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Interactions between ambient air pollutants and temperature on emergency department visits: Analysis of varying-coefficient model in Guangzhou, China

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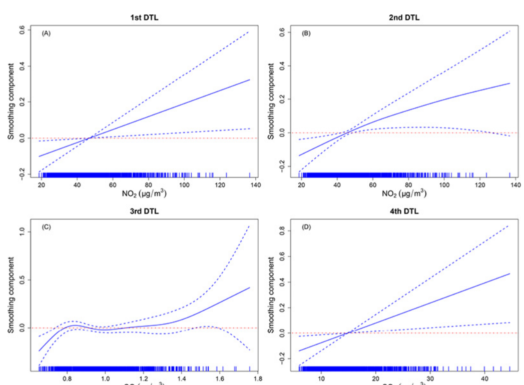
HIGHLIGHTS

- Interactions between air pollutants and daily temperature levels (DTLs) on cause-specific emergency department visits (EDVs) were assessed.
- Interactions between NO2 and DTLs, and SO2 and DLTs had adverse effects on the EDVs of neurologic and respiratory diseases, respectively.
- People aged ≤ 75 years were susceptible to neurological EDVs due to the interactions between air pollutants and DTLs.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: At present, there are few studies on the effect of short-term interactions between ambient air pollutants and temperature on cause-specific emergency department visits in China. This study aimed to explore their short-term interactions on cause-specific emergency department visits using data collected from a total of 65 public hospitals in Guangzhou city, south China.

Material and methods: We included a total of 226,443 emergency department visits which were diagnosed as neurological, respiratory and circulatory disease in Guangzhou from January 1, 2014 to December 31, 2017. Average daily concentrations of air pollutants including carbon monoxide (CO), particulate matter having a median diameter of 2.5 μm or less ($PM_{2.5}$), sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and ozone (O_3) were collected from the Guangzhou Environmental Protection Bureau. We employed quasi-Poisson varying coefficient regression models to assess the interaction effects between air pollutants and daily temperature levels (DTLs) on emergency department visits for neurological, respiratory and circulatory diseases, respectively.

Results: Average number of emergency department visits for neurological, respiratory and circulatory diseases were 92, 26 and 38, respectively. After controlling for other pollutants, meteorological factors and other time-varying confounders, we found the interactions between NO_2 and the 1st DTL (3.4–17.1 °C), NO_2 and the 2nd DTL (17.1–23.5 °C) for neurological emergency department visits were statistically significant, displaying a

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nonlinear relationship. Additionally, we found that the interactions between SO_2 and the 4th DTL (27.4–31.1 °C) also had a significantly adverse effect on respiratory emergency department visits.
Conclusions: Our findings provide novel evidence on SO_2-by-temperature interactions, and NO_2-by-temperature interactions for emergency department visits of cause-specific diseases.

1. Introduction

In recent years, a growing body of literature has shown the effect of ambient air pollutants and temperature on death for various kinds of diseases (Carder et al., 2008; Guo et al., 2017; Stafoggia et al., 2008; Ren et al., 2006; Ren et al., 2008; Ren and Tong, 2008), but the evidence on the interactions between ambient air pollutants and temperature still remains inconsistent. For example, particulate matter (PM) with aerodynamic diameter ≤10 μm (PM_{10}) and ozone (O_3) have been suggested a significant effect on cause-specific death under modifying temperature, respectively (Carder et al., 2008; Stafoggia et al., 2008; Ren et al., 2006; Ren et al., 2008). Some studies suggested that sulfur dioxide (SO_2) pollutant has a significant effect on neurologic and circulatory system by different levels of temperature (Guo et al., 2017; Katsouyanni et al., 1993). Tian et al. found stronger interactions between PM_{10} and high temperature levels for non-accidental, cardiovascular and respiratory mortality than low temperature levels in Beijing, China (Tian et al., 2018). Xia et al. found evidence that extreme high temperature increased the associations of PM_{10} with respiratory, cardiovascular and total mortality in eight Chinese cities (Meng et al., 2012). Qin et al. found statistically significant associations of air pollutants with respiratory mortality at high temperatures than medium temperatures in Hefei city, China (Qin et al., 2017). Also, Cheng et al. found a statistically significant interaction between low temperature and the air pollutants including PM_{10} and O_3 on non-accidental and cardiovascular mortality in Shanghai, China, respectively (Cheng and Kan, 2012). Overall, these studies mentioned mainly focused on the effects of ambient temperature and air pollutants on mortality.

In fact, for interactions of air pollutants and temperature on department visits or hospital admissions of diseases, relevant literature is rarely reported. A study from the western city in China showed that the effects of PM_{10}, SO_2 and NO_2 on department visits of respiratory diseases were more pronounced in low temperature days, while insignificant associations in higher temperature were observed (Min et al., 2013). Qiu et al. also found that low temperature significantly enhanced the effects of $PM_{2.5}$, PM_{10} and SO_2 on hospital admissions for chronic obstructive pulmonary disease in Chengdu's urban area, China (Qiu et al., 2018). In total, we found that these studies had a certain degree of inconsistent with each other because some of them suggested air pollutants had an enhanced effect on cause-specific mortality or morbidity with high temperature, while others indicated the enhanced effect was seen with low temperature. Actually, the effects of air pollutants and temperature on cause-specific mortality or morbidity are dynamic and time-dependent. We speculate that these inconsistent results may be partly due to the improper use of conventional statistical models. In addition, the limited sample size may also have an impact on the estimation results of previous studies.

Therefore, we proposed to use varying coefficient models (Fan and Zhang, 2008) for exploring interactions of air pollutants and temperature on cause-specific emergency department visits upon the consideration of time-dependent impacts of covariates. We are also interested in the morbidity of air pollutants related diseases, such as neurological, respiratory and circulatory since the burden of these diseases in China is relatively high (Guo et al., 2017). Furthermore, we want to explore whether heterogeneous outcomes exist in different subgroups defined by the characteristics such as age or gender because the possible modification effects of demographic factors may have impacts on the air pollutants-disease associations.

Our study aimed to examine the short-term associations of interactions between daily exposures of ambient air pollutants and temperature on cause-specific emergency department visits in Guangzhou, the most densely populated city in South China. The geographical location of the study site is shown in Fig. 1. According to National Bureau of Statistics of China (http://www.stats.gov.cn/tjsj/), Guangzhou, the capital of Guangdong province, has a year-end census register population of roughly 8.705 million in 2016. As economic and trade contacts with other countries in the world and industrial production and traffic within Guangzhou continue to increase, more local people are facing the problem of air pollutants. Besides, Guangzhou is a coastal city, located at the junction of the Asian continent and the Pacific Ocean and has a subtropical monsoon climate, which leads to a perennial temperature of 20 °C–22 °C. All the unique conditions including the demographic, geographic and urban development characteristics make Guangzhou as an ideal spot for the study of air-pollutants-by-temperature interactions. We used data for a total of approximately 0.22 million emergency department visits which were diagnosed as neurological, respiratory and circulatory diseases in Guangzhou from January 1, 2014 to December 31, 2017 to assess interactions between daily temperature levels (DTLs) and air pollutants including O_3, carbon monoxide (CO), SO_2, nitrogen dioxide (NO_2), and $PM_{2.5}$, respectively.

