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Sex differences in associations of fine particulate matter with non-accidental deaths: an ecological time-series study

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Abstract

Sex differences in the impact of exposure to air pollution have been reported previously and epidemiological studies indicate that fine particulate matter ($PM_{2.5}$) effects on nonaccidental death are modified by sex; however, the results are not conclusive. To introduce a new method incorporating the monotone nonlinear relationship between $PM_{2.5}$ and deaths to reveal the sex difference in the relationship, we illustrated the use of the constrained generalized additive model (CGAM) to investigate the sex difference in the effects of $PM_{2.5}$ on nonaccidental deaths in Shanghai, China. Information on daily non-accidental deaths, air pollution, meteorological data, and smoking prevalence between 1 January 2012 and 31 December 2014 was obtained in Shanghai. The CGAM was used to assess the association of interaction between sex and daily $PM_{2.5}$ concentrations with daily nonaccidental deaths, adjusting for weather type and smoking rate. A 2-week lag analysis was conducted as a sensitivity analysis. During the study period, the total number of non-accidental deaths in Shanghai was 336,379, with a daily mean of 163 deaths and 144 deaths for men and women, respectively. The average daily concentration of $PM_{2.5}$ in Shanghai was 55.0 μg/m^3 during the same time period. Women showed a lower risk for non-accidental death (risk ratio (RR) = 0.892, 95% confidence interval (CI): 0.802–0.993). Compared with men, the risk for nonaccidental death in relation to increasing $PM_{2.5}$ concentration was smaller in women (RR = 0.998, 95% CI: 0.996–1.000, per 10 μg/m^3 increase in $PM_{2.5}$ concentration. The difference is consistent during the two lag weeks and more obvious when adjusting for the interaction between $PM_{2.5}$ concentration and smoking prevalence. The effects of $PM_{2.5}$ on daily nonaccidental death are different between men and women in Shanghai, China, and women tend to have a lower risk. The underlying mechanisms of the sex difference of $PM_{2.5}$ effects on death need further investigation. The method displayed in the manuscript can be used for other environmental stressors as well.

Keywords Fine particulate matter · $PM_{2.5}$ · Nonaccidental death · Ecological study · Time-series study · Constrained generalized additive model

Introduction

According to the latest urban air quality database of the World Health Organization (WHO), more than 80% of people living in urban areas that monitor air pollution are exposed to air quality levels with pollutants exceeding the WHO's limits (World Health Organization 2016). The greatest impact is among populations in low-income cities. Among the cities with a population larger than 100,000 in low- and middle-income countries, 98% do not meet WHO air quality guidelines (World Health Organization 2016). Even in high-income countries, the percentage is as high as 56% (Osseiran and Chriscaden 2016). Air pollution has a substantial impact on human health and has become a global public health risk (Orellano et al. 2020).

Fine particulate matter or particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) is a

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major air pollutant, which has been associated with multiple adverse effects on human health, especially on the respiratory and circulatory systems. The short-term effects of $PM_{2.5}$ on human health have been reported in numerous epidemiological studies (Apte et al. 2015; Janssen et al. 2013; Kloog et al. 2013), and the effects vary by air pollution levels, composition of $PM_{2.5}$, geographic location, as well as demographic characteristics (Brauer et al. 2016).

Epidemiologic studies have provided some evidence indicating sex differences in the relationship between short-term $PM_{2.5}$ exposure and various health effects (Bell et al. 2015). According to a narrative literature review, air pollutants, including $PM_{2.5}$, nitrogen dioxide, and ozone, exerted stronger impact in boys than in girls (Clougherty 2010). There are more studies of adults reporting higher magnitude effects among women (Clougherty 2010). However, there are also studies suggesting that women might be more susceptible to $PM_{2.5}$ for some respiratory and cardiovascular causes (Bell et al. 2015), and the negative effect on cognitive performance is stronger for men than for women (Chen et al. 2017b). Although results are not conclusive, epidemiological studies indicate that air pollution effects on health are significantly modified by sex (Kan et al. 2008). However, it is still unclear whether socially derived sex-specific exposures and/or sex-linked physiological differences contribute to the modifications. Sex analysis receives growing attention in air pollution epidemiology, which aims to differentiate the biological differences and the social ones between genders, and illuminate possible sources of the differences (Clougherty 2010).

