Atmospheric Environment 186 (2018) 136–143

Contents lists available at ScienceDirect

Atmospheric Environment

journal homepage: www.elsevier.com/locate/atmosenv

Association between multi-pollutant mixtures pollution and daily cardiovascular mortality: An exploration of exposure-response relationship

Yuanren Tong[a,1], Kai Luo[b,c,1], Runkui Li[d,e], Lu Pei[b,c], Ang Li[b,c], Mingan Yang[f], Qun Xu[b,c,*]

[a] Chinese Academy of Medical Sciences & Peking Union Medical College Beijing 100005, China
[b] Department of Epidemiology and Biostatistics, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, School of Basic Medicine, Peking Union Medical College, Beijing 100005, China
[c] Center of Environmental and Health Sciences, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100005, China
[d] College of Resources and Environment, University of Chinese Academy of Sciences, Beijing 100049, China
[e] State Key Laboratory of Resources and Environmental Information System, Institute of Geographic Sciences and Natural Resources Research, Chinese Academy of Science, Beijing 100101, China
[f] Division of Biostat & Epidemiology, Graduate School of Public Health, San Diego State University, San Diego, Ca 92182, USA

ARTICLE INFO

Keywords:
Air pollution
Bayesian kernel machine regression
Exposure-relationship
Cardiovascular mortality

ABSTRACT

Evidence of combined mortality effects of multi-pollutant on cardiovascular diseases (CVD) and the corresponding exposure-response (ER) relationship is limited. In this paper, we examined the association between four ambient air pollutants (i.e., fine particulate matter, $PM_{2.5}$, particulate matter, PM_{10}, nitrogen dioxide, NO_2, and sulfur dioxide, SO_2.) and CVD mortality and the corresponding ER relationship after incorporating the potential interaction among the multiple pollutants. Bayesian kernel machine regression (BKMR) was used to evaluate the ER relationship and to explore the interactions between pollutants. The results showed that PM_{10} and SO_2 were dominant pollutants from 0 to 2 days, while $PM_{2.5}$ and NO_2 had strong effect on CVD mortality from 3 to 4 days. Generally, $PM_{2.5}$ and NO_2 had the similar ER relationship across different moving average concerning the CVD mortality. For the interaction among the multiple pollutants, we found that there is no interaction between particle pollutants (i.e. $PM_{2.5}$ and PM_{10}) and gaseous pollutants (i.e.NO_2 and SO_2). On the contrary, there might be an interaction between $PM_{2.5}$ and PM_{10} though this interaction was detected by visually comparing the slopes of ER curves of a given particle pollutant at different levels of the other particle pollutant. But there is a lack of statistical significance test for this interaction. This study suggests that different ambient air pollutants might have the dominant effect on CVD deaths during different moving average, though there might not be statistical significant interactions among the ambient air pollutants in present study.

1. Introduction

It is well known that ambient air pollution is associated with a variety of adverse health outcomes, ranging from preclinical changes to death (Di et al., 2017; Mustafic et al., 2012; Rich et al., 2012; Sarnat et al., 2001). The latest estimated deaths attributed to ambient fine particulate matter were approximate 4.2 million worldwide and 1.1 million in China in 2015 (Cohen et al., 2017). A recent simulation study estimated that 241,000 life-years would benefit from the reduction in concentration of ambient $PM_{2.5}$ that reached the level during 2008 Beijing Olympic period (Huang et al., 2017). These studies have greatly promoted the understanding of the effects of individual pollutant but were mainly based on the epidemiologic studies of single pollutant, where effect estimations were obtained from models with single pollutant or adjusted for col-pollutant in the same statistical model.

Although it is essential to understand the effects of exposure to a single pollutant, people are invariably exposed to a multi-pollutant mixture instead of a single pollutant (Braun et al., 2016). Diseases related to ambient air pollution are rarely attributed to a single pollutant, the contribution of multi-pollutant would be more important and significant. Thus, it is important to study the effects of multi-pollutant exposure to elaborate its hazard health effects and to provide scientific evidence for air pollution control policy (Dominici et al., 2010). Actually, the unknown interaction among air pollutants have made it a daunting task to estimate the effects of the multi-pollutant exposure on health (Davalos et al., 2017). Some statistical methods exploring multi-

* Corresponding author. Department of Epidemiology and Biostatistics, Institute of Basic Medicine Sciences, Chinese Academy of Medical Sciences, School of Basic Medicine, Peking Union Medical College, Beijing 100005, China.
E-mail address: xuqun@ibms.cams.cn (Q. Xu).
[1] Authors contribute equally to this work.

https://doi.org/10.1016/j.atmosenv.2018.05.034
Received 23 October 2017; Received in revised form 14 May 2018; Accepted 15 May 2018
Available online 24 May 2018
1352-2310/

pollutant adverse health effects have been proposed. For instance, Schildcrount et al. (Schildcrout et al., 2006) proposed an additive effect model with decomposed effects to examine the combined effect of a simultaneous increase in air pollution concentrations on asthma exacerbations. But this approach is highly dependent on the selected models. Other researchers have proposed approaches based on dimension reduction techniques such as factor analysis, principle component analysis, latent class analysis, to allow for the correlation and additive/motive interaction of air pollutants (Pachon et al., 2012; Roberts, 2006; Sacks et al., 2012; Yang et al., 2013; Zanobetti et al., 2014). However, all these models are not flexible in assessing the interaction of different air pollutants and the corresponding combined effects, particularly for the potential nonlinear exposure response relationship.

Recently, Bobb et al. (2015) proposed a statistical learning method, based on Bayesian kernel machine regression (BKMR), to estimate joint effects of multiple pollutants, while allowing for potential nonlinear or nonadditive associations between a given pollutant and health outcome of interest. This approach has some appealing advantages in estimating health effects caused by multi-pollutant and identifying the dominant pollutants that have the strongest effect on the health outcome under certain condition (Bobb et al., 2015; Coull et al., 2015). Moreover, the complicated nonlinear exposure-response(ER) relationship can be easily estimated with this method.

Given the limited evidence of effects of multi-pollutant exposure on daily mortality and the corresponding ER relationships, in present study, we adopted this approach to identify the ambient air pollutants that were most closely associated with daily cardiovascular mortality, and to calculate the ER relationship between air pollutants and cardiovascular mortality while incorporating the interaction of multiple pollutants.

2. Materials and method

2.1. Analysis plan

This study was comprised of two parts: simulation study for the selection of prior distributions of parameters of BKMR and its application. We presented the detailed introduction of simulation in supplementary materials online for conciseness. The implementation of BKMR was based on the information generated from the simulation study. The flow path of BKMR modeling in this study was demonstrated in S.Fig. 1 in supplementary materials.

