_{ij} = f\left(Y_{ij}, AP_j, P_{ij}, E_j, NO_{ij}\right) \tag{1}$$

where LS_{ij} exhibits life satisfaction level of an individual i living at j. Y_{ij} shows income level of an individual i living at j. AP_j displays air pollution level in physical place j. P_{ij} reveals certain noticeable characteristics of an individual i living at j. E_j exhibits certain other external variables living at j. NO_{ij} acts as a group of non-observables characteristics of an individual i living at j.

The data on life satisfaction (LS_{ij}), personal income (Y_{ij}), and the set of noticeable characteristics of an individual (P_{ij}), such as age, sex, job status, academic qualification, and similar other variables, were acquired by means of a primary survey. Subjective well-being is measured as both cardinal (by psychologists) and ordinal (by economists) in the research literature (56). The results are unchanged by whether SWB is considered as cardinal or ordinal (56–58), however we apply OLS and ordered probit methods with robust standard errors to address heteroscedasticity problems (59). AP_j depicts the degree of air pollution (subjective measure), an external variable. The other external variables (E_j) consider determinants absent from the survey, such as, temperature and precipitation. The set of non-observable characteristics of a person (NO_{ij}) are harder to acquire and need a more comprehensive examination of personality features and other elements of well-being. The current study proposes the following econometric followed by Welsch and Kühling (52) and Frey et al. (11). The estimation aims to first test the impact of air pollution on individual happiness, represented in Eq.2. The determinants of WTP are studied, particularly the WTP are in forms of tax and personal income, corresponding to equation (3) and (4), respectively:

$$\begin{aligned} &Life\ satisfaction_i = c + a_1 airp_i + a_2 gender_i + a_3 age_i \\ &+a_4 age2_i + a_5 work_i + a_6 mamarital\ status_i \\ &+a_7 No.of\ child_i + a_8 edu_i + a_9 health_i + a_{10} income_i + \varepsilon_i \end{aligned} \tag{2}$$

$$\begin{aligned} &Envirtax_i = c + a_1 airp_i + a_2 gender_i + a_3 age_i + a_4 age2_i \\ &+a_5 mamarital\ status_i + a_6 No.of\ child_i + a_7 edu_i + a_8 health_i \\ &+a_9 income_i + a_{10} envimp_i + a_{12} avoidtax_i + a_{13} govresp_i \\ &+a_{14} Lifesatisfaction_i + a_{15} work_i + \varepsilon_i \end{aligned} \tag{3}$$

$$\begin{aligned} &Payfenvir_i = c + a_1 airp_i + a_2 gender_i + a_3 age_i + a_4 age2_i \\ &+a_5 mamarital\ status_i + a_6 No.of\ child_i + a_7 edu_i + a_8 health_i \\ &+a_9 income_i + a_{10} envimp_i + a_{12} avoidtax_i + a_{13} govresp_i \\ &+a_{14} Lifesatisfaction_i + a_{15} work_i + \varepsilon_i \end{aligned} \tag{4}$$

In the model, a_i are coefficients; c and ε_i represent the constant and the error term. The dependent variables (DV) have a discrete and ordinal form, therefore the econometric method is an Ordered Probit (OP) or an Ordered Logit (OL). Furthermore, some empirical studies that employed Ordinary Least Squares (OLS) found that this classical econometric method offers robust findings (10, 50) and there is absence of any significant variation in the impact of the relevant variables (3, 60, 61).

The Survey Area

Two cities have been included in the current study: Lahore and Faisalabad. Lahore is the capital city of the most populated province in Pakistan which is located 31.55°N, 74.36°E. It possesses a rich culture and social diversity. It is the richest Pakistani city contributing around 58.14 billion US$ to the GDP per annum. The two biggest causes of poor air quality in Lahore are industries and vehicles, which surpass National Ambient

Air Quality Standards (NAAQS). The second city under survey is Faisalabad, the third most populated city in the country, located 31°25′0″N 73°5′28″E. On account of its central location and facilitated with all types of transportations, the city is a main center for industry and distribution contributing around 20% to the provincial GDP with a yearly GDP of 20.5 billion US$. Apart from agriculture, Faisalabad is known for its agro-based and textile industries. There is no regular air quality management system in Faisalabad, and air pollution is measured on *ad hoc* basis. The current situation can worsen in the face of population growth, industrial expansion, deforestation, ever-increasing construction work, and growing motorization. Owing to its dense population, a large number of citizens of Faisalabad are at air pollution risk. The poor air quality poses serious and unavoidable effects on citizens' health. On account of the aforementioned facts and circumstances, the two cities have been selected for the assessment of household WTP for improved air quality.