In our previous study, we investigated the association between $PM_{2.5}$ exposure and nonaccidental mortality in Shanghai, China, and found statistically significantly higher magnitude associations in women than in men when adjusting for age and age-specific smoking rate (Fang et al. 2017). Possible reasons for such a pattern might include sex hormones which have a function in the smoking-related morbidity and mortality and women are suggested having greater risk (Allen et al. 2014). However, in that study, we did not consider the interaction between sex and $PM_{2.5}$, and considered the associations of $PM_{2.5}$ and smoking with nonaccidental deaths as linear (Fang et al. 2017). Therefore, in this study, we applied a constrained generalized additive model (CGAM) analysis, including an interaction term between sex and $PM_{2.5}$ exposure and nonlinear exposure-response relationships between $PM_{2.5}$ and smoking and death (Li et al. 2019), to further investigate the sex difference in the effects of $PM_{2.5}$ on nonaccidental death. Due to the relative old and limited data, the purpose of the current study is not to duplicate the previous methods and findings, but to introduce a new method incorporating the monotone nonlinear relationship between $PM_{2.5}$ and deaths to reveal the relative rarely investigated sex difference in the relationship. The method presented in the paper can be applied to other environmental stressors as well.

Methods

Study setting

The study is an ecological time-series study using the data from a population causes of death register between January 1st, 2012, and December 31st, 2014, in Shanghai, China. Daily average $PM_{2.5}$ concentrations and meteorological conditions were also obtained during the same time period.

Shanghai is the largest and the most populous city in east China, with longitude and latitude of 121° E and 31° N, located in the Yangtze River Delta Region. It has a territory of about 6340 km^2, and an average permanent resident population of around 24.05 million during the study period (Shanghai Bureau of Statistics 2013, Shanghai Bureau of Statistics 2014; Shanghai Bureau of Statistics 2015).

Data collection

The data collection of the study has been described in detail elsewhere (Fang et al. 2017; Leepe et al. 2019; Tian et al. 2020). In brief, hourly $PM_{2.5}$ concentrations in 2012 were obtained from the United States Consulate General in Shanghai, and daily average $PM_{2.5}$ concentrations calculated from hourly data in 2013 and 2014 were obtained from the Shanghai Meteorological Bureau. The data were collected from the same single air monitor during the study period to present the $PM_{2.5}$ level for the entire city. The consistency of the $PM_{2.5}$ data from the two sources has been verified by a previous study (Liang et al. 2016). Daily weather meteorological data during the same period were obtained from the Shanghai Meteorological Bureau. To better investigate the interaction between PM2.5 and weather conditions, we categorized the observed days into synoptic weather types (SWTs) as proposed previously (Kalkstein et al. 1987). This approach categorizes weather patterns using clustering technique and offers categories that represent groupings of meteorological variables as they actually occur at a locale. SWT comprises more than just humidity, temperature, and diurnal temperature; instead, it includes the already known and potentially unknown meteorological characteristics relevant to mortality. If we only include individual meteorological variables as covariates in the regression models, bias could be produced in the model because of the exclusion of other variables. In the current study, weather conditions were categorized into six SWT, including hot dry, warm humid, cold dry, cool dry, cool humid, and cold humid, based on the cluster analysis using 18 meteorological variables. The details of the categorization were described previously (Fang et al. 2017). Daily nonaccidental mortality (identified using the International Classification of Diseases and Related Health Problems, version 10 (ICD-10) codes: A00-R99) data in Shanghai during the study period were obtained from the Causes of Death

Register of Shanghai (CDRS) provided by the Shanghai Municipal Center for Disease Control and Prevention (SCDC). Population level smoking rates by 5-year age groups were also obtained from SCDC. Nonaccidental mortality was represented using daily death counts for nonaccidental reasons. Because the total population was relatively stable during the study period, we treated it as if it remained unchanged to produce mortality rates.