2.2. Data collection

Data of daily mortality caused by cardiovascular disease (ICD-10, I00-I99) from 2008 to 2011 was retrieved from Causes of Death Registry of Chinese Center for Disease Control and Prevention (China CDC). Data of daily air pollutants, including PM_{10}, NO_2 and SO_2, was collected from 12 national air quality monitoring stations (NAQM) in Beijing during the same period. To evaluate the association between $PM_{2.5}$ and CVD mortality and the ER relationship, we also obtained the daily $PM_{2.5}$. Because $PM_{2.5}$ was not yet routinely monitored in China until late December 2012, data of daily $PM_{2.5}$ during the same period were obtained from the air quality monitoring station of the U.S. Embassy in China, which is located in the Chaoyang district of Beijing. Meteorological data, including daily mean temperature and relative humidity were retrieved from the Beijing Observatory (Station No.: 54511) of the China Meteorological Administration, which is located in the Daxing district in Beijing. Table 1 shows the descriptive statistics of daily death counts and ambient air pollutants in Beijing, China.

In order to explicitly interpret results of multiple pollutants within the BKMR framework, data of ambient pollutants were first standardized before implementing BKMR.

Table 1
Descriptive statistics of daily death counts and air pollutants used in the application.

	Mean	SD	Min	P25	P50	P75	Max
Pollutants							
$NO_2(\mu g/m^3)$	49.82	23.13	5.37	33.17	45.90	60.00	180.67
$PM_{10}(\mu g/m^3)$	117.75	74.14	4.91	65.09	104.00	146.55	651.18
$PM_{2.5}(\mu g/m^3)$	95.68	70.83	5.83	41.79	80.09	127.92	492.75
$SO_2(\mu g/m^3)$	32.27	31.66	3.00	10.96	20.00	42.00	202.00
Death Count							
CVD	99.57	20.36	54.00	85.00	97.00	113.00	173.00

*P25, P50, P75 refer to 25th, 50th and 75th percentile, respectively.

2.3. Statistical analysis

To accommodate for the potential synergistic and nonlinear effects among multiple air pollutants, we used BKMR, a novel approach for multi-pollutant mixtures that flexibly models the joint effect of mixtures using a kernel function (Bobb et al., 2015). This method allows estimation of nonlinear or nonadditive ER function for a set of correlated pollutants accounting for uncertainty.

Specifically, kernel machine regression is a data processing which is also known as kernel trick. The process is a mapping from the low-dimension data space to a new high-dimension space. The link of the two spaces is the kernel function. In this study we used the Gaussian kernel function because it is available for general conditions. However, it is valuable to point out that according to Mercer's theorem, each positive semi-definite function can perform as a kernel function. The general Gaussian kernel function is shown below as formula (1):

$$K(\mathbf{z}, \mathbf{z}') = e^{\left\{-\frac{1}{\rho}\sum_{m=1}^{M}(z_m - z'_m)^2\right\}} \quad (1)$$

where $\mathbf{z} = (z_1, ..., z_M)^T$ and $\mathbf{z}' = (z'_1, ..., z'_M)^T$ are the two $M \times 1$ vectors representing two pollutants' concentration of M days, respectively.

Posterior inclusion probabilities (PIPs) are calculated to conduct the variable selection process (Coull et al., 2015), with larger PIPs of a pollutant indicating the stronger association with health outcome.

To specify the model, we use $\mathbf{pol} = (\mathbf{c(CO)}, \mathbf{c(NO_2)}, \mathbf{c(NO_x)}, \mathbf{c(PM_{10})})$ as the matrix of the variables. For the convenience of expression here, we present $(\mathbf{c(CO)}, \mathbf{c(NO_2)}, \mathbf{c(NO_x)}, \mathbf{c(PM_{10})})$ as $(\mathbf{z_1}, \mathbf{z_2}, \mathbf{z_3}, \mathbf{z_4})$, while $\mathbf{z_i}$ was a 1461×1 vectors containing the corresponding pollutant's concentration through 1461 days (four years, 2008–2011) in the dataset. We defined $h(\mathbf{pol}) = \sum_{i,j=1}^{4} K(\boldsymbol{z_i}, \boldsymbol{z_j})$ while $K(\boldsymbol{z_i}, \boldsymbol{z_j})$ is the Gaussian kernel shown in formula (1). The model can be written as:

$$\log(E(deaths)) = h(c(CO), c(NO_2), c(NO_x), C(PM_{10})) + \boldsymbol{X_i^T \beta} \quad (2)$$

where X_i is a vector contains potential confounders and here X_i is the meteorological conditions. The prior distribution of β is set as the defaulted flat distribution.

The selection of the prior distribution is important for BKMR. It is advised to avoid overfitting or underfitting, which can easily cause oscillations, in the environmental health studies. Following this line, we performed a simulation study, which was demonstrated in supplementary materials.

We first conducted a simulation study in this experiment to study the performance of BKMR in the air pollution exposure-response researches. The simulation study also helped us to find a proper prior distribution in BKMR. Details of the simulation study can be found in the supplementary materials.

Given the potential lagged effect of ambient air pollutants on daily CVD mortality, we fit BKMR with 0–1, 0–2, 0–3, 0–4 days (MV01-04) moving average, for the cumulative effects of air pollutants. The curves of ER relationship and PIPs were fitted and calculated in the process of

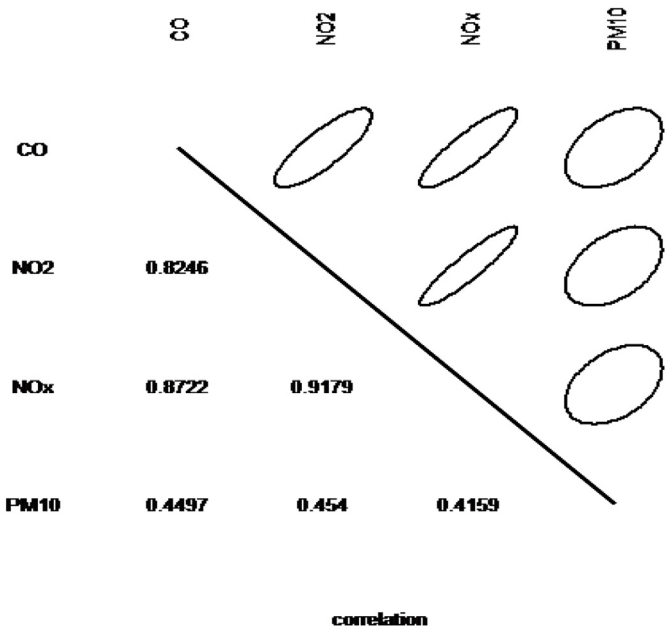

Fig. 1. Correlation between predictors in the simulation study.

BKMR simultaneously due to its Bayesian nature. Regarding the interaction analysis, we limited this exploration to two certain pollutants, varying one pollutant continuously while fixing the other pollutant at three given levels. The interaction of pollutants was evaluated by assessing the parallelism of the exposure-response curves of a certain pollutant at different level of the other given pollutant, in a series of bivariate-exposure-response curves. The long-term time trend and seasonal pattern of the time series data were controlled through modeling natural cubic spline of time and factor of day of week in BKMR models. The details were also introduced in simulation section in supplementary materials. The statistical analysis was performed using the R package 'bkmr' (Bobb et al., 2015). The statistical significance is set at 0.05.