2. Material and methods

2.1. Information on air pollutants and meteorological factors

Daily air pollutants data on CO, O_3, NO_2, SO_2, and $PM_{2.5}$ from January 1, 2014 to December 31, 2017 were collected from the daily air quality report of Guangzhou Environmental Protection Bureau. The 24-hour samples of CO, NO_2, SO_2, $PM_{2.5}$ and the 8-hour samples of O_3 were collected from 36 general air quality monitoring stations widely distributed in Guangzhou. The average 24-hour daily concentrations of CO, NO_2, SO_2 and $PM_{2.5}$ and the maximum 8-hour daily concentrations of O_3 were calculated for the same sites. Then, the territory-wide average concentration (Pun et al., 2014) based on all the stations was calculated to remove the station-specific influence on the measurements of each pollutant. The concentrations of O_3, NO_2, SO_2, and $PM_{2.5}$ pollutants are measured in micrograms per cubic meter (μg/m^3), and that of CO are measured in milligrams per cubic meter (mg/m^3), respectively. Data on daily mean ambient temperature and relative humidity for the same period were publicly available from the China Meteorological Data Sharing System (http://data.cma.cn/). Daily mean temperature and relative humidity were used as potential confounding effects of meteorological factors included in the model.

2.2. Emergency department visits data

We obtained daily number of emergency department visits for neurological, respiratory and circulatory diseases from the Guangzhou Emergency Medical Command Center during the period between January 1, 2014 and December 31, 2017. The database of emergency center used in this study covers a total of 65 designated hospitals for emergency department visits monitoring. These hospitals, representing the majority of hospital beds serving Guangzhou residents, provide 24-

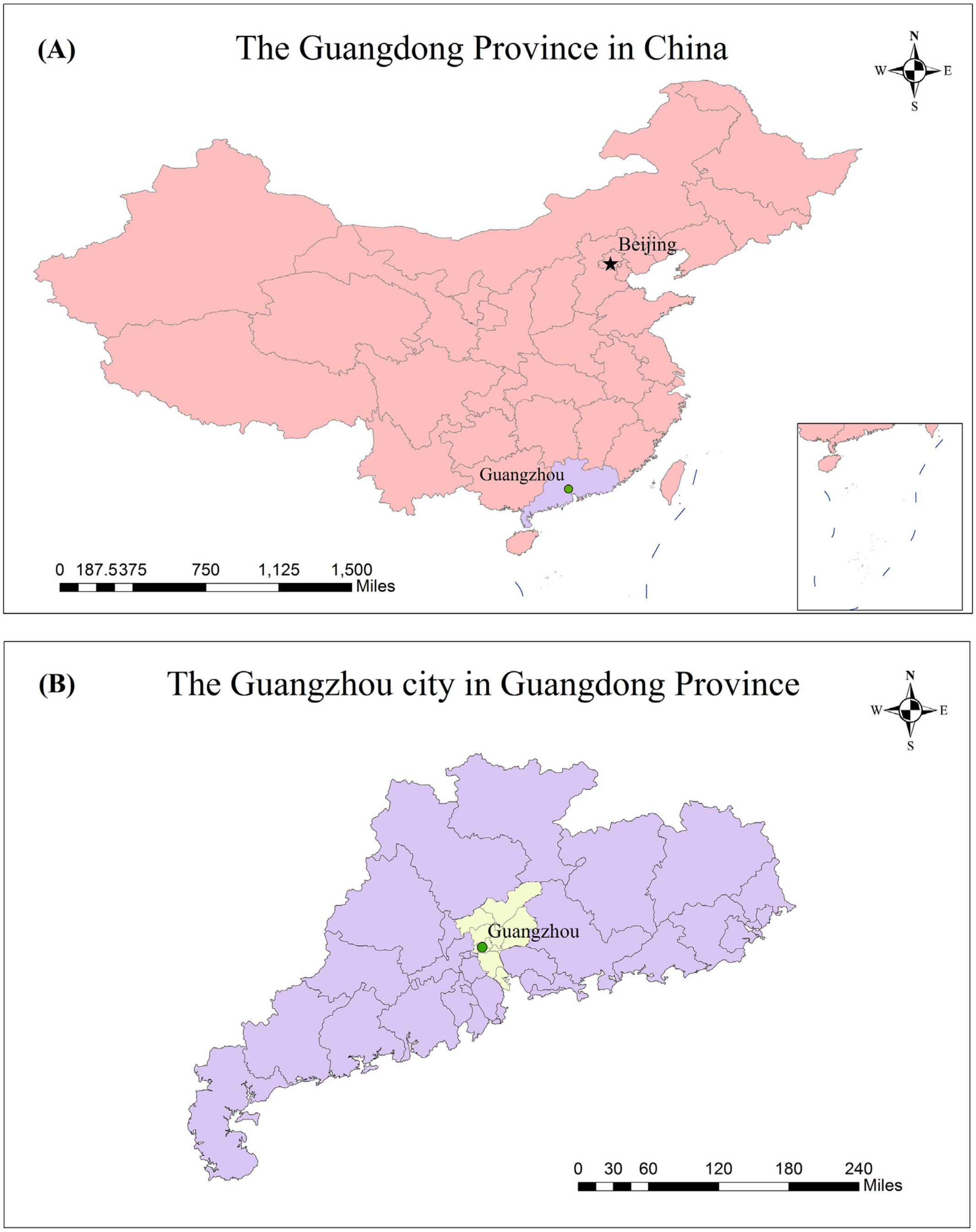

Fig. 1. The geographical location of the study site, Guangzhou city, in south China.

hour accident and emergency services. A series of systematic quality control strategies were applied to ensure the quality of data. Data entry was done by trained medical service employees, and the double entry method was also performed to reduce data entry errors. Two researchers independently examined all the entry of emergency department visits to remove duplicate records in the data.

2.3. Statistical analysis

To examine interactions between ambient temperature and air pollutants on cause-specific emergency department visits, we used the indicator of daily temperature levels (DTLs) which was defined as four grades of temperature corresponding to the three cutoffs including the 25%, 50%, 75% quartiles of the distribution of daily mean temperature (Zhao et al., 2014). Therefore, we obtained the 1st DTL (from 3 .4 °C to 17.1 °C), the 2nd DTL (from 17.1 °C to 23.5 °C), the 3rd DTL (from 23.5 °C to 27.4 °C), and the 4th DTL (from 27.4 °C to 31.1 °C) for our analysis.

Daily number of cause-specific emergency department visits, average concentrations of air pollutants, and average values of meteorological variables were temporally matched. We performed varying coefficient regression models to estimate interactions between air pollutants and DTLs on emergency department visits of neurological, respiratory and circulatory diseases. In the analysis, the response variable was the number of cause-specific emergency department visits which showed the presence of over-dispersion in our data. The *D* statistics derive from a Chi-square distribution and can be used to infer whether the samples are over-dispersed. For more detail, the results of over-dispersion test (Wetherill and Brown, 1991) showed that the D statistic was 2621.468 (P-value <0.001) for neurological emergency department visits, 2761.831 (P-value <0.001) for respiratory emergency department visits and 2369.21 (P-value <0.001) for circulatory emergency department visits, respectively. As a result, the dependent variables for the three types of diseases showed a quasi-Poisson distribution due to P-value <0.05. Therefore, we assume that the dependent variable follows a quasi-Poisson distribution because a quasi-Poisson regression model is capable of dealing with over-dispersed count data (Beritner et al., 2014).