Statistical analysis

Descriptive statistical methods were used to describe the characteristics of the variables. A CGAM was used to assess the interaction of $PM_{2.5}$ exposure and sex on daily non-accidental deaths, adjusting for temperature, SWT, and time trend. In the CGAM, the logarithm was used as the link function, and the Poisson distribution was the assumed probability distribution of the daily nonaccidental deaths (Liao and Meyer 2019). In a CGAM, we may specify the shapes of the smooth functions, including smooth or isotonic, as well as increasing, decreasing, convex, or concave. The constraints allow us to model the nonlinear relationships more in line with reality, such as the reversed J-shape relationship of $PM_{2.5}$ with mortality (Li et al. 2019), capturing therefore the sex-related difference more accurately. In the CGAM used in the current study, an increasing shape-restriction was used for the smoothing nonlinear association of $PM_{2.5}$ with daily nonaccidental mortality, and smoothing nonlinear associations without restrictions were assumed for time and temperature. The number of knots for the smoothness was selected based on the cone information criterion (CIC) (Meyer 2013; Oliva Avilés 2018). The sex difference in the $PM_{2.5}$ effects on mortality was investigated by including an interaction term between sex and $PM_{2.5}$ in the CGAM and presented using risk ratio (RR). The analysis was also adjusted for day of week (DOW) and average age of the daily deaths. National holidays were assigned as Saturday or Sunday whichever was the nearest. A nonlinear association of population-standardized smoking rate with daily nonaccidental deaths was also added with an increasing shape-restriction.

The CGAM that linked the number of daily deaths and the explanatory variables can be expressed as:

$$\begin{aligned}\log(E(y)) = \beta_0 + s.incr(PM_{2.5}) + s.incr(\text{smoking}) \\ + s(t) + s(\text{Temp}) + \beta_1 \cdot Age + \beta_2 \cdot \text{Sex} \\ + \beta_3 \cdot \text{Sex} \cdot incr(PM_{2.5}) + \beta_4 \cdot SWT \\ + \beta_5 \cdot DOW\end{aligned}$$

where $E(y)$ refers to expected number of daily deaths, β_0 is the baseline mortality rate, $s.incr(PM_{2.5})$ and $s.incr(\text{smoking})$ denote the nonlinear smoothing increasing effects of $PM_{2.5}$ and smoking, $s(t)$ denotes the nonlinear smoothing time trend of the daily deaths, $s(\text{Temp})$ denotes the nonlinear smoothing effects of temperature, and β_1–β_5 are coefficients for age, sex, interaction between sex and $PM_{2.5}$, SWT, and DOW, respectively.

As a sensitivity analysis, we also examined the interaction of sex with single-day lag and weighted moving average of $PM_{2.5}$ concentrations up to 2 weeks in the sensitivity analysis (Mahajan et al. 2018). A nonlinear monotone increasing interaction term between smoking rate and PM2.5 concentration was also included in the models as another sensitivity analysis. To further investigate whether the interaction effect between sex and $PM_{2.5}$ was modified by age or different between causes of death, we conducted stratified analyses for age groups (< 40 years, ≥ 40, and < 60 years, ≥ 60, and < 80 years, and ≥ 80 years) and four specific causes of deaths, including respiratory disease (ICD-10 codes J00–J99), cardiovascular disease (ICD-10 codes I00–I52, I70–I79), cerebrovascular disease (ICD-10 codes I60–I69), and other circulatory system diseases (I80–I99).

Because there were only 5 of 1096 days having missing values (missing rate < 0.5%), the listwise deletion method was used for handling missing data. All statistical analyses were performed in the software R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), and the CGAM analysis was achieved using the package *cgam* in R (Liao and Meyer 2019). Two-sided statistical tests were performed, and a RR with a P value < 0.05 was considered statistically significant.

Results

Characteristics of nonaccidental deaths and $PM_{2.5}$ concentration

During the study period, a total of 336,379 nonaccidental deaths occurred in Shanghai, with a mean of 307 daily deaths. About 53% of these deaths were men and the average ages at death were 74.9 and 79.3 years for men and women, respectively (Table 1).

The detailed results of PM2.5 concentrations and weather conditions during the study period were published previously (Fang et al. 2017; Tian et al. 2020). Overall, the average daily concentration of PM2.5 in Shanghai was 55.0 μg/m3, with a similar seasonal trend as the daily nonaccidental deaths (i.e., high values in cold seasons and low values in warm seasons) (Tian et al. 2020).