Data Collection

Primary sources were used through a survey questionnaire in order to collect data. The questionnaire, originally designed in English, was translated into Urdu, the lingua franca of the area, so that accurate and true responses could be obtained. Before administering the study questionnaire, a pilot survey was carried out on November 5, 2017 to verify if the questionnaire items covered everything in accordance with the study objectives. The pilot study included academics and researchers numbering 50, who were satisfied with the questionnaire. The study survey was carried out between December 2017 and February 2018 employing face to face survey of 600 households which were selected randomly. During the process, each question was explained to the respondents in their native language for complete understanding and for obtaining true responses. Most respondents consumed 30–40 min in completing the questionnaire. The total of 700 questionnaire forms (350 from each city) were filled and obtained, but 100 were rejected on account of incomplete filling, mistaken filling, forged filling and so forth, making the total sample size to 600.

Variable Description and Measurement Method

Dependent Variables

The self-reported "well-being or Life Satisfaction Approach (LSA)," in addition to the most commonly used Contingent Valuation Method (CVM), is gaining popularity among environmental researchers for measuring the non-marketed benefits of environmental improvements through the use of response survey to elicit respondents' behavior in welfare and cost-benefit analysis (46, 47). By developing an econometric model, this technique is frequently employed in numerous aspects of environmental valuation, minimizing the potential difficulty with the contingent valuation method of having skewed data from respondents during survey. Because individuals are asked to score their overall happiness level, the research considers data on life satisfaction or SWB acquired using self-reported questionnaires to be the best acceptable measure for persons' utility. The researcher then quantifies the monetary value of an environmental good or service using data constituted of a set of factors. Since then, the results are identical to those obtained using the CVM. As a result, the LSA emerges as a helpful complement to more established methodologies, while also broadening the range of tools accessible for environmental economic valuation (51–53). We adopted unipolar liket scale question to measure the self-reported SWB from respondents; "How satisfied are you with your life as a whole?" in the light of extant literature (62, 63). The responses were recorded on the 0 to 10 scale, where 0 indicated "very dissatisfied" and 10 "very satisfied" (64, 65). **Supplementary Table S1** illustrates the distribution of responses to the life satisfaction perception for urban areas in Punjab. A high percentage of households reveal low level of life satisfaction: 45.03% of individuals with life satisfaction obtained scores between 7 and 10.

The survey contains two questions about the WTP for environmental quality improvement. First: *"I would agree to an increase in taxes if the extra money were used to prevent environmental pollution" and* translates to the variable envtax. The value 1 to 4 is awarded to responses of *strongly disagree, disagree, agree and strongly agree*, with greater values linked to higher willingness of tax payment. Second: *"Are you willing to sacrifice part of your income to lower the risk of extreme events, such as heat waves, smog pollution, air quality, floods, droughts and hurricanes, which occur because of climate change?"* in accordance with the variable *income contribution* with values 1, 2, 3, 4 and 5 representing:

Yes, I am willing to sacrifice between 0.1 and 1% of my income
Yes, I am willing to sacrifice between 1 and 5% of my income
Yes, I am willing to sacrifice between 5 and 10% of my income
Yes, I am willing to sacrifice more than 10% of my income
No.

Different from the mandatory tax payment imposed by governments, the personal payment reveals more like a social contribution. The two variables show varied payment preferences for pollution control, with mean 2.31 and 2.21, respectively. In addition, 65.34% of the sample population opts to agree or strongly agree, whereas 47.17% respondents choose to give up 1% to 5% of their personal income. 13.50% refused to share any amount of their income. The common people are found to have comparatively high WTP. Moreover, comparing mandatory and voluntary cost bearing for the prevention of pollution, the tax system appears less favorable than that of personal payment.