Since our data covered a time span of four years which included a total of 48 months, we adopted a cubic P-spline (*ps*) of second-order differential penalty (Assaf, n.d.) with 48 knots to construct a time smoothing term to control for time trend in our models. Although the number of knots in the spline function can be set to a maximum number of the days to estimate without causing over-fitting in the model, it will greatly increase the computation time of model fit and result in improper estimations of model parameters (Ruppert, 2002).

We applied varying coefficient models (Hastie and Tibshirani, 1993) to characterize the interactions of air pollutants and temperature in this study. The varying coefficient model can be applied to avoid the curse of dimensionality while other traditional nonparametric methods fail. Unlike the traditional regression models, there are not constants regression coefficients but a set of regression coefficients depend on some other covariates. In addition, the varying coefficient model inherits the simplicity and interpretability of the traditional linear model (Hastie and Tibshirani, 1993). The varying coefficient model is a type of regression model in which the regression coefficients can vary non-parametrically as functions of an effect modifying covariate. Particularly, the relationship of independent variables and response variable has different smoothing component at different levels of effect modifier. A simple varying coefficient model with a single effect modifier can be denoted as follows:

$$E(Y|X = x, Z = z) = f(x_1, \beta_1(z)) + \ldots + f(x_d, \beta_d(z)),$$

where Y is the response variable, $X = (x_1, \ldots, x_d)^{\mathrm{T}}$ and $Z = z$ represent the covariates, and f is the smooth function with regression coefficients β_i which varying over different levels of effect modifier z. In our work, a partially linear varying coefficient term (Park et al., 2015) with the variable of temperature was used as the effect modifier z to adjust the effect of air pollutants.

Initially, we constructed a basic model containing none of the pollutants but only meteorological factors and other time-dependent covariates. In the basic model (Model 1), day of week (*DOW*), public holiday effect and DTLs were fitted in linear function with constant parameter, and relative humidity was modeled in a thin-plate (*tp*) penalty spline function with 10 knots. The structure of Model 1 is depicted as follows:

Model 1:

$$\ln(E(y)) = \alpha + holiday + DOW + DTLs + tp(humidity, k) + ps(time, k),$$

where α is the intercept, *holiday* is the public holiday effect, *DOW* denotes the day of week, *DTLs* represents daily temperature levels, *tp* and *ps* is the thin-plate spline and P-spline function, respectively, and k is the knots used in the spline function. In any given basis dimension of constructing smoother, *tp* spline function is suggested as the optimized function comparing with others in sense that the truncation is designed to result in the minimum possible perturbation of the thin plate spline smoothing problem (Wood, 2003). The number of knots set to 10 was enough for our data because the degree of nonlinearity of the association between the response variable and independent variables was not too large. Also, we used the gam.check function from the mgcv package in the R software to check whether the knots set enough. If the effective degree of freedom (*EDF*) for individual smooth terms of the established model is close to the value of *k-1*, the result indicates the number of knots is not enough (Wood, n.d.). The *EDF* indicator was used for determining a non-linear relationship between the independent variables and the dependent variable. According to Simon (Wood, n.d.), the *EDF* value >1 or <1 means that the smooth function change is nonlinear, and that of *EDF* equal to 1 is linear. If it is nonlinear, it is necessary to use a smooth function to fit the corresponding term in the model. If it is linear, the effect of smooth function fitting is similar to that of fitting as a non-smooth function. The EDF values of the smooth term derived from varying coefficient model characterize the shape (linear or non-linear) of the smooth component.

Second, we added a smoothing term of each air pollutant in Model 1, and then constructed a single-pollutant varying coefficient model as follows:

Model 2:

$$\ln(E(y)) = \alpha + holiday + DOW + DTLs + tp(humidity, k) + ps(time, k) + tp(pollutant, k) + tp(pollutant, k) : DTLs,$$

where the $tp(pollutant, k) : DTLs$ represents the varying coefficient term of interactions between each air pollutant of interest and DTLs assessed. The smoothing term and the varying coefficient term were also modeled in a *tp* penalty spline function with 10 knots as suggested above.

We finally constructed a multi-pollutant varying coefficient model in which all the air pollutants were included simultaneously to assess the stability of effect estimation. The structure of multi-pollutant model is depicted as follows:

Model 3:

$$\ln(E(y)) = \alpha + holiday + DOW + DTLs + tp(humidity, k) + ps(time, k) + \sum_{i=1}^{5} tp(pollutant_i, k) + \sum_{i=1}^{5} tp(pollutant_i, k) : DTLs \quad ,$$

where the $pollutant_i$ represents the i-th air pollutant. The $tp(pollutant_i, k) : DTLs$ term denotes the varying coefficient term of interaction between the i-th air pollutant and DTLs. We assessed the model performance and the effect estimations of interactions of air pollutants with temperature.

3. Results

Table 1 shows basic characteristics of cause-specific emergency department visits, climate variables and ambient air pollutants. In total, there were 226,443 emergency department visits in Guangzhou during the study period. The daily number of cause-specific emergency department visits for neurological, respiratory, and circulatory diseases were 92 (standard deviation (SD): 13), 26 (SD: 7), and 38 (SD: 8), respectively. The daily concentration of CO, SO_2, NO_2, $PM_{2.5}$ and O_3 was 0.98 mg/m^3, 14.85 μg/m^3, 46.86 μg/m^3, 39.02 μg/m^3, and 116.28 μg/m^3, respectively. In addition, daily mean temperature and relative humidity was 22.02 °C and 79.68%, respectively. Fig. 2 displays daily time series of cause-specific emergency department visits and indicates some correlations between the values of air pollutant concentrations and those of meteorological factors. Table 2 gives the 5th, 25th, 50th, 75th, 95th percentiles of daily average concentrations of air pollutants, daily mean temperature and that of relative humidity. Table 3 shows the correlations between daily concentrations of air pollutants. There was a strong positive correlation among daily levels of the three pollutants including $PM_{2.5}$, NO_2 and SO_2.

Results of model selection for varying coefficient models using the metrics including R-square, restricted maximum likelihood (REML) score and effective residual degrees of freedom of the model (Residual *df*) are shown in Table 4. It was visible that model 2 consistently outperformed model 1 based on the three assessment metrics for each

Table 1
Descriptive statistics of cause-specific emergency department visits, meteorological factors and concentrations of air pollutants in Guangzhou city, south China, 2014–2017.