3. Results

3.1. Simulation study

The results of regression demonstrate that BKMR performs very well in studying the ambient air pollutants. Fig. 1 shows the correlation between the four ambient air pollutants used in the simulation study. Table 2 shows the result of regression between h and $\tilde{h}$ (shown in supplementary materials), while S.Figs. 2–4 show the exposure-response relationship. PIPs are shown in Table 3. The supplementary material provides a more detailed description of the simulation study. From the result of the simulation study, we can see that BKMR performs well in all the different simulation scenarios.

3.2. Selection of prior distributions

We choose the non-informative prior in our analysis. The details of prior selection are provided in the supplementary materials.

Table 2
The Result of Regression Between h and $\tilde{h}$ in the Simulation Study.

Test Function	Intercept	Slope
h_1	0.002	0.9993
h_2	−0.025	0.9962
h_3	−0.0061	0.9991

Table 3
PIPs of pollutants in the simulation study.

Pollutants	PIPs	
CO	h1	1.000
	h2	1.000
	h3	1.000
NO_2	h1	0.000
	h2	0.999
	h3	1.000
NO_x	h1	0.000
	h2	1.000
	h3	0.000
PM_{10}	h1	0.000
	h2	0.000
	h3	0.000

3.3. Application

3.3.1. Descriptive results

A total of 145,477 deaths caused by CVD were recorded in this study from 2008 to 2011. Old people aged over 65 accounted for 81% of the total death. There are approximately 100 CVD deaths per day.

3.3.2. Association of single pollutants and the CVD deaths

From the result of PIPs, we found that the dominant pollutants strongly associated with cardiovascular mortality varied across the different moving average periods For MV01 and MV02, PM_{10} is the dominant ambient air pollutant. SO_2 also has strong positive effect during MV01 and MV02. However, when the moving average is extended to four days, that is MV04, $PM_{2.5}$ becomes the dominant pollutant. Of all the results obtained above, particle pollutants (i.e. PM_{10} and $PM_{2.5}$) showed stronger cardiovascular mortality effect when compared with gaseous pollutants (i.e. NO_2 and SO_2) (Table 4).

Figs. 2–5 demonstrated the ER relationship of independent effects of each pollutant after incorporating the collinearility among col-pollutants. For the result of MV01, there were approximately linear effect on CVD mortality for NO_2, $PM_{2.5}$, SO_2 and a slight nonlinear trend was observed for PM_{10} at higher concentration, as shown in Fig. 2. At MV02, linear effects of NO_2, $PM_{2.5}$, SO_2 and the slight nonlinear effect of PM_{10} persisted, but the ER relationship of NO_2 was reversed (Fig. 3). For longer moving average period (i.e. MV03 and MV04) shown in Figs. 4 and 5, there was an apparent nonlinear trend of ER relationship between CVD mortality and NO_2 and $PM_{2.5}$, whereas the ER curves for SO_2 and PM_{10} showed a linear trend. We note that NO_2 and $PM_{2.5}$ have the same trend on the ER relationship, while the trends of PM_{10} and SO_2 are similar for longer moving average periods.

3.3.3. Association of multiple pollutants and the CVD deaths

Fig. 6 shows the bivariate ER relationship using MV03, while S.Figs. 9–11 show the bivariate ER relationship during MV01, 02 and 04 for conciseness. The percentiles were fixed at 25th, 50th and 75th points of each pollutant. As depicted in Fig. 6, the ER curves for a given pollutant's exposure response relationship at three percentiles of NO_2 or SO_2 showed parallel pattern and were generally highly overlapped, suggesting that NO_2 or SO_2 would not modify the cardiovascular

Table 4
PIPs of pollutants in the application.

Pollutants	PIPs during moving average days			
	1 d	2 d	3 d	4 d
NO_2	0.5765	0.3910	0.5955	0.9693
PM_{10}	0.8325	0.6207	0.5960	0.6080
$PM_{2.5}$	0.7015	0.4857	0.7315	1.0000
SO_2	0.7585	0.5883	0.6415	0.6447

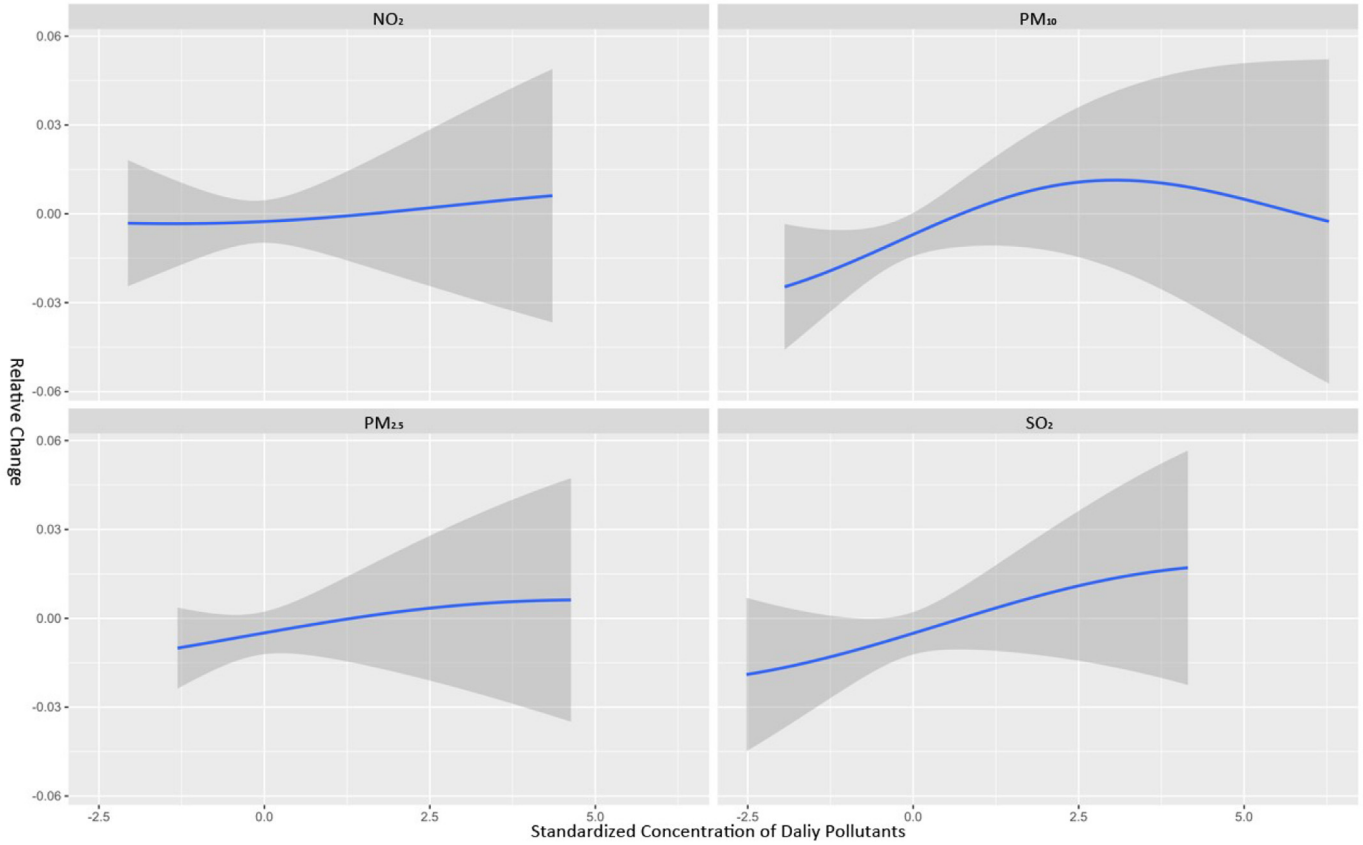

Fig. 2. The exposure-response relationship between moving average 0–1 days of single pollutants and CVD deaths.