Sex difference in effect of $PM_{2.5}$ on nonaccidental mortality

When considering the nonlinear associations of $PM_{2.5}$, temperature, and smoking with nonaccidental death, and adjusting weather types and day of week, statistically

Table 1 Characteristics of nonaccidental deaths in Shanghai, China, 2012–2014

Variables	Men	Women
Total numbers of nonaccidental deaths during the study period (%)	178,786 (53.1%)	157,593 (46.9%)
Average population (million) during the study period (%)	12.53 (52.1%)	11.52 (47.9%)
Average daily death during the study period (SD)	163 (27)	144 (27)
Average age (years) at death (SD)	74.9 (13.0)	79.3 (11.7)
Population-standardized smoking rate of the deceased people (SD)	29.71% (15.25%)	0.92% (0.71%)

significant difference in $PM_{2.5}$ effect on nonaccidental death was found between women and men (RR = 0.892, 95% confidence interval (CI): 0.802–0.993 for women, and RR = 0.998, 95% CI: 0.996–1.000 for the interaction of women and $PM_{2.5}$, respectively) (Table 2). A slightly reversed J shape relationship between $PM_{2.5}$ and nonaccidental deaths among men and women was observed (Fig. 2). The average increases in RRs (per 10 μg/m^3 increase in $PM_{2.5}$ concentration) of $PM_{2.5}$ at the mean $PM_{2.5}$ level (55 μg/m^3) during the study period in Shanghai were 0.018 (95% CI: 0.017–0.019) and 0.016 (95% CI: 0.015–0.017) for men and women, respectively.

SWT, synoptic weather type

The predicted numbers of daily nonaccidental deaths by day and $PM_{2.5}$ concentration, and by temperature and $PM_{2.5}$ concentration are shown in the 3D perspective plots in Fig. 1. Daily nonaccidental deaths fluctuated with season and increased with PM.2.5 concentration (Fig. 1a), and a U-shape exposure-response relationship was observed between temperature and daily nonaccidental deaths (Fig. 1b). The predicted values by the CGAM indicate that 66.2% of the deviance can be explained by the model.

A low magnitude but statistically significant interaction was found between sex and $PM_{2.5}$ concentration, i.e., compared with men, the risk ratio for nonaccidental death in relation to increasing $PM_{2.5}$ concentration was smaller in women (Fig. 2). Per 10 μg/m^3 increase in $PM_{2.5}$ concentration, the RR (0.998, 95% CI: 0.996–1.000) was 0.2% smaller for women, compared to men (Table 2). When including the nonlinear interaction term between smoking rate and $PM_{2.5}$ concentration in the model, although the conditional mortality rate for women was higher than that of men, the increased risk for non-accidental death per 10 μg/m^3 increase in $PM_{2.5}$ concentration for women compared to men was even lower (RR = 0.983 for the interaction of women and $PM_{2.5}$, 95% CI: 0.979–0.988, $P < 0.001$).

Table 2 Risk ratios of sex and its interaction with $PM_{2.5}$ for nonaccidental mortality

	Risk ratio (RR)	95% confidence interval (CI)		*P* value
		Lower limit	Upper limit	
Age	1.025	1.021	1.029	< 0.001
Female	0.892	0.802	0.993	0.036
Female × $PM_{2.5}$ (per 10 μg/m^3)	0.998	0.996	1.000	0.010
SWT				
Hot dry	Reference			
Warm humid	0.996	0.980	1.012	0.596
Cold dry	0.979	0.956	1.003	0.090
Cool dry	1.006	0.988	1.025	0.486
Cool humid	1.044	1.025	1.064	<0.001
Cold humid	1.010	0.986	1.035	0.409
Day of week				
Sunday	Reference			
Monday	1.017	1.004	1.030	0.009
Tuesday	1.011	0.998	1.024	0.110
Wednesday	1.013	1.000	1.026	0.050
Thursday	1.006	0.993	1.019	0.358
Friday	1.004	0.991	1.017	0.598
Saturday	0.997	0.984	1.010	0.624