Variables	Mean (SD)	Maximum	Minimum	IQR
Daily No. of emergency department visits				
Nervous system	92.00(13)	150.00	57.00	17.00
Respiratory system	26.00 (7)	51.00	9.00	9.00
Circulatory system	38.00 (8)	69.00	18.00	11.00
Pollutant concentrations				
CO, mg/m^3	0.98 (0.16)	1.76	0.65	0.20
NO_2, μg/m^3	46.86 (16.63)	136.70	18.65	21.26
O_3, μg/m^3	116.28 (53.76)	380.04	17.31	74.60
$PM_{2.5}$, μg/m^3	39.02 (20.40)	134.02	8.31	26.13
SO_2, μg/m^3	14.85 (5.30)	44.59	5.93	6.41
Metrological factors				
Mean temperature, °C	22.02 (6.19)	31.10	3.40	10.30
Relative humidity, %	79.68(10.18)	100.00	31.00	13.00

SD: Standard Deviation.
IQR: Interquartile range.

air pollutant, irrespectively of the disease. That is to say, the pollutant-by-temperature interactions have a good explanation of the model's residuals. In addition, on the comparison with single-pollutant varying coefficient models, multi-pollutant varying coefficient models generally achieved better performance than single-pollutant models in terms of R-square, REML score and *df* statistics, indicating that it should control the confounding factors of other pollutants to enhance the model fitting and get more stable results.

Table 5 shows that CO or SO_2 has statistically significant interactions with some DTLs on emergency department visits for respiratory and circulatory diseases in single-pollutant models, respectively. After adjusting for other pollutants and potential covariates, statistically significant interactions between CO and the 3rd DTL, SO_2 and the 4th DTL still persisted for respiratory emergency department visits. For further explanation, the interactions between CO and the 3rd DTL mean that the CO effect of the 3rd DTL and the CO effect of other DTL's are

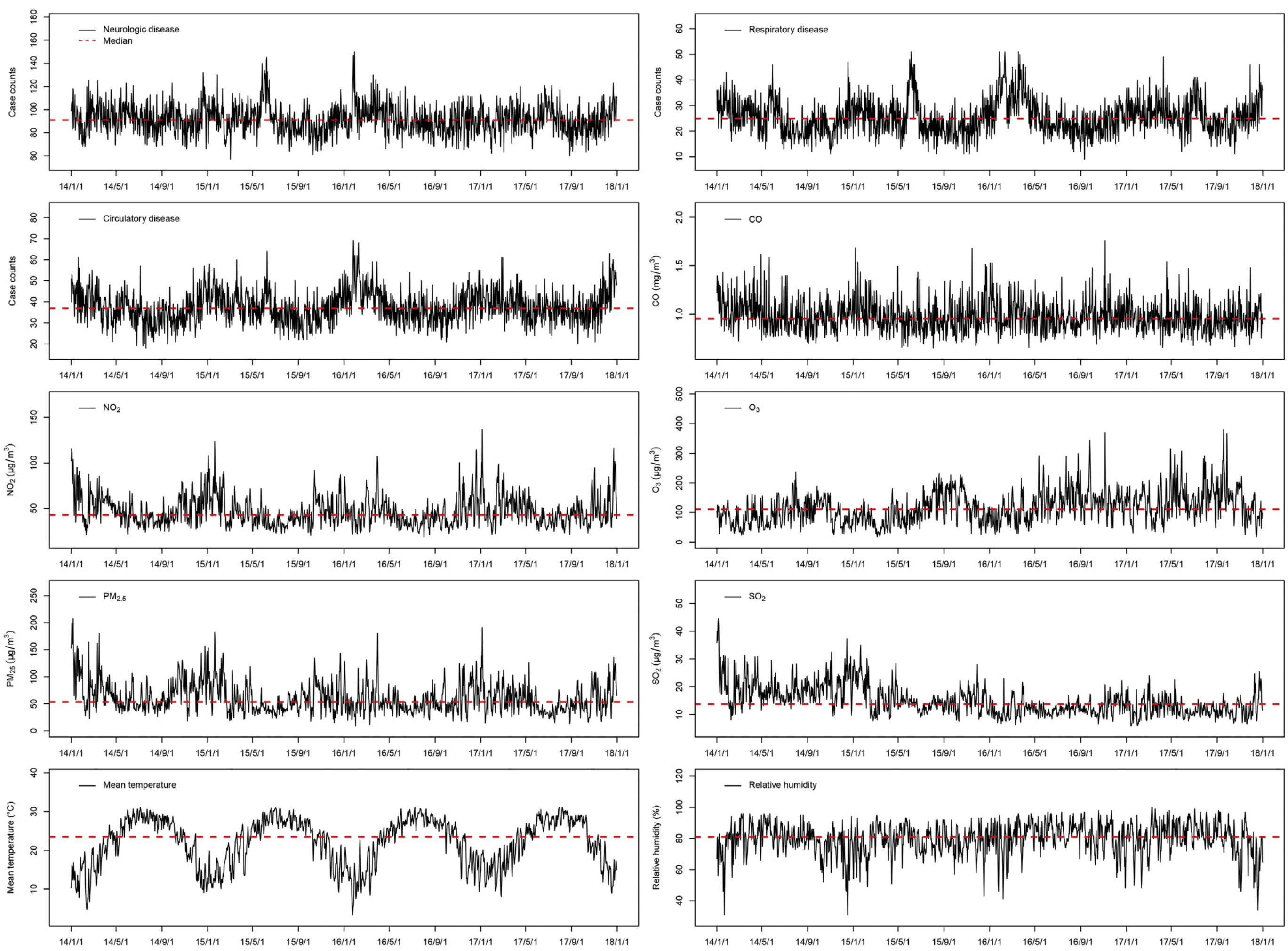

Fig. 2. Daily time-series plots of case-specific emergency department visits, concentrations of air pollutants (CO, SO_2, NO_2, O_3 and $PM_{2.5}$), and metrological variables (mean temperature and relative humidity) in Guangzhou city, south China, 2014–2017.

Table 2
Summary statistics of daily average concentrations of air pollutants and meteorological factors in Guangzhou city, south China, 2014–2017.

Variables	Mean ± SD	Percentiles				
		5th	25th	50th	75th	95th
CO (mg/m^3)	0.98 ± 0.16	0.76	0.87	0.96	1.07	1.28
SO_2 ($\mu g/m^3$)	14.85 ± 5.30	8.48	11.04	13.72	17.45	25.14
NO_2 ($\mu g/m^3$)	46.86 ± 16.63	26.94	34.76	42.83	56.01	79.56
O_3 ($\mu g/m^3$)	116.28 ± 53.76	41.52	74.63	111.34	149.23	205.73
$PM_{2.5}$ ($\mu g/m^3$)	39.02 ± 20.40	15.64	23.47	34.49	49.60	78.42
Temperature (°C)	22.02 ± 6.19	11.20	17.10	23.50	27.40	29.80
Relative humidity (%)	79.68 ± 10.18	61.00	74.00	81.00	87.00	94.00

Table 3
Pearson correlation coefficients among daily average concentrations of air pollutants in Guangzhou city, south China, 2014–2017.

Pollutants	CO	SO_2	NO_2	O_3	$PM_{2.5}$
CO	1.00				
SO_2	0.20*	1.00			
NO_2	0.28*	0.65*	1.00		
O_3	−0.09*	0.00	0.06*	1.00	
$PM_{2.5}$	0.28*	0.73*	0.82*	0.11*	1.00

* This symbol indicates the corresponding P-value < 0.05.

different where the CO effect was significant under modifying by the 3rd DTL but not for other DTL's, so as other interactions. In addition, we further identified statistically significant interactions between NO_2 and the first two DTLs on neurological emergency department visits, respectively. It is evident that the interactions identified by varying coefficient models are stable regardless of model structure. Fig. S1 shows autocorrelation function (ACF) plots and residuals histogram of multi-pollutant varying coefficient models for emergency department visits on neurologic, respiratory and circulatory diseases, respectively. It is also evident that the model's residuals approximately obey normal distribution and do not have any obvious autocorrelation.