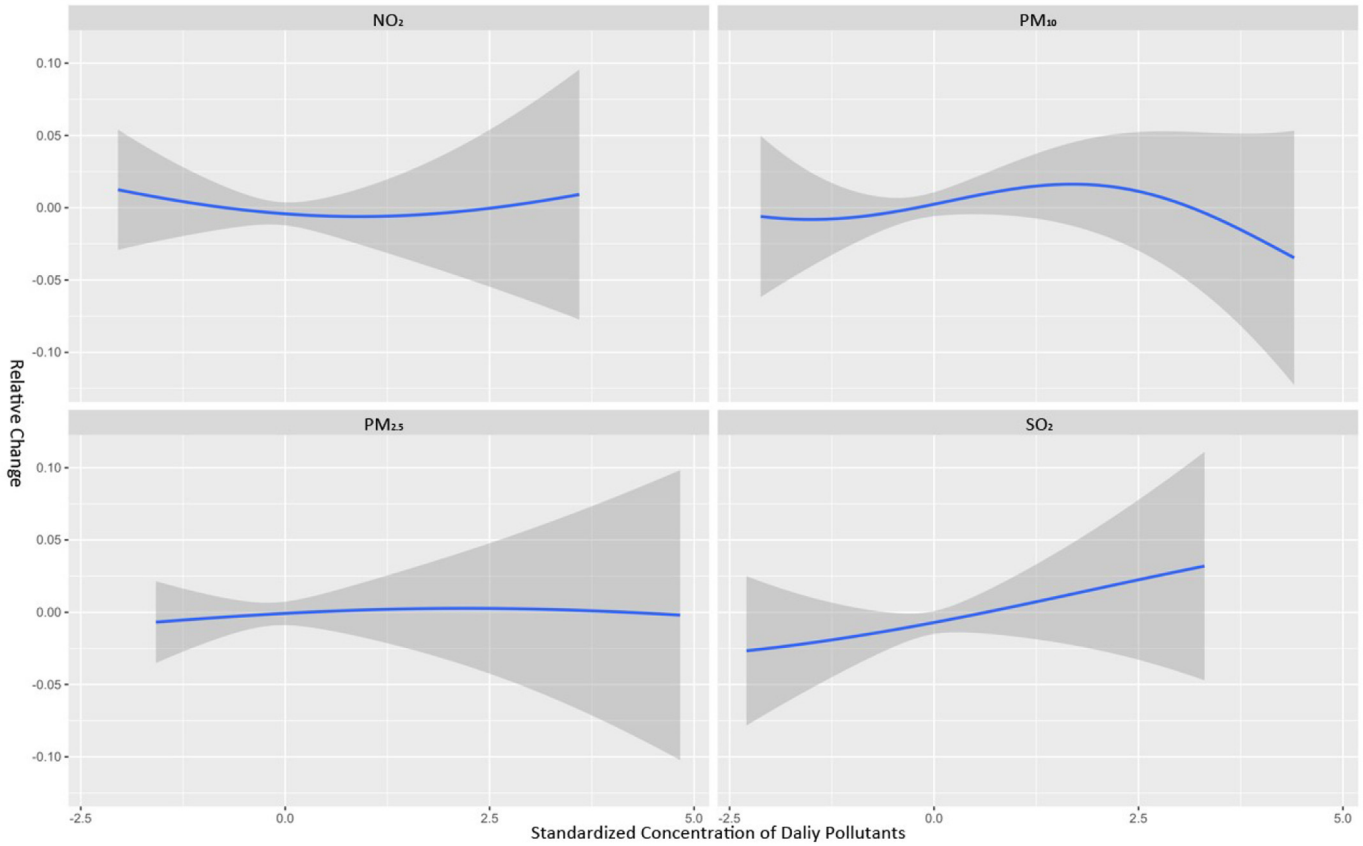

Fig. 3. The exposure-response relationship between moving average 0–2 days of single pollutants and CVD deaths.