Independent Variables

In the current study, the air pollution index, used as a main variable concerning its impact on happiness and WTP, covers two aspects of measurement: objective pollution record, which is mostly represented through the density of SO_2, NO_2, PM_{10}, and $PM_{2.5}$, and subjective pollution, which is the respondent's perception. The objective measurement reveals only the absolute value of pollution level, whereas the subjective assessment contains both the objective air pollution and the relative level of satisfaction comparing the air quality in other parts of the region. Because of its recording mostly at municipal and occasionally the district level, the objective pollution level density

TABLE 1 | The effect of air pollution on subjective life satisfaction.

	Dependent variable: life satisfaction	
Variables	**OLS**	**Ordered–probit**
Air pollution	−2.967***	−1.492***
	(0.270)	(0.139)
Gender	0.096	0.026
	(0.179)	(0.085)
Age	−0.080*	−0.026**
	(0.178)	(0.336)
Age^2	0.474*	0.042*
	(0.178)	(0.084)
Edu	0.333***	0.146***
	(0.068)	(0.033)
Work	−0.033	−0.016
	(0.052)	(0.025)
Marital status	0.111*	0.067**
	(0.081)	(0.044)
Children	0.134*	0.059**
	(0.069)	(0.033)
Income	0.208***	0.113***
	(0.078)	(0.037)
Health issues	−0.417**	−0.231*
	(0.250)	(0.120)
Observations	600	600
R^2 Pseudo R^2	0.581	0.19

*Standard errors in parentheses. ***p < 0.01, **p < 0.05, *p < 0.1.*

may vary significantly even within a perimeter of a single city. Therefore, the current study uses subjective perception about local air pollution, which appears to be wide-ranging, powerful, and apparent to individuals (37). Seriousness of air pollution is measured using four-point Likert scale from "Not serious at all" = 1 to "Very serious" = 4 but for regression purpose we classified this index to *not serious at all and very serious*, and is rated as 1 and 2. 87.5% of the people of Punjab are not aware of the air pollution problem to which they are exposed day after day. 12.5% rates the intensity of air pollution as very serious. The results show that only 13% of respondents are not willing to pay for income contribution for environmental quality improvement reporting indifferent attitude and insufficient knowledge of the environment.

The survey contains the main study variables about environment or tax attitude. Taking care of the local environment is important and is rated as 1 in envimp variable, otherwise, 2. The envimp evaluates people's concern on the environment. Another variable govtresp characterizes the responsibility of environmental organizations, corresponding to the reply of the government must decrease environmental pollution; however, this ought not to put any financial burden on me. The values range from 1 to 4, with various degrees of agreement and disagreement responses. People's attitude toward environmental organizations and government play an important role in people's WTP for the prevention of pollution, and it also points to trust in the markets. The trust in environmental organizations and trust in government are indicated by envot and trustgov, with various degrees ranging from 1 to 4. Finally, people's attitude toward tax compliance is a major contributing factor for their inclination toward tax payment to protect the environment. The study uses avoid tax to measure incentives on tax evasion, with integer value "Always be justified" = 1 to "I do not know" = 4. These variables reveal individual attitude, social trust, and sense of duty influencing the WTP in return.

The estimation also includes a number of socio-demographic variables: gender, age, academic qualification, job status, marital status, and having a child. The education variable entails the number of years in formal education: 0, 5, 8, 12, 14 and 16 equivalent to no formal education, primary school, secondary school, high school, university, master's and above. About the health status of the respondents, the question is: *"Have you suffered severe health problems over the past 2 years?"*. The study reveals that the maximum number of the respondents (32.76%) has a monthly income of PKR17, 001 to PKR22, 000. The second-largest category belongs to the people (26.33%) possessing the monthly income of PKR22001 to PKR27, 000, whereas 16.17% and 9.5% of the respondents earn monthly PKR12, 001-PKR17, 000, and PKR7, 000 - PKR12, 000, respectively. Only 9% of respondents have a monthly income of more than PKR27, 000.