Fig. 3 and Fig. S2 give more details about the estimation results of multi-pollutant varying coefficient models. We can see that the smoothing component diagram of the interactions of NO_2 with the first two DTLs shows a monotone rise, respectively. Besides, there was an approximately linear increasing trend in the smoothing component diagram characterizing the interactions of SO_2 and the 4th DTL on respiratory emergency department visits. Overall, the smoothing component curve characterizing the interactions between CO and the 3rd DTL on respiratory emergency department visits exhibited an upward trend, although most of the curve fluctuated around zero. However, some confidence intervals do not contain 0, for example, when the concentration of CO is around 1.5 $\mu g/m^3$ (Fig. 3). In fact, the interactions

Table 4
Model selection for varying-coefficient regression models using the metrics including R-square, restricted maximum likelihood (*REML*) score and effective residual degrees of freedom of the model (Residual *df*) on the associations between air pollution exposure and emergency department visits for neurologic, respiratory and circulatory diseases, respectively. Larger values of the R-square and *REML* score or smaller value of the Residual *df* indicate the better model fit.

Diseases	Models	Description	R-square	*REML* score	Residual *df*
Neurologic system	Model I[a]	None pollution	0.208	1078.759	1422.625
	Model I (CO)	Model I + s(CO)[b]	0.208	1083.426	1421.569
	Model I (SO_2)	Model I + s(SO_2)	0.223	1058.157	1424.603
	Model I (NO_2)	Model I + s(NO_2)	0.219	1065.461	1423.463
	Model I (O_3)	Model I + s(O_3)	0.215	1079.854	1420.337
	Model I ($PM_{2.5}$)	Model I + s($PM_{2.5}$)	0.216	1073.190	1422.144
	Model II (CO)	Model I (CO) + s(CO):DTLs[c]	0.211	1091.182	1416.977
	Model II (SO_2)	Model I (SO_2) + s(SO_2):DTLs	0.222	1066.086	1420.753
	Model II (NO_2)	Model I (NO_2) + s(NO_2):DTLs	0.217	1071.953	1420.040
	Model II (O_3)	Model I (O_3) + s(O_3):DTLs	0.218	1087.534	1416.089
	Model II ($PM_{2.5}$)	Model I ($PM_{2.5}$) + s($PM_{2.5}$):DTLs	0.213	1082.397	1419.565
	Model III	Model I + s(CO) + s(CO):DTLs + s(SO_2) + s(SO_2):DTLs + s(NO_2) + s(NO_2):DTLs + s(O_3) + s(O_3):DTLs + s($PM_{2.5}$) + s($PM_{2.5}$):DTLs	**0.237**[d]	**1105.609**[d]	**1395.540**[d]
Respiratory system	Model I	None pollution	0.375	940.716	1420.129
	Model I (CO)	Model I + s(CO)	0.376	943.841	1419.126
	Model I (SO_2)	Model I + s(SO_2)	0.378	940.403	1419.086
	Model I (NO_2)	Model I + s(NO_2)	0.378	941.108	1419.134
	Model I (O_3)	Model I + s(O_3)	0.376	944.182	1418.825
	Model I ($PM_{2.5}$)	Model I + s($PM_{2.5}$)	0.380	939.315	1418.764
	Model II (CO)	Model I (CO) + s(CO):DTLs	0.382	949.167	1411.722
	Model II (SO_2)	Model I (SO_2) + s(SO_2):DTLs	0.384	941.193	1414.058
	Model II (NO_2)	Model I (NO_2) + s(NO_2):DTLs	0.377	948.205	1416.158
	Model II (O_3)	Model I (O_3) + s(O_3):DTLs	0.376	950.627	1414.903
	Model II ($PM_{2.5}$)	Model I ($PM_{2.5}$) + s($PM_{2.5}$):DTLs	0.380	946.280	1415.767
	Model III	Model I + s(CO) + s(CO):DTLs + s(SO_2) + s(SO_2):DTLs + s(NO_2) + s(NO_2):DTLs + s(O_3) + s(O_3):DTLs + s($PM_{2.5}$) + s($PM_{2.5}$):DTLs	**0.389**[d]	**976.776**[d]	**1392.929**[d]
Circulatory system	Model I	None pollution	0.328	863.149	1430.845
	Model I (CO)	Model I + s(CO)	0.327	867.574	1429.862
	Model I (SO_2)	Model I + s(SO_2)	0.334	858.725	1429.922
	Model I (NO_2)	Model I + s(NO_2)	0.334	859.057	1429.971
	Model I (O_3)	Model I + s(O_3)	0.328	866.922	1429.337
	Model I ($PM_{2.5}$)	Model I + s($PM_{2.5}$)	0.333	862.748	1427.990
	Model II (CO)	Model I (CO) + s(CO):DTLs	0.326	876.868	1426.904
	Model II (SO_2)	Model I (SO_2) + s(SO_2):DTLs	0.335	865.912	1426.598
	Model II (NO_2)	Model I (NO_2) + s(NO_2):DTLs	0.333	867.251	1426.897
	Model II (O_3)	Model I (O_3) + s(O_3):DTLs	0.334	872.951	1421.172
	Model II ($PM_{2.5}$)	Model I ($PM_{2.5}$) + s($PM_{2.5}$):DTLs	0.332	869.962	1425.609
	Model III	Model I + s(CO) + s(CO):DTLs + s(SO_2) + s(SO_2):DTLs + s(NO_2) + s(NO_2):DTLs + s(O_3) + s(O_3):DTLs + s($PM_{2.5}$) + s($PM_{2.5}$):DTLs	**0.339**[d]	**908.942**[d]	**1404.413**[d]

[a] Model I: fitting the generalized additive model after controlling for meteorological variables, time trend, day of week, public holiday and DTLs (daily temperature levels).
[b] s(CO): spline of the concentration of the pollutant CO.
[c] s(CO):DTLs: the varying-coefficient interaction item between the concentration of the pollution CO and DTLs.
[d] This number in bold indicates that the models have the best model fit according to the statistical metrics assessed.