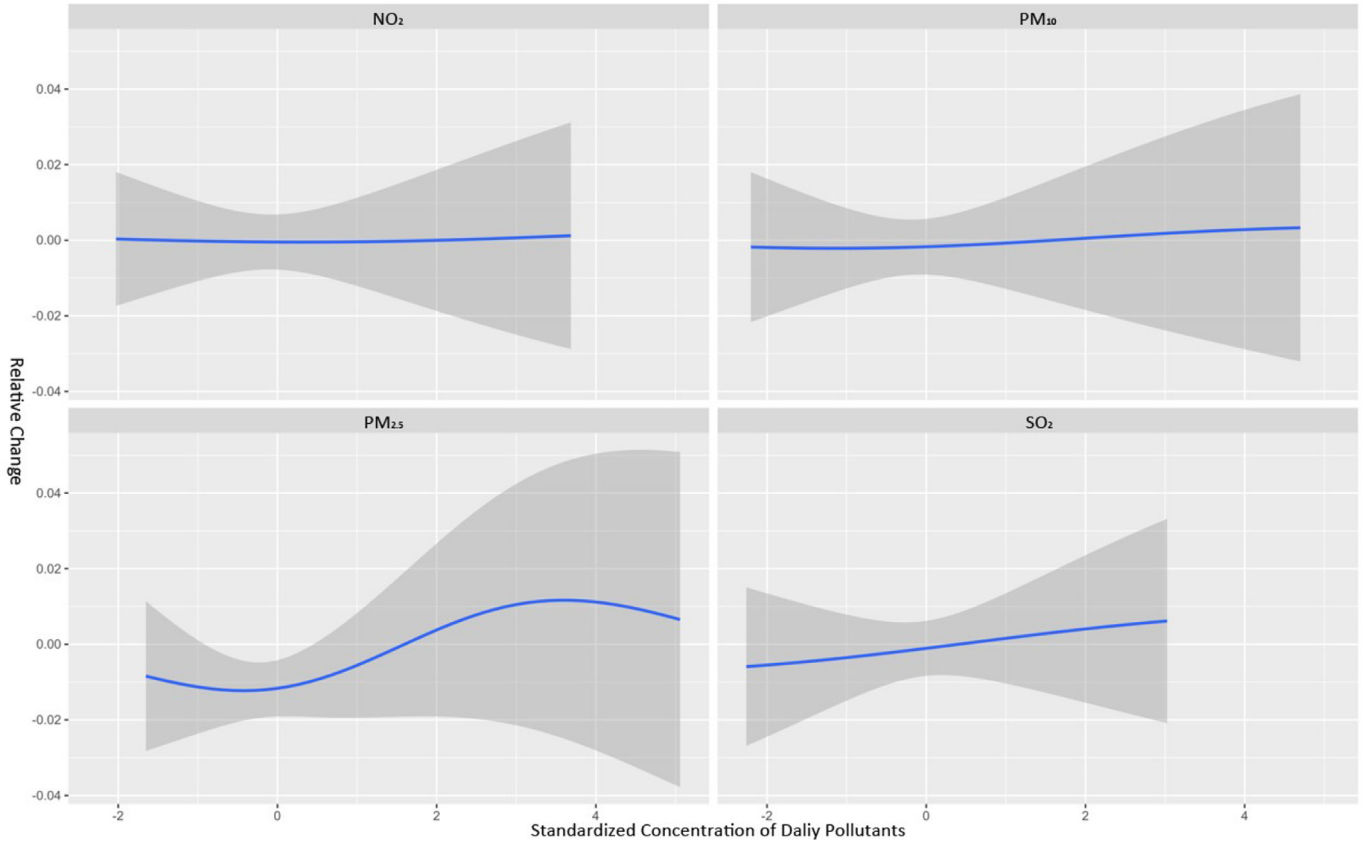

Fig. 4. The exposure-response relationship between moving average 0–3 days of single pollutants and CVD deaths.

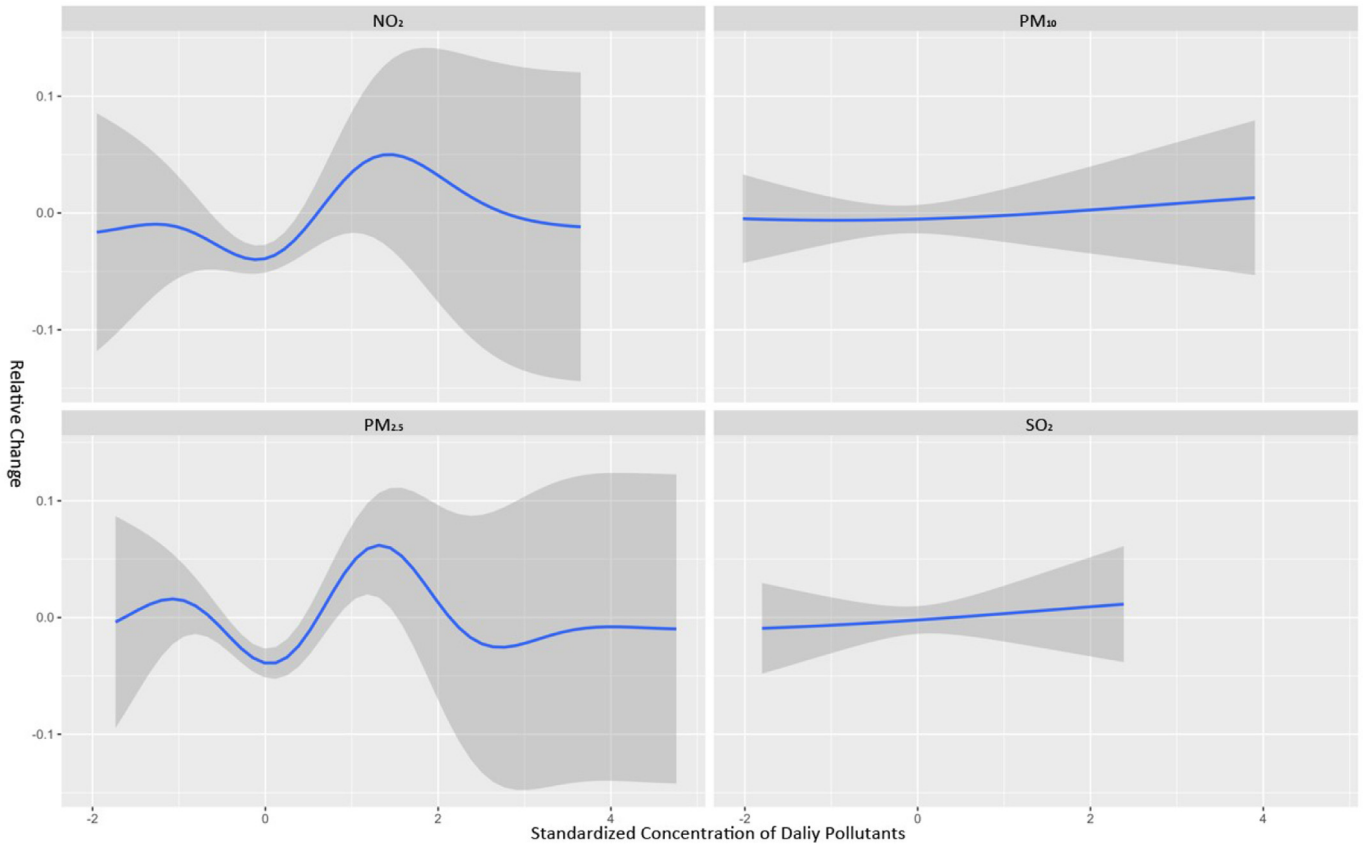

Fig. 5. The exposure-response relationship between moving average 0–4 days of single pollutants and CVD deaths.