THE REGRESSION RESULTS AND DISCUSSIONS

Results

The purpose of employing ordered-probit models is to approximate the probability of respondents. **Table 1** displays the regression results from model (1). In model 1, the regression results reveal that the coefficient of air pollution is negative, −2.967. There is a significantly positive relationship between life satisfaction and the annual household income. Furthermore, results suggest that age and health exert significantly negative impact on SWB. It implies that if the respondent is elder with health issues, he or she is less likely to be happy (40). The sign, coefficient and significance of both OLS and Probit estimation, is consistent. As for other variables, happiness signifies a U-shape association with age (62). In line with general perception and existing literature, education and income positively influence personal happiness. The variable gender turns out to be insignificant, which aligns with (66, 67), that there is no significant variation in happiness perceptions of males and females. Air pollution aggravates personal happiness as proven; therefore improvement in the quality of the environment improves personal and social welfare. The protection of the environment needs financing and the following regressions estimate the determinants that affect the WTP for pollution reduction.

Model 2 results are highlighted in **Table 2**. New DV variable WTP for environmental tax is introduced in this model. The air pollution coefficient is significantly negative (68). This result shows that the individual perception of air pollution does not reveal significance on people's willingness to pay, implying that

TABLE 2 | Determinants of the tax payment for pollution prevention.

	Dependent variable: envtax	
Variables	**OLS**	**Ordered–probit**
Life satisfaction	−0.020*	−0.029**
	(0.014)	(0.021)
Air pollution	−0.026**	−0.039**
	(0.013)	(0.051)
Gender	0.014	0.021
	(0.062)	(0.091)
Age	−0.114	−0.172
	(0.249)	(0.363)
Age^2	0.015	0.025
	(0.062)	(0.091)
Edu	−0.059**	−0.087**
	(0.024)	(0.036)
Work	−0.016	−0.023
	(0.018)	(0.027)
Marital status	0.027**	0.039**
	(0.032)	(0.047)
Children	−0.059**	−0.085**
	(0.024)	(0.035)
Income	0.016**	0.021*
	(0.027)	(0.041)
Health issue	0.003	0.008
	(0.088)	(0.127)
Env Priority	0.016*	0.022*
	(0.059)	(0.087)
Env org trust	0.019**	0.028**
	(0.035)	(0.051)
Avoid tax	−0.084***	−0.125**
	(0.036)	(0.053)
Govt reduce pollution	−0.170***	−0.249**
	(0.035)	(0.052)
Observations	600	600
R^2/ Pseudo R^2	0.395	0.045

*Standard errors in parentheses. ***p < 0.01, **p < 0.05, *p < 0.1.*

TABLE 3 | Determinants of the social payment for pollution prevention.

	Dependent variable: income contribution (Payfenvir)	
Variables	**OLS**	**Order–probit**
Life satisfaction	0.015**	0.039*
	(0.023)	(0.021)
Air pollution	0.021**	0.024**
	(0.074)	(0.071)
Gender	−0.011	−0.001
	(0.098)	(0.091)
Age	−0.328**	−0.319*
	(0.391)	(0.363)
Age^2	0.085	0.082
	(0.098)	(0.091)
Edu	0.006	0.028
	(0.038)	(0.035)
Work	0.083***	0.073***
	(0.029)	(0.027)
Marital status	−0.105**	−0.099**
	(0.050)	(0.047)
Children	−0.048	−0.052
	(0.038)	(0.035)
Income	0.081*	0.072*
	(0.043)	(0.040)
Health issues	0.057	0.078
	(0.137)	(0.128)
Env Priority	0.051**	0.069**
	(0.093)	(0.087)
Env org trust	0.099*	0.093*
	(0.055)	(0.051)
Avoid tax	−0.041***	−0.067**
	(0.056)	(0.052)
Govt reduce pollution	−0.416***	−0.306***
	(0.055)	(0.053)
Observations	600	600
R^2 / Pseudo R^2	0.132	0.040

*Standard errors in parentheses. ***p < 0.01, **p < 0.05, *p < 0.1.*

those who think air pollution is dangerous are most likely not to pay more tax to reduce pollution.