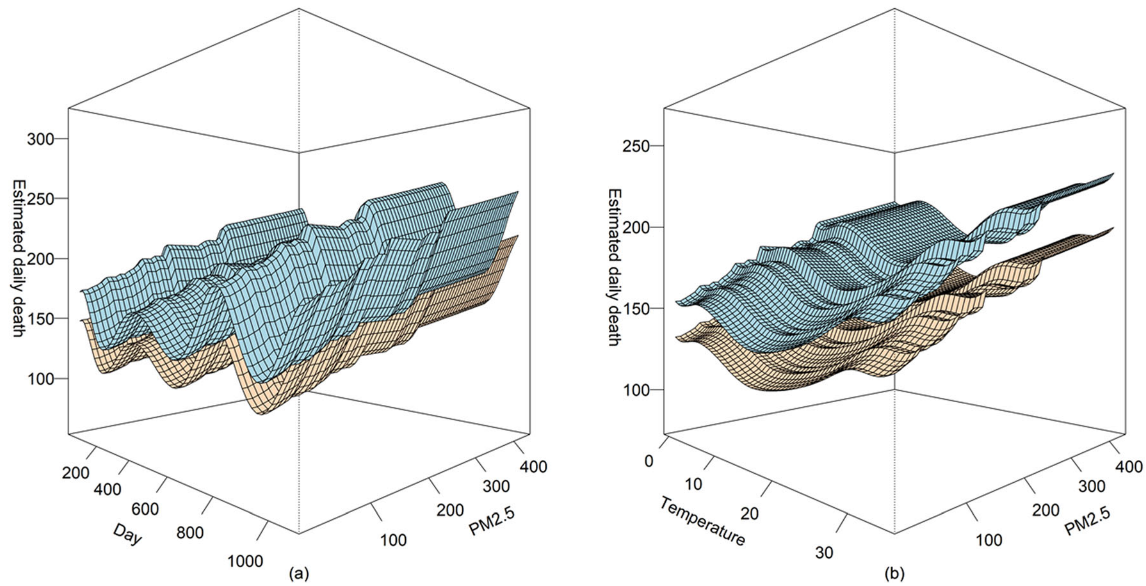

Fig. 1 Predicted daily non-accidental deaths by **a** day and $PM_{2.5}$ concentration (μg/m^3), and **b** temperature (°C) and $PM_{2.5}$ concentration (μg/m^3). *Blue surface, men; khaki surface, women

Lag structure of interaction between sex and $PM_{2.5}$ concentration

In our sensitivity analysis investigating the interaction effect of sex after applying up to 14 lag days of $PM_{2.5}$ concentration, we got consistent results. During the two lag weeks' exposure to $PM_{2.5}$, in general, the increased risk for nonaccidental death is about 0.2–0.4% lower in women than in men, per 10 μg/m^3 increase in $PM_{2.5}$ concentration (Table 3). The results for the weighted moving average of $PM_{2.5}$ concentrations up to 14 days indicate that the risk ratio of nonaccidental deaths for cumulative effects of $PM_{2.5}$ was 0.3–0.6% lower in women compared to men, and the results are all statistically significant and consistent throughout the 14-day time window (Table 3).

RR risk ratio; *CI* confidence interval

Subgroup analysis by age groups and specific causes of death

The reduced incremental effects of $PM_{2.5}$ on nonaccidental deaths in women were consistent in the subgroup analyses. Although not statistically significant in the aged 40 years or younger group (might be due to the small proportion, i.e.,