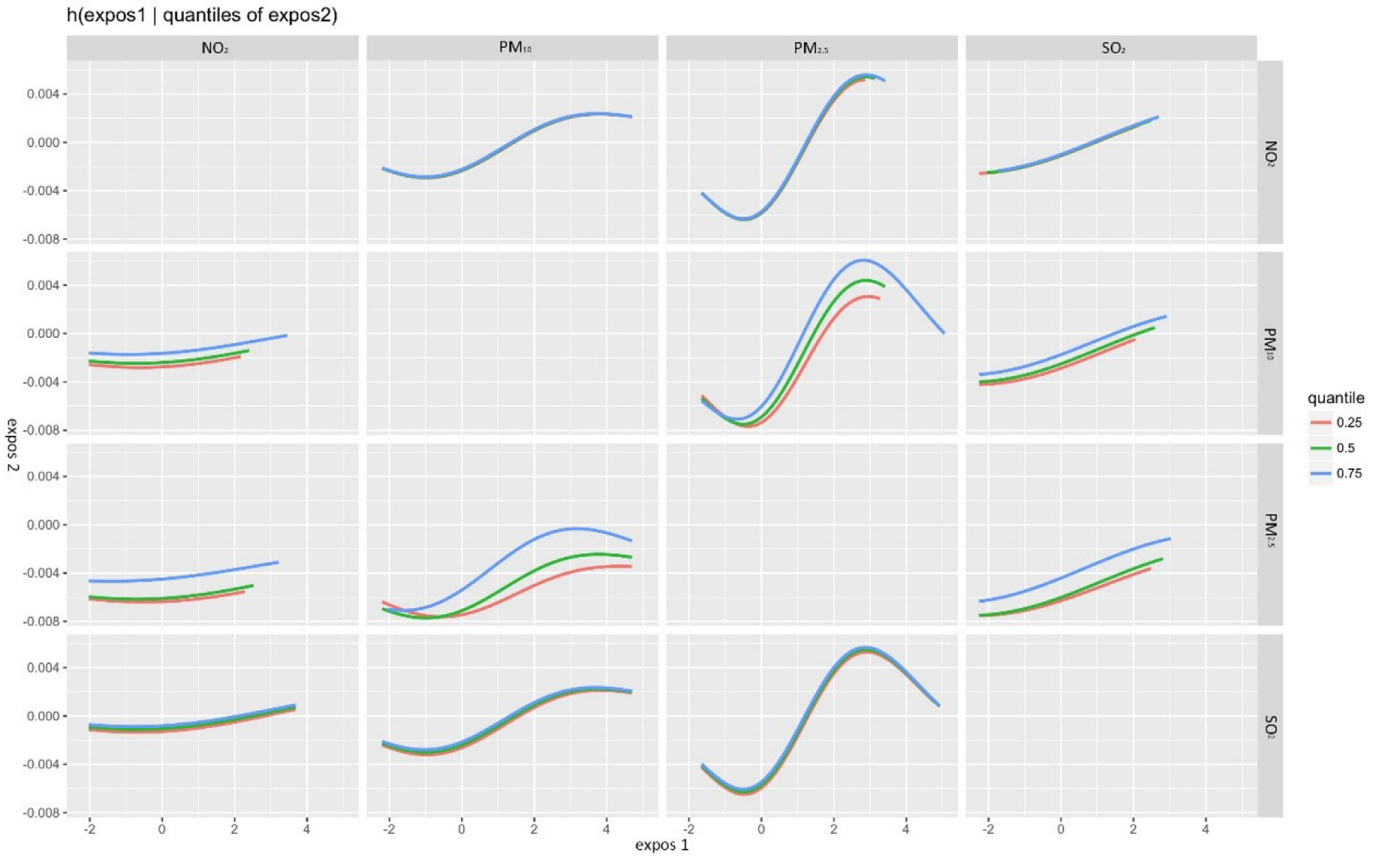

Fig. 6. The bivariate exposure-response relationship during moving average 0–3 days.

mortality effects of the other pollutants. Meanwhile, the ER curves of NO_2 and SO_2 at different percentiles of PM_{10} and $PM_{2.5}$ presented similar patterns. All these indicate the absence of interaction or synergetic effects between gaseous pollutants and particle matters. For the ER relationship of a given particle pollutant (i.e., $PM_{2.5}$ or PM_{10}) at the percentiles of the other particle pollutant, the curves present non-parallel trend, especially at higher concentration of the given pollutant. This result, at least via visually presentation in curves, indicated the potential interaction among particle matter.

However, the current version BKMR does not support the statistical significance test for the interaction. Similar patterns were also demonstrated in other moving averages in S.Figs. 9–11.

4. Discussion

To our best knowledge, this is the first study to use BKMR based on time series data to examine the non-linear relationship between ambient air pollutants and the CVD mortality as well as the potential synergetic effects among these pollutants. Our study indicated that the dominant pollutants vary by different moving average periods. For interaction exploration, we found no joint effect between particle pollutants (i.e. $PM_{2.5}$ and PM_{10}), gaseous pollutants (NO_2 and SO_2), as well as between NO_2 and SO_2, though there exists a potential synergetic effect between PM_{10} and $PM_{2.5}$. But we did not find the significant evidence for this interaction effect given the lack of available significance test in version of BKMR (Bobb et al., 2015).

Previous studies focusing on effect of single ambient air pollutants have shown that the four ambient air pollutants included in our study (i.e.NO_2, PM_{10}, $PM_{2.5}$, and SO_2) were associated with the increased risk of CVD mortality. For example, a study in 75 cities reported a 0.6% increase (95% CI, 0.5–0.7%) for non-accidental mortality caused by PM_{10} (Anderson et al., 2005). A meta-analysis study in four Asian cities, including Bangkok, Hong Kong, Shanghai and Wuhan, indicated that the excess non-accidental associated with a 10 $\mu g/m^3$ increase of SO_2 is 1.00% (95%CI, 0.75–1.24%) (Kan et al., 2010). Despite studies focusing on single pollutant can explore the relationship between exposure and health outcome, they are limited and unable to evaluate the dominant pollutants that show stronger effects on mortality in multi-pollutant context.

The interest of determining the effect of simultaneous multiple pollutants exposure on health outcome, and the identification of dominant pollutant has been growing in recent years. A research conducted in South Korea investigated the relationship between total mortality and multi-pollutant mixtures, including PM_{10}, NO_2, SO_2, and CO, found that the multi-pollutant mixtures can explain the health outcome much better than single pollutant (Hong et al., 1999). Another time series study conducted in U.S. which focused on the association between ambient air pollutants and mortality used supervised principal component analysis (SPCA) as the statistical method to address mixtures' effects (Roberts and Martin, 2006). In this SPCA study, researchers investigated a multi-pollutant mixture including O_3, NO_2, CO and SO_2 and reported that only O_3 contributed to the mortality significantly. Although these studies considered the multi-pollutant, there were still some limitations. The complex interactions among multi-pollutant mixtures were not taken into consideration due to the inherent defect of general statistical methods, such as generalized additive models (GAM) and dimension reduced approaches, such as principal component analysis (PCA) and the aforementioned SPCA (Davalos et al., 2017). Thus the reported pollutant which has caused adverse effect to the health outcome may not be the dominant pollutant. And these conventional approaches failed to disclose the full picture of the potential interaction among coexisted multiple pollutants both in terms of effects estimation and exploration of exposure response relationships.

BKMR is a flexible and versatile statistical approach that can effectively conduct the variable selection among toxicants by comparing PIPs (Coull et al., 2015). From the PIPs value in the result part (Table 4), we found that the four pollutants (i.e. NO_2, PM_{10}, $PM_{2.5}$, and SO_2) included in this study showed varying effects on CVD mortality by moving average ranging from 0 to 4 days. Specifically, PM_{10} and SO_2 showed a relative stronger effects at MV01-MV02 while the other two pollutants, NO_2 and $PM_{2.5}$, showed lagged effect and become dominant pollutant later. The dominant effects of PM_{10} and SO_2 only lasts for 2 days. This result is consistent with a research conducted in Thailand which fitted a Bayesian hierarchical statistical model. (Guo et al., 2014). NO_2 and $PM_{2.5}$ also contribute to CVD mortality during 1–2 days (Guo et al., 2014). As with the decline of the effect of PM_{10} and SO_2 on CVD mortality, NO_2 and $PM_{2.5}$ become dominant pollutants at longer moving average, especially during lagged 3–4 days (Table 4), showing stronger effect. Since these two pollutants are both highly traffic-related and shared some common emission sources, our results suggested that traffic related pollutants, marked as $PM_{2.5}$ and NO_2, might present stronger cardiovascular mortality related hazard during longer moving average. This indicates the control of traffic pollution may reduce the overall risk significantly. But whether this pattern persisted in long-term exposure, such as yearly exposure, should be determined in future cohort studies.