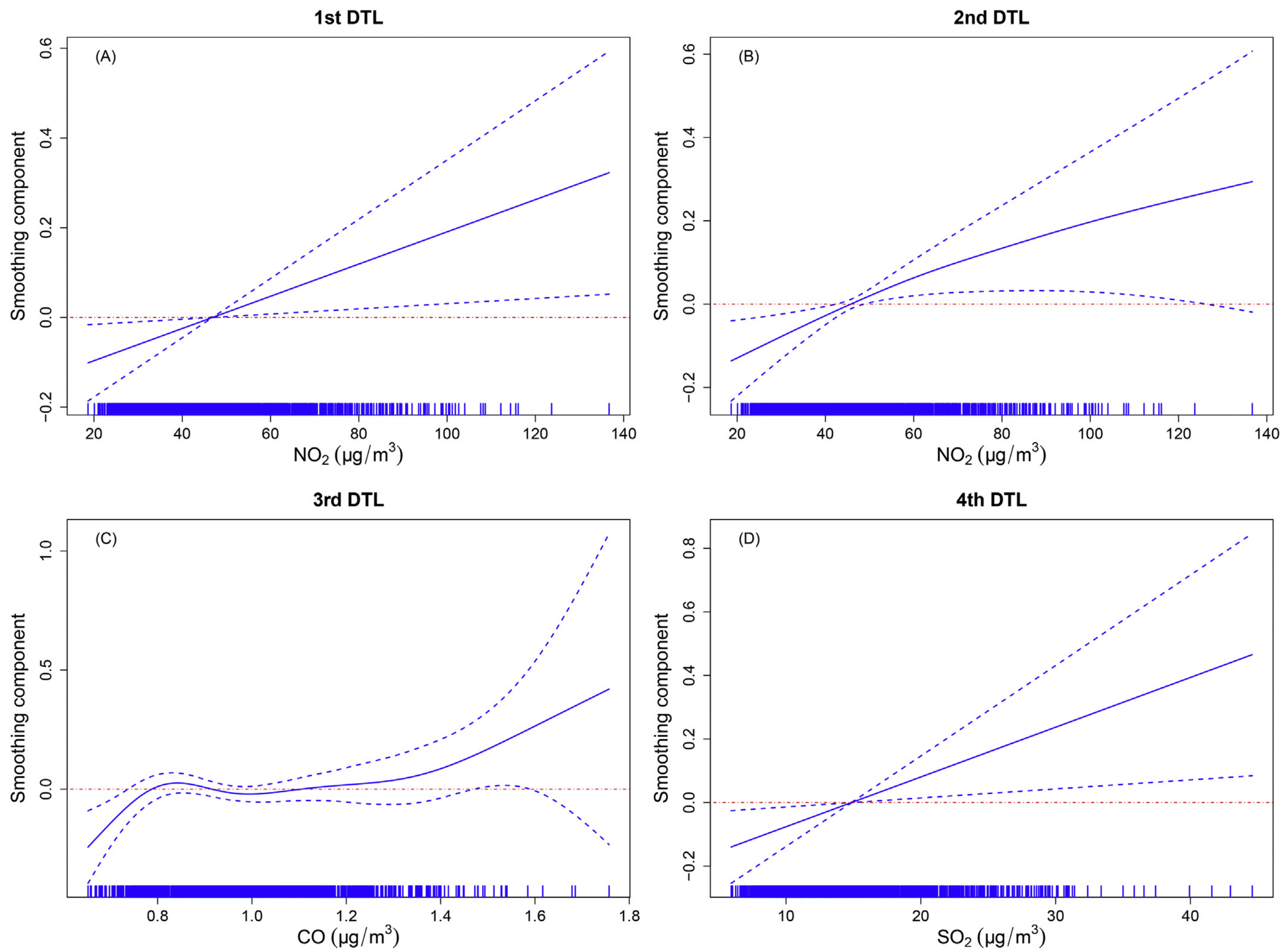

Fig. 3. Plots of smoothing component derived from multi-pollutant varying-coefficient regression models displaying the interactions between the concentrations of air pollutants and daily temperature levels (DTLs). (A) The significant interaction effect between NO_2 and the 1st DTL for neurologic diseases. (B) The significant interaction effect between NO_2 and the 2nd DTL for neurologic diseases. (C) The significant interaction effect between CO and the 3rd DTL for respiratory diseases. (D) The significant interaction effect between SO_2 and the 4th DTL for circulatory diseases.

Table 5
The smoothing component (SC) result of pollutants' main effect and interaction effect between pollutant and daily temperature levels (DTLs) according to the metric of the effective degrees of freedom (*EDF*) for individual smooth term derived from single-pollutant and multi-pollutant varying-coefficient models after controlling for meteorological variables, time trend, day of week and public holidays in Guangzhou city of China, 2014–2017. The *EDF* indicator was used for determining a non-linear relationship between the independent variables and the dependent variable. For example, when the value of *EDF* is not equal to 1, it indicates that the corresponding smoothing component is nonlinear. Otherwise, when the *EDF* value is equal to 1, it indicates that the smoothing component is linear.

Diseases	Effects	*EDF* of SC in single-pollutant model					*EDF* of SC in multi-pollutant model				
		CO	SO_2	NO_2	O_3	$PM_{2.5}$	CO	SO_2	NO_2	O_3	$PM_{2.5}$
Neurologic system	Main effect	1.00	1.00	1.00	1.00	1.00	1.00	1.00	2.10	1.00	1.00
	Interaction with the 1st DTL	1.00	1.00	1.00	1.44	1.00	<0.01	1.00	1.00*	1.50	4.03
	Interaction with the 2nd DTL	1.00	2.52	2.07	1.00	1.00	1.00	2.22	1.89*	1.00	2.81
	Interaction with the 3rd DTL	2.78	1.00	0.26	1.00	1.00	2.86	1.18	1.00	1.00	<0.01
	Interaction with the 4th DTL	<0.01	0.33	1.00	0.63	<0.01	1.00	0.04	<0.01	1.19	1.00
Respiratory system	Main effect	1.00	1.00	1.00	1.00	1.00*	1.00	1.00	1.00	1.00	1.00
	Interaction with the 1st DTL	<0.01	1.00	1.00	1.00	1.00	1.00	1.00	1.00	<0.01	1.00
	Interaction with the 2nd DTL	1.36	3.61	1.00	1.00	1.02	1.00	3.61	1.00	1.00	1.82
	Interaction with the 3rd DTL	5.09*	<0.01	1.00	2.19	1.00	4.91*	<0.01	1.00	2.15	<0.01
	Interaction with the 4th DTL	1.00	1.00*	<0.01	<0.01	<0.01	<0.01	1.00*	<0.01	1.00	1.00
Circulatory system	Main effect	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Interaction with the 1st DTL	<0.01	1.00	1.00	1.00	2.21	1.00	1.00	1.00	1.00	2.35
	Interaction with the 2nd DTL	1.00	1.00	1.00	1.00	1.00	1.00	1.00	<0.01	1.00	1.00
	Interaction with the 3rd DTL	1.00	1.41	1.00	3.39	1.01	1.00	1.58	1.00	3.26	1.00
	Interaction with the 4th DTL	1.00	1.00*	1.00	1.00	1.00	<0.01	<0.01	1.00	3.06	<0.01

* This symbol indicates *P*-value <0.05, which is meaning that the corresponding smoothing component effect is statistically significant.

Table 6
Subgroup analysis of the smoothing component (SC) result of pollutants' main effect and interaction effect between pollutant and daily temperature levels (DTLs) according to the metric of the effective degrees of freedom (*EDF*) for individual smooth term derived from multi-pollutant varying-coefficient model by sex after controlling for meteorological variables, time trend, day of week and public holidays in Guangzhou city of China, 2014–2017. The *EDF* indicator was used for determining a non-linear relationship between the independent variables and the dependent variable, for example, when the value of *EDF* is not equal to 1, it indicates that the corresponding smoothing component is nonlinear. Otherwise, when the *EDF* value is equal to 1, it indicates that the smoothing component is linear.