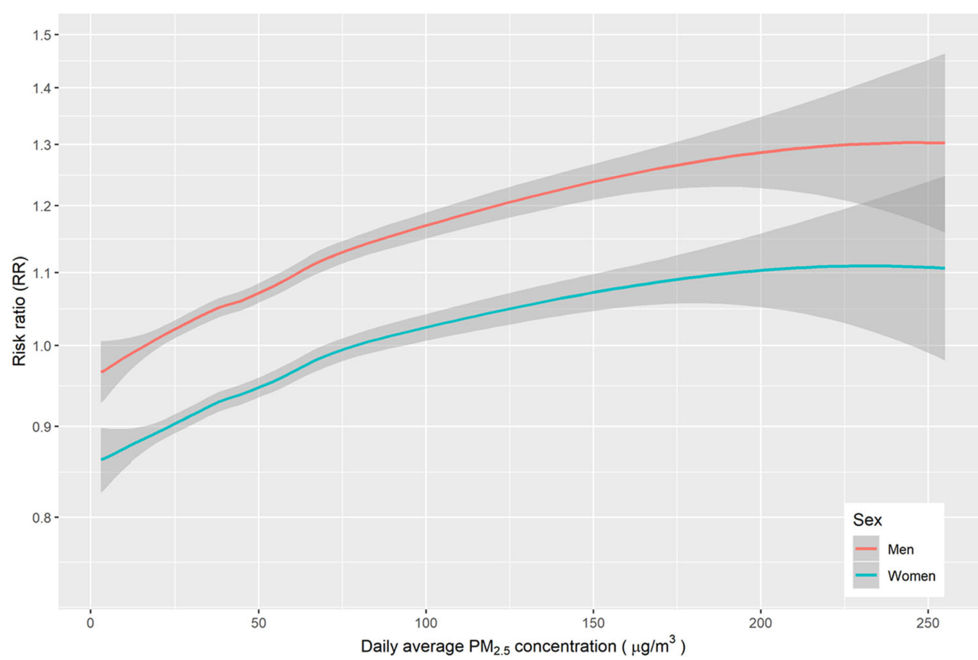

Fig. 2 Risk ratios for nonaccidental death by $PM_{2.5}$ concentrations in men and women

Table 3 Risk ratio of the interaction between sex and $PM_{2.5}$ (per 10 μg/m^3) for nonaccidental death, after applying different lag times for exposure

Lag	Single-day			Lag	Weighted moving average		
	RR	95% CI	*P* value		RR	95% CI	P value
Lag 1	0.998	0.997–1.000	0.014	Lag 0–1	0.997	0.995–0.999	0.001
Lag 2	0.999	0.997–1.000	0.135	Lag 0–2	0.997	0.995–0.999	0.001
Lag 3	0.997	0.995–0.998	0.000	Lag 0–3	0.997	0.995–0.999	0.004
Lag 4	0.996	0.995–0.998	0.000	Lag 0–4	0.996	0.994–0.999	<0.001
Lag 5	0.997	0.996–0.999	0.000	Lag 0–5	0.996	0.994–0.998	0.001
Lag 6	0.997	0.995–0.999	0.000	Lag 0–6	0.996	0.993–0.998	0.001
Lag 7	0.997	0.995–0.998	0.000	Lag 0–7	0.995	0.993–0.998	0.001
Lag 8	0.997	0.996–0.999	0.000	Lag 0–8	0.995	0.993–0.998	0.001
Lag 9	0.997	0.996–0.999	0.000	Lag 0–9	0.996	0.993–0.998	0.001
Lag 10	0.997	0.995–0.998	0.000	Lag 0–10	0.995	0.993–0.998	< 0.001
Lag 11	0.999	0.997–1.000	0.082	Lag 0–11	0.995	0.992–0.997	< 0.001
Lag 12	0.999	0.997–1.000	0.084	Lag 0–12	0.995	0.992–0.997	< 0.001
Lag 13	0.998	0.997–1.000	0.008	Lag 0–13	0.995	0.992–0.997	< 0.001
Lag 14	0.998	0.996–1.000	0.014	Lag 0–14	0.994	0.992–0.997	< 0.001

1.3%, of the total deaths), the risk ratio was 0.4–1.0% lower for women, compared to men (Table 4) Regarding the case-specific deaths, in general, the risk ratio was 0.2–0.8% lower for women, compared to men. However, the reduction was not statistically significant for cerebrovascular deaths (Table 4).

Discussion

In our study, we explored the interaction between sex and $PM_{2.5}$ exposure for nonaccidental mortality in Shanghai, China, between 2012 and 2014. Apart from the statistically significantly lower risk of nonaccidental death in women and the monotone increasing nonlinear exposure-response association between $PM_{2.5}$ and mortality, we found a smaller risk increase in non-accidental death (0.2% lower), per 10 μg/m^3 increase in $PM_{2.5}$ concentration, among women compared to men. In sensitivity analysis for the lags, we noticed that the sex differences in $PM_{2.5}$ effects in lag days 2, 11, and 12 were not statistically significant (Table 3). It might be due to chance or some undetected confounding or modification, and deserves further investigation using a larger dataset. However, all the lag days show the same trend, and 11 of 14 signal-day effects and all 14 cumulative lag effects are statistically significant, which indicates the robustness of our findings. Meanwhile, we also observed statistically significantly higher mortality risk on Monday and Wednesday compared with that on Sunday, which might be attributed to the higher $PM_{2.5}$ levels in the 2 days (averagely, 55.7 μg/m^3 and 56.4 μg/m^3 vs. 53.6 μg/m^3). No statistically significant difference was found for other weekdays.