We also modeled the ER relationship between the ambient air pollutants and daily cardiovascular mortality while adjusting the collinearity among col-pollutant by using BKMR. Our results demonstrated a linear relationship during the MV01 when the concentration is not very high. This linear ER relationship is consistent with many of the previous studies. As the modeled exposure-response relationship of present study showed, the curves for NO_2 and $PM_{2.5}$ have very similar trends and lagged effects on CVD mortality. This might be related to the fact that NO_2 and $PM_{2.5}$ shared some common emission sources and studies also suggested that these two pollutants are highly relative and can be replaced by each other in some situation (Brook et al., 2007). Specifically, a previous study showed that the correlation between $PM_{2.5}$ and NO_2 is 0.54 (95%CI, 0.45–0.71), which is the highest among 16 ambient air pollutants and toxicants except NO (Brook et al., 2007), an analogous pollutant of NO_2. Another study conducted in Shanghai, China, employed Land Use Regression (LUR) found that NO_2 and $PM_{2.5}$ showed many similar characteristics, such as the two pollutants both anti-correlated with coastal proximity and correlated with industrial intensity and highway (Liu et al., 2016). In current study, we found that NO_2 and $PM_{2.5}$ have similar lagging effects on CVD mortality, which provides further evidence that NO_2 and $PM_{2.5}$ behave intertwined in the health damage caused by air pollution.

Aside from the above mentioned advantages in estimating the effects of the simultaneous multiple pollutants exposure and identifying the dominant pollutant, BKMR enables one to explore the potential interaction or synergetic effects among pollutants by comparing the slopes of estimated ER curves of a given pollutant at different levels of the other pollutant. This greatly facilitates the exploration of interaction among multiple pollutants. In our study, it is likely that there is no interaction between particle matters and gaseous pollutants because the ER curves of particle matter were highly parallel and even overlapped across specified levels of gaseous pollutant, and vice versa. The absence of interaction is also observed among gaseous pollutants. These results are in line with previous study in Hong Kong (Wong et al., 2002), where the interaction was assessed by testing the interaction terms, and its main result did not show the statistical significant interaction between SO_2 and PM_{10} in terms of cardiovascular mortality. However, two European studies reported the potential interaction between black smoke and SO_2 (Touloumi et al., 1996; Zmirou et al., 1996). The discrepancies might be due to the different concentrations of the pollutants in these cities as well as different population susceptibility. In addition, the differences might be potentially attributed to the statistics approaches, since our results were generated after adjusting the collinearity among col-pollutant via BKMR.

When assessing the possible interaction between PM_{10} and $PM_{2.5}$, we found that the ER curves of PM_{10} presented an non-parallel trend at different levels of $PM_{2.5}$, showing a steeper slope of ER curve at higher percentile of conditioned pollutant. Similar patterns were also found when PM_{10} was fitted in the model as the conditioned pollutant as well. Since no studies have explored the interaction among particle matters before, we hypothesized that this visually detected interaction might reflect the synergetic effects between coarse particle ($PM_{2.5\text{-}10}$) and $PM_{2.5}$. Note that the major difference between PM_{10} and $PM_{2.5}$ is their aerodynamic equivalent diameter or size and the $PM_{2.5}$ dominates the major proportion of PM_{10}. Thus the simultaneous exposure to PM_{10} and $PM_{2.5}$ actually represent the co-exposure to $PM_{2.5\text{-}10}$ and $PM_{2.5}$. Studies have reported that $PM_{2.5\text{-}10}$ also contributed to the increased risk of cardiovascular mortality (Lee et al., 2015; Malig and Ostro, 2009). Some part of $PM_{2.5\text{-}10}$ will first deposit in the bronchioles or alveoli instead of entering the circulation system immediately after inhalation which $PM_{2.5}$ does. Thus $PM_{2.5\text{-}10}$ may cause local lung oxidative stress and inflammation. (Brook et al., 2010; Franklin et al., 2015). The local oxidative stress and inflammation would then contribute to the subsequent systematic inflammation and oxidative stress. By this point of view, the $PM_{2.5\text{-}10}$ would initiate the impairment of cardiovascular system once both $PM_{2.5\text{-}10}$ and $PM_{2.5}$ were inhaled. However, to date, we have not found support in either experiment studies or epidemiologic studies to corroborate our hypothesis. In addition, the observed interaction among PM_{10} and $PM_{2.5}$ was merely based on visually detection rather than the statistical significance test, and the data of $PM_{2.5}$ used in our studies was retrieved from one fixed monitoring site. These aspects together contribute to uncertainty of our detected interaction. Further studies, both in toxicology and epidemiology, are needed to address interaction among ambient air pollutants given that their joint effects would be more significant than that related to single pollutant.

There are some limitations in this study. First, although BKMR is very flexible, it is also very intense in computation. The author of package 'bkmr' also points out this disadvantage of BKMR in her report (Coull et al., 2015). Second, the data of $PM_{2.5}$ comes from the American Embassy located in Chaoyang district in the central area of Beijing, thus the $PM_{2.5}$ levels do not represent the real conditions of the whole city. Last, we only consider first order interaction effects, though higher order effects might disclose more insightful information. As mentioned above, all this might provide limited information in our study.

5. Conclusion

By using BKMR, we examined the effects of multiple pollutants exposure on CVD mortality, identified the dominant pollutants at different moving average. Moreover, our study explored the potential interaction among ambient air pollutants. Generally we found that the identified dominant pollutants varied by tested moving average, with PM_{10} was identified as the dominant pollutant during MV01 and MV02, and NO_2 and $PM_{2.5}$ become dominant during MV03 and MV04. For the interaction analysis, we found the potential synergetic effect between $PM_{2.5}$ and PM_{10} in terms of daily CVD mortality. But the lack of available significance test in BKMR hinders us from drawing the conclusion the existence of statistical interaction. Further studies are needed to confirm our findings.

Acknowledgment

We sincerely thank all the people who offered their aid in the data collection and management of the present study. We would also thank Yijun Zhou for his endeavor on the modeling calibration. This study was supported by the funding from the Gong-Yi Program of the Chinese Ministry of Environmental Protection (Grant Number 200909016), the China Medical Board (Grant Number 15-230) and the Chinese Academy of Medical Science Innovation Fund for Medical Sciences (Grant

Number 2017-I2M-1-009). The authors declare they have no competing financial interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atmosenv.2018.05.034.

References

Anderson, H.R., Atkinson, R.W., Peacock, J.L., Sweeting, M.J., Marston, L., 2005. Ambient particulate matter and health effects: publication bias in studies of short-term associations. Epidemiology (Cambridge, Mass.) 16, 155–163.

Bobb, J.F., Valeri, L., Claus Henn, B., Christiani, D.C., Wright, R.O., Mazumdar, M., Godleski, J.J., Coull, B.A., 2015. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics (Oxford, England) 16, 493–508.

Braun, J.M., Gennings, C., Hauser, R., Webster, T.F., 2016. What can epidemiological studies tell us about the impact of chemical mixtures on human health? Environ. Health Perspect. 124, A6–A9.

Brook, J.R., Burnett, R.T., Dann, T.F., Cakmak, S., Goldberg, M.S., Fan, X., Wheeler, A.J., 2007. Further interpretation of the acute effect of nitrogen dioxide observed in Canadian time-series studies. J. Expo. Sci. Environ. Epidemiol. 17 (Suppl. 2), S36–S44.