Diseases	Effects	*EDF* of SC for males					*EDF* of SC for females				
		CO	SO_2	NO_2	O_3	$PM_{2.5}$	CO	SO_2	NO_2	O_3	$PM_{2.5}$
Neurologic system		Sample size: 70994					Sample size: 62393				
	Interaction with the 1st DTL	<0.01	1.00	1.00*	1.00	4.12	<0.01	1.00	1.00	0.84	1.00
	Interaction with the 2nd DTL	1.00	2.50	1.00*	1.00	1.00	1.30	1.00	1.06	1.00	2.37
	Interaction with the 3rd DTL	2.86	2.02	1.00	1.00*	0.90	1.00	1.00	1.00	1.00	3.16
	Interaction with the 4th DTL	1.00	<0.01	<0.01	<0.01	1.00	1.00	<0.01	1.00	3.20*	<0.01
Respiratory system		Sample size: 22805					Sample size: 14436				
	Interaction with the 1st DTL	<0.01	1.00*	1.00	1.00	1.70	2.45	1.00*	1.00	<0.01	1.00
	Interaction with the 2nd DTL	1.00	3.20*	<0.01	1.08*	1.03	1.00	1.00*	1.00	1.00	1.00
	Interaction with the 3rd DTL	5.03	1.00*	1.00	1.00	<0.01	3.34	2.06	1.00	1.00	<0.01
	Interaction with the 4th DTL	1.00	<0.01	1.00	<0.01	1.00	<0.01	0.05	0.83	2.55	1.00
Circulatory system		sample size: 31113					sample size: 23848				
	Interaction with the 1st DTL	1.00	1.00	1.00	1.00	2.21	1.00	1.59	1.00	1.01	1.00
	Interaction with the 2nd DTL	1.00	1.00	1.00	1.00	1.00	1.48	1.00	1.00	1.00	1.00
	Interaction with the 3rd DTL	1.92	1.00	1.57	1.75	0.92	1.00	0.17	1.00	1.00	1.00
	Interaction with the 4th DTL	<0.01	<0.01	<0.01	<0.01	1.00	<0.01	1.02	<0.01	1.47	<0.01

* This symbol indicates *P*-value <0.05, which is meaning that the corresponding smoothing component effect is statistically significant.

were overall statistically significant according to the results of our hypothesis test. Among them, we found that the interactions between CO and the 3rd DTL significantly increased the risk of respiratory emergency department visits. In total, a rising trend in the diagram for characterizing the pollutant-by-DTLs interactions indicated that higher concentrations of air pollutants were linked to greater risks of emergency department visits, which were modified by temperature. A comparison of the interactions of air pollutants (CO, NO_2 and SO_2) with different DTLs can be seen in Fig. S2. The smooth component diagrams characterizing the interaction effects showed that there were no other significant interactions of the rest of pollutants with different DTLs.

Tables 6 and 7 show the results of subgroup analyses by gender and age group, respectively. We found that NO_2-by-temperature and O_3-by-temperature interactions significantly increased the risk of neurological emergency department visits in females and both genders, respectively. The SO_2-by-temperature interactions also increased the risk of respiratory diseases in both genders. In addition, the significant interactions between O_3 and the 2nd DTL for males were visible. Among different groups of age, interactions of CO, NO_2 and $PM_{2.5}$ modified by DTLs on the risk of neurological emergency department visits were significant in participants aged <75 years, but not in participants aged ≥75 years. Regardless of age group, the effect of SO_2 interacting with the 4th DTL increasing the risk of emergency department visits for respiratory diseases was observed.

4. Discussion

Our study used a large-scale multi-center database of disease emergency department visits to analyze interactions between air pollutants (CO, SO_2, NO_2, $PM_{2.5}$, and O_3) and ambient temperature on the risk of cause-specific emergency department visits. With a large study population, this study provides evidence on interactions between air pollutants and ambient temperature in southern China. The results of multi-pollutant varying coefficient model show statistically significant interactions between NO_2 and the 1st DTL, NO_2 and the 2nd DTL on emergency department visits for neurological diseases after adjusting relative humidity, DOW, public holiday and time trends. For the 1st DTL and the 2nd DTL, the higher the concentrations of NO_2 were linked to the higher risk of neurological emergency department visits. Besides, the interactions between SO_2 and the 4th DTL were positively

Table 7
Subgroup analysis of the smoothing component (SC) result of pollutants' main effect and interaction effect between pollutant and daily temperature levels (DTLs) according to the metric of the effective degrees of freedom (*EDF*) derived for individual smooth term from multi-pollutant varying-coefficient model by age groups (<75, or ≥ 75 years old) after controlling for meteorological variables, time trend, day of week and public holidays in Guangzhou city of China, 2014–2017. The *EDF* indicator was used for determining a non-linear relationship between the independent variables and the dependent variable, for example, when the value of *EDF* is not equal to 1, it indicates that the corresponding smoothing component is nonlinear. Otherwise, when the *EDF* value is equal to 1, it indicates that the smoothing component is linear.

Diseases	Effects	*EDF* of SC for participants aged <75					*EDF* of SC for participants aged ≥75				
		CO	SO_2	NO_2	O_3	$PM_{2.5}$	CO	SO_2	NO_2	O_3	$PM_{2.5}$
Neurologic system		Sample size: 93116					Sample size: 38601				
	Interaction with the 1st DTL	<0.01	1.00	1.00*	1.34	1.00*	0.14	1.31	1.00	1.00	1.00
	Interaction with the 2nd DTL	1.00*	1.01	2.75*	1.00	2.56*	1.00	2.87	1.00	1.00	1.67
	Interaction with the 3rd DTL	3.16	1.00	1.00	1.00	1.00	1.00	1.00	1.57	1.00	1.00
	Interaction with the 4th DTL	1.00	<0.01	<0.01	1.7	<0.01	1.00	0.75	<0.01	0.97	0.98
Respiratory system		Sample size: 16777					Sample size: 20148				
	Interaction with the 1st DTL	1.00	1.00	1.00	1.00	1.00	0.90	2.67	1.00	<0.01	1.00
	Interaction with the 2nd DTL	1.17	<0.01	1.00	1.00	1.70	1.00	2.56	1.00	1.00	1.00
	Interaction with the 3rd DTL	3.95	1.00	1.00	1.00	1.00	1.00	<0.01	1.00	1.00	1.00
	Interaction with the 4th DTL	<0.01	1.00*	<0.01	<0.01	<0.01	1.00	1.00*	<0.01	2.22	0.84
Circulatory system		Sample size: 32015					Sample size: 22508				
	Interaction with the 1st DTL	<0.01	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.70
	Interaction with the 2nd DTL	1.00	1.20	<0.01	1.00	1.00	1.00	2.74	<0.01	1.00	1.81
	Interaction with the 3rd DTL	1.00	1.00	1.00	1.00	1.00	1.00	0.33	1.00	2.88	1.00
	Interaction with the 4th DTL	1.62	<0.01	1.00	0.51	<0.01	<0.01	1.00	1.00	1.12	<0.01

* This symbol indicates *P*-value <0.05, which is meaning that the corresponding smoothing component effect is statistically significant.

associated with respiratory emergency department visits. For the interactions between SO_2, we found a higher risk of respiratory emergency department visits was associated with higher the concentrations of the pollutant for the 4th DTL. Additionally, the interactions between CO and the 3rd DTL were also significantly associated with respiratory emergency department visits while its 95% confidence interval mostly contained the value of 0, indicating that the collinearity between the air pollutants may partly contribute to this unclear boundary.