The coefficient of environment priority and environment organization trust are significantly positive. It reveals that the likelihood of positive WTP carries a positive association with public's trust in the environmental organization and priorities for environment, which implies an increasing trust in the environmental organization and environmental priority, which implies that an increasing trust in the environmental organization contributes to a higher probability of having a positive WTP (69).

Model 3 results in **Table 3** highlight the factors affecting WTP in relation to individual income, referred to as social contribution, different from the mandatory tax payment. We run the regression with OLS and Ordered probit models, where the results are not much different. The study finds that air pollution is positively significant at 5% level with income contribution, implying that those who think air pollution is dangerous are most likely to pay more social payment to reduce pollution. The awareness about environmental protection is more associated with WTP than awareness about air pollution's effect on health and quality of life (68–70). The results show that almost 87.5% of the inhabitants of Faisalabad and Lahore do not consider the air pollution problem a serious problem to which they are exposed day after day. The lack of awareness about the severity of air pollution in Pakistan may cause to reinterpret the people's WTP more taxes for clean air. Therefore, educating the general population about pollution prevention should be a significant step toward environmental governance.

The social WTP must not be underestimated because it implies if individuals trust environmental organizations for the protection of environment (envot). Moreover, it also involves individual perception about pollution reduction being a social duty rather than a governmental responsibility (govt resp), higher incentives of tax payment (avoid tax), and family income (income), and they all persuade citizens to pay more for environmental protection. The environmental organizations, excluding the governmental agencies, serving as main bodies aiming for improvement in environmental quality are likely to have a significant impact on WTP (at 1% level) depending on using the donations capably and carrying out adequate environmental work.

Further Discussion

The results suggest that Pakistanis are not aware of air pollution's effect on health and quality of life. They are willing to pay more in social payment in return for different environmental attributes (such as climate change mitigation, water pollution control, and control of air pollution). However, the variable, importance of environment, appears significant at 1% level signifying that those who care more about the environment are most likely to pay more in tax in return for a better environment. The range of people's willingness to consent to a tax increase for pollution prevention depends not on the severity of air pollution but on their perception of damage to the environment and their preference for cleaner air (26, 27, 70). Moreover, the judgment on one's responsibility of environmental protection (govt resp) negatively affects WTP, implying that individuals may likely resist an increase in tax if they think pollution reduction is a governmental obligation rather than a social one. Citizens' trust in government plays a pivotal role in people's WTP in taxes for pollution reduction (27). Public service also includes the improvement of environmental quality, which is a common choice, and tax payment is used as the most convenient method to look after environmental management. In this connection, people's trust in the government being capable to decrease pollution plays a central part in people's perception of their contribution to tax for environmental improvement. This clearly suggests that trust-building by the government and the consequent people's trust in government serve as the foundation of tax collection and implementation of pollution prevention plan. The variable avoid tax about tax payment, symbolizing the individual behavior of general tax evasion and deficient social responsibility, is found to have a negative association with WTP tax for the improvement of the environment. Another determinant that is likely to affect WTP is family income, which reveals that families with higher financial status are likely to be comparatively less sensitive and more demanding about the improved environment (68). Factors influencing the WTP also include the household income, where people with higher income are relatively less sensitive in money and more desirous of a pleasant environment, thereby more willing to pay for pollution reduction.