Brook, R.D., Rajagopalan, S., Pope 3rd, C.A., Brook, J.R., Bhatnagar, A., Diez-Roux, A.V., Holguin, F., Hong, Y., Luepker, R.V., Mittleman, M.A., Peters, A., Siscovick, D., Smith Jr., S.C., Whitsel, L., Kaufman, J.D., 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121, 2331–2378.

Cohen, A.J., Brauer, M., Burnett, R., Anderson, H.R., Frostad, J., Estep, K., Balakrishnan, K., Brunekreef, B., Dandona, L., Dandona, R., Feigin, V., Freedman, G., Hubbell, B., Jobling, A., Kan, H., Knibbs, L., Liu, Y., Martin, R., Morawska, L., Pope 3rd, C.A., Shin, H., Straif, K., Shaddick, G., Thomas, M., van Dingenen, R., van Donkelaar, A., Vos, T., Murray, C.J.L., Forouzanfar, M.H., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet (London, England) 389, 1907–1918.

Coull, B.A., Bobb, J.F., Wellenius, G.A., Kioumourtzoglou, M.A., Mittleman, M.A., Koutrakis, P., Godleski, J.J., 2015. Part 1. Statistical Learning Methods for the Effects of Multiple Air Pollution Constituents. Research report (Health Effects Institute). pp. 5–50.

Davalos, A.D., Luben, T.J., Herring, A.H., Sacks, J.D., 2017. Current approaches used in epidemiologic studies to examine short-term multipollutant air pollution exposures. Ann. Epidemiol. 27, 145–153 e141.

Di, Q., Wang, Y., Zanobetti, A., Wang, Y., Koutrakis, P., Choirat, C., Dominici, F., Schwartz, J.D., 2017. Air pollution and mortality in the medicare population. N. Engl. J. Med. 376, 2513–2522.

Dominici, F., Peng, R.D., Barr, C.D., Bell, M.L., 2010. Protecting human health from air pollution: shifting from a single-pollutant to a multipollutant approach. Epidemiology (Cambridge, Mass.) 21, 187–194.

Franklin, B.A., Brook, R., Arden Pope 3rd, C., 2015. Air pollution and cardiovascular disease. Curr. Probl. Cardiol. 40, 207–238.

Guo, Y., Li, S., Tawatsupa, B., Punnasiri, K., Jaakkola, J.J., Williams, G., 2014. The association between air pollution and mortality in Thailand. Sci. Rep. 4, 5509.

Hong, Y.C., Leem, J.H., Ha, E.H., Christiani, D.C., 1999. PM(10) exposure, gaseous pollutants, and daily mortality in Inchon, South Korea. Environ. Health Perspect. 107, 873–878.

Huang, C., Moran, A.E., Coxson, P.G., Yang, X., Liu, F., Cao, J., Chen, K., Wang, M., He, J., Goldman, L., Zhao, D., Kinney, P.L., Gu, D., 2017 Oct 24. Potential cardiovascular and total mortality benefits of air pollution control in urban China. Circulation 136 (17), 1575–1584.

Kan, H., Wong, C.M., Vichit-Vadakan, N., Qian, Z., 2010. Short-term association between sulfur dioxide and daily mortality: the Public Health and Air Pollution in Asia (PAPA) study. Environ. Res. 110, 258–264.

Lee, H., Honda, Y., Hashizume, M., Guo, Y.L., Wu, C.F., Kan, H., Jung, K., Lim, Y.H., Yi, S., Kim, H., 2015. Short-term exposure to fine and coarse particles and mortality: a multicity time-series study in East Asia. Environmental pollution (Barking, Essex : 1987) 207, 43–51.

Liu, C., Henderson, B.H., Wang, D., Yang, X., Peng, Z.R., 2016. A land use regression application into assessing spatial variation of intra-urban fine particulate matter (PM2.5) and nitrogen dioxide (NO2) concentrations in City of Shanghai, China. Sci. Total Environ. 565, 607–615.

Malig, B.J., Ostro, B.D., 2009. Coarse particles and mortality: evidence from a multi-city study in California. Occup. Environ. Med. 66, 832–839.

Mustafic, H., Jabre, P., Caussin, C., Murad, M.H., Escolano, S., Tafflet, M., Perier, M.C., Marijon, E., Vernerey, D., Empana, J.P., Jouven, X., 2012. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. Jama 307, 713–721.

Pachon, J.E., Balachandran, S., Hu, Y., Mulholland, J.A., Darrow, L.A., Sarnat, J.A., Tolbert, P.E., Russell, A.G., 2012. Development of outcome-based, multipollutant mobile source indicators. J. Air Waste Manag. Assoc. 62, 431–442 (1995).

Rich, D.Q., Kipen, H.M., Huang, W., Wang, G., Wang, Y., Zhu, P., Ohman-Strickland, P., Hu, M., Philipp, C., Diehl, S.R., Lu, S.E., Tong, J., Gong, J., Thomas, D., Zhu, T., Zhang, J.J., 2012. Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. Jama 307, 2068–2078.

Roberts, S., 2006. A new model for investigating the mortality effects of multiple air pollutants in air pollution mortality time-series studies. J. Toxicol. Environ. Health Part A 69, 417–435.

Roberts, S., Martin, M.A., 2006. Investigating the mixture of air pollutants associated with adverse health outcomes. Atmos. Environ. 40, 984–991.

Sacks, J.D., Ito, K., Wilson, W.E., Neas, L.M., 2012. Impact of covariate models on the assessment of the air pollution-mortality association in a single- and multipollutant context. Am. J. Epidemiol. 176, 622–634.

Sarnat, J.A., Schwartz, J., Suh, H.H., 2001. Fine particulate air pollution and mortality in 20 U.S. cities. N. Engl. J. Med. 344, 1253–1254.

Schildcrout, J.S., Sheppard, L., Lumley, T., Slaughter, J.C., Koenig, J.Q., Shapiro, G.G., 2006. Ambient air pollution and asthma exacerbations in children: an eight-city analysis. Am. J. Epidemiol. 164, 505–517.

Touloumi, G., Samoli, E., Katsouyanni, K., 1996. Daily mortality and "winter type" air pollution in Athens, Greece–a time series analysis within the APHEA project. J. Epidemiol. Community Health 50 (Suppl. 1), s47–51.

Wong, T.W., Tam, W.S., Yu, T.S., Wong, A.H., 2002. Associations between daily mortalities from respiratory and cardiovascular diseases and air pollution in Hong Kong, China. Occup. Environ. Med. 59, 30–35.

Yang, Y., Li, R., Li, W., Wang, M., Cao, Y., Wu, Z., Xu, Q., 2013. The association between ambient air pollution and daily mortality in Beijing after the 2008 olympics: a time series study. PLoS One 8, e76759.

Zanobetti, A., Austin, E., Coull, B.A., Schwartz, J., Koutrakis, P., 2014. Health effects of multi-pollutant profiles. Environ. Int. 71, 13–19.

Zmirou, D., Barumandzadeh, T., Balducci, F., Ritter, P., Laham, G., Ghilardi, J.P., 1996. Short term effects of air pollution on mortality in the city of Lyon, France, 1985-90. J. Epidemiol. Community Health 50 (Suppl. 1), S30–S35.