Most of the current studies mainly focused on the interactions between O_3, SO_2 and PM_{10} and temperature on morbidity or mortality of diseases, but the evidence on the interactions between CO, NO_2 and $PM_{2.5}$ and temperature is still limited. According to Stafoggia et at., in a study for nine cities in Italy, after controlling season and temperature, the interactions between PM_{10} and temperature were strongly modified the PM_{10}-mortality association, but in most cases, there was no significant statistically significant coefficient (Stafoggia et al., 2008). InyJhun et al. found that the association of interaction between O_3 and temperature to mortality was not statistically significant in the time series studies of US 97 cities, but the risk of death was U-shaped, at low temperatures (below 25%) and high temperature (75% or more) (Jhun et al., 2014). Breitner et al. believed that the time series in Bavaria, Germany when the levels of PM10 and O_3 were higher, there was a strong correlation between high temperature and mortality, but not at low temperatures (Beritner et al., 2014). Katsouyanni et al. used multiple linear regression to investigate interactions between air pollutants and high temperatures in the Heats of July 1987, and found that high levels of SO_2 and high temperature were mutual promotive when the main effect indicators of air pollutants were not statistically significant (Katsouyanni et al., 1993). Roberts found that the effect of particulate air pollutants on mortality depended on temperature, but their mutual promotion was sensitive to the selection of degrees of freedom to adjust for confounding factors (Roberts, 2004). Ren et al. found a symmetrical improvement in temperature and particulate matter (Ren and Tong, 2006). Thus, several multi-site studies have found evidence on the effects of temperature and air pollutants interactions on human health, but the nature and size of these interactions vary from geographic to geographic. Also, using a conventional analysis method to evaluate interactions between air pollutants and ambient temperature are limited by complex forms of interactions between nonlinear variables on the response which may result in inconsistent results. Therefore, in order to improve the accuracy of analysis, we employed the varying coefficient model to capture potential complex relationships in data.

In this study, we found that NO_2 or SO_2 interacted with temperature, and the interactions between SO_2 and high temperature (27.4 °C–31.1 °C) had a detrimental effect on the respiratory system which was consistence with previous studies (Guo et al., 2017; Katsouyanni et al., 1993). The interactions between NO_2 and low temperature (3 .4 °C–23.5 °C) had an adverse effect on the neurological system. The newly discovered evidence indicates the interactions between pollutants (NO_2 and SO_2) and temperature have an adverse effect on public health. The findings were derived from the varying coefficient models adjusted for relative humidity. In fact, we should point out that it is better to use the indicator of absolute humidity to adjust for the amount of moisture in the air in our models. However, we can't get the surveillance data of absolute humidity in this study. In fact, the value of the Pearson correlation coefficient r between daily mean temperature and relative humidity for our data was 0.28, which means there is a weak correlation between the two variables. Additionally, the autocorrelation graphs of the models for different diseases showed the residuals were also white noise (Fig. S1), which suggesting that the models we built were effective. Therefore, the correlation between mean temperature and relative humidity had less influence on the construction of the models.

In the gender subgroup analysis, there have some significant interactions for neurological diseases in both genders. It tends to have an adverse effect of interactions of air pollutants with ambient temperature in males compared to females, which was consistent with a previous study (Kim et al., 2015). Owning to doing more effort to fight for air pollutants in female, such as making a facial mask, staying at home, these behaviors can reduce the exposure of air pollutants to them. In addition, among the different group of age, participants aged <75 years was more susceptible to the adverse effects of low temperature adjusted air pollutants on the neurological system, whereas participants aged 75 years and above was not. This may be because participants aged <75 years have more out-of-life activities and more sensitive neurological system. Hence, they are prone to expose in a higher concentration of air pollutants and have nausea and headache. For the respiratory diseases, both age groups were affected by SO_2 modified by the 3rd DTL. For circulatory diseases, the results showed there were no significant interaction effects in both genders. There are several researches using age of 65 or 85 to divide into two age subgroups (Kim et al., 2015; Beritner et al., 2014), and the studies suggested that the mortality or morbidity of the older group was more susceptible to the interactions of air pollutants with high temperature, while the interactions were not observed for low temperature, which is not completely consistent with our research. And it is possible that specific diseases and different grouping methods of age could lead to dispersion. This reminded us that age should be treated as an important confounding effect in a subsequent study. Our findings derived from the subgroup analysis were consistent with the results of multi-pollutant model, which in turn supported the stability of the results of multi-pollutant models.

There are several preponderant points in this study. First, a variety of technical methods were used to ensure the quality of air pollutant data, and these large samples of high quality data further improved the robustness of the interaction estimations. Second, this study used single-pollutant and multi-pollutant varying coefficient models to compare the analysis results and further determine the true relationship identified. Third, this is a rare study of the interactions between air pollutants and temperature in one of the most densely populated cities in southern China, and provides novel evidence on the adverse effects of ambient air pollutants interacting with temperature on disease morbidity.

Our study has some limitations. First, limited by data source, our study was based on the total number of cause-specific emergency department visits per day, without taking into account the specific individual information of each patient, such as lifestyle, behavior, educational level and socioeconomic status, which may have a potential impact on the estimated associations. Second, personal geographic information was not but better being considered in our study to control the spatial heterogeneity of measurement of air pollutants and meteorological factors. Our future studies will adopt the method of spatial interpolations to calculate weighted mean pollutant concentrations to yield more robust results.

5. Conclusions

In summary, based on this present study in Guangzhou city with an extremely high population density in China, we found the interactions between NO_2 and the 1st DTL, NO_2 and the 2nd DTL for neurological emergency department visits. The interactions between SO_2 and the 4th DTL significantly increased the risk of the emergency department visits of respiratory diseases. Participants aged <75 years were more susceptible to the adverse interaction effects of NO_2 with the first two DTLs on the neurological diseases than those aged 75 years and above. In addition, the higher hazard effects of $PM_{2.5}$ interacting with the first two DTLs on the neurological diseases were also seen in participants aged <75 years. Overall, the interactions of temperature with NO_2 were statistically significant but not with $PM_{2.5}$. Our study provides evidence on the interactions of temperature of different grades with air pollutants (SO_2 and NO_2) on the risk of emergency department visits of diseases, respectively. The findings will help medical services and emergency agencies develop targeted protection strategies and provide better protection for susceptible population.

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Competing interest

The authors declare no conflict of interest.

Author contributions

Conceived of or designed study: YLC, WRF, PG and WYH.
Performed research: YLC, WRF, MRZ, JYL, TXS, YW and PDL.
Analyzed data: YLC, WRF and PG.
Wrote and revised the paper: YLC, WRF, PG and WYH.

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