In most developing countries including Pakistan, the most significant causes for indifference toward environmental concerns is people's low level of sensitization. This apathy and lack of understanding, coupled by uncompromising nature act as fundamental determinants for pollution and the consequent effects on health. With reference to Pakistan, the major decision-makers ought to be taken on board concerning the measures they have taken to espouse the policy recommendations forwarded for the resolution of issues relating to air pollution. Due to Pakistan's lack of political stability throughout its political life, several most pressing issues have failed to seek governmental attention, particularly environment and health. The Pakistani policy feedback mechanism at regulatory authorities is absent. The unsuccessful legislation is caused by insufficient support from the policymakers and low awareness among the ordinary population as well as members of parliament. With reference to Pakistan, efforts should be made for the formulation of well-defined institutional roles and responsibilities and their successful coordination. In order to fulfill adaptation and mitigation aims in all sectors, Pakistan needs to introduce modern technology and technological partnerships. In order to solve the repeated damage caused by extreme weather events and air pollution, Pakistan undertook a Technology Need Assessment (TNA) in 2017. The evaluation might lead to Pakistan developing a comprehensive plan for national climate change mitigation technology development. Punjab province has long battled to decrease pollution. Punjab local government should take the following steps to control air pollution; Bans on municipal garbage burning, adoption of the Punjab Clean Air Action Plan, public release of air quality data, and the implementation of digital smog response systems. The negative relationship between pollution and health is well documented in the literature, yet results from specific regions are frequently inapplicable to other situations. Pakistan has to do a better job of measuring the entire costs of long-term air pollution exposure. The research must not just look at mortality, morbidity, and cognition, but also at the effects of pollution on behavioral decisions including fertility, migration, time usage, and defensive spending. Such proof of effect will highlight the potential consequences of air pollution and encourage governments to take action. Researchers must focus on willingness to pay indicators to understand how much improving air quality matters to Pakistanis. We presently have limited evidence on how much individuals are ready to pay for better air quality and how this desire to pay varies with information and across heterogeneous criteria such as income, education, and gender. Pakistan may benefit from the experiences of other developing countries in regulating air quality. Despite the fact that many Indian cities suffer from severe pollution, many provinces have begun to implement evidence-based policies to enhance air quality. A decade ago, China had some of the world's worst air quality, but it has since made significant progress in lowering pollution. Some of the policies implemented by both countries can be used to improve Pakistan's pollution policy.

CONCLUSION

Out of a host of challenges facing Pakistan, the environmental problem has become a hot and daunting issue. Reduction in air pollution and protection of the environment demands a huge amount of money that the citizens must pay in direct or indirect ways. Thus, investigating the effect of air pollution on individual welfare, the people's WTP for pollution prevention, and socio-economic factors influencing WTP deserves immense worth in environmental policymaking. The current study evaluates the problem through a micro-level prism employing primary survey data obtained from two major Pakistani cities: Lahore and Faisalabad and finds that personal happiness is significantly affected by air pollution. Two aspects of WTP, obligatory tax payment and voluntary social contribution, are used. The social WTP is found to be a little > the WTP obligatory tax, proposing a governmental preference of voluntary contribution to a tax increase for meeting the expenditure on the environment. Furthermore, the determinants affecting the WTP are similar: Household income, trust in government or the environmental organization, incentives for tax payment, duties on environmental protection. It is not the gravity of air pollution that generates an impact on WTP rather it is the people's concern for the environment that influences WTP.

The current investigation offers the following policy recommendations to Pakistani policymakers to successfully combat the pressing problem of air pollution. Concerning the challenges posed by air pollution and its subsequent effects on the environment and health, Pakistani authorities should address the lack of sensitization by raising awareness among all the stakeholders. The stern legislative instrument should be used to reduce air pollution. Subsidies and incentives should be introduced in favor of eco-friendly manufacturing. Extensive monitoring of air pollutants should be ensured. Improved air pollution management practices should be adopted. Emission inventories and source apportionment of pollutants should be developed in order to strategize affordable and effective air pollution control plans. The governmental policy implications to get public support and execute environmental policies successfully may include tax collection and utilization founded on transparency and pragmatism, public awareness of environmental protection, and improved social responsibility. Progressive taxation should be devised since people with the sound financial condition are able and more likely to pay taxes. Moreover, pollution reduction cannot be the sole responsibility of the government. Since the public pays the amount allotted for the protection of the environment, the government ought to generate consensus among the general population about environmental importance, individual responsibility, and social duties, thereby lessening the free-rider problem and increasing the WTP.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

MR: introduction, conceptualization, methodology, and data collection. JS: literature review and reviewing. AL: results, discussion, and reviewing. YL: concluding remarks and implications. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.825387/full#supplementary-material

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