Table 4 Risk ratio of the interaction between sex and $PM_{2.5}$ (per 10 μg/m^3) for nonaccidental death, by age groups and specific causes of death

Subgroup	Risk ratio (RR)	95% confidence interval (CI)		*P* value
		Lower limit	Upper limit	
Age (years)				
<40	0.990	0.978	1.003	0.118
≥40, <60	0.991	0.985	0.996	0.001
≥60, <80	0.996	0.994	0.999	0.008
≥80	0.996	0.994	0.998	<0.001
Causes of death				
Respiratory disease	0.992	0.987	0.997	0.001
Cardiovascular disease	0.993	0.990	0.997	<0.001
Cerebrovascular disease	0.998	0.994	1.001	0.164
Other circulatory system diseases	0.997	0.994	0.999	0.003

The effects of ambient $PM_{2.5}$ on mortality have been widely studied at global and national levels (Apte et al. 2015; Chen et al. 2017a; Fang et al. 2016; Liu et al. 2019). $PM_{2.5}$ pollution is ranked as the 6th leading cause of mortality and disability-adjusted life-years (DALYs) globally, and is estimated to contribute to 4.24 million deaths and 103.1 million DALYs in the Global Burden of Diseases project (GBD Risk Factors Collaborators 2015). Although the modification of sex in the $PM_{2.5}$ effects has been widely investigated, the sex/gender difference in the $PM_{2.5}$ effects on humans was rarely investigated and reported. Nevertheless, men and women have exhibited different health responses to various outdoor air pollutants in earlier studies. Sex-related differences have been seen in the associations of PM_{10} with asthma in children (Dong et al. 2011), PM_{10} and SO_2 with type 2 diabetes (Sohn and Oh 2017), NO_2 and SO_2 with cardinal symptoms (Oiamo and Luginaah 2013), and PM_{10}, $PM_{2.5}$, NO_2, and smog with declined cognition (Chen et al. 2017b; Kim et al. 2019). The literature is however far from consistent. For example, a previous study indicated that women might be at greater risk of fatal coronary heart disease as a result of exposure to particulate matter (PM), than men. The authors suspected that PM deposits differently and perhaps more harmfully in women's lungs compared to men's lungs (Chen et al. 2005). However, a metaanalysis indicated that the association of $PM_{2.5}$ with lung cancer was stronger for men than for women (Huang et al. 2017), which was later confirmed by a 10-year time-series study (Xue et al. 2018). Analyses of sex differences are more common in occupational epidemiology than in environmental health, because persistent job stratification by sex has produced marked differences in occupational exposures to chemical agents, ergonomic demands, injury, and psychosocial stressors (Clougherty 2010; Keitt et al. 2004). So far, few studies investigating the sex-related exposure-response difference in the effects of $PM_{2.5}$ on all-cause nonaccidental mortality, by adjusting for sex in analysis (Alessandrini et al. 2016) or stratifying the analysis by sex (Wang et al. 2017). The former showed a statistically nonsignificant ($P = 0.76$) modification of sex on overall natural mortality, while the latter indicated a higher risk among men (no numerical result reported). The inconsistency of the findings might be due to that the former focused on the short-term exposure to PM2.5; however, the latter focused on the long-term exposure.

Previous studies have suggested that observed difference in the air pollution effects between men and women might be a result of sex-linked biological differences (e.g., hormonal complement, body size) or gender differences in activity patterns, coexposures, or accuracy of measurement (Clougherty 2010). The weaker association between $PM_{2.5}$ and nonaccidental mortality in women, compared to men, as found in our study might be due to different reasons. One possibility is that $PM_{2.5}$ interacts with male-specific factors that are known to be associated with increased risk of the causes of non-accidental deaths, including male hormones (Menke et al. 2010), lifestyle factors (Lemaire 2002), occupational exposures (GBD 2017 Risk Factor Collaborators, 2019; GBD Risk Factors Collaborators 2015), etc. For instance, in China, the prevalence of smoking is 47.2% among men whereas 2.7% among women (Wang et al. 2019). Interaction between smoking and $PM_{2.5}$ has been proposed earlier for different chronic diseases, including cardiovascular mortality (Turner et al. 2017) and depression (Lin et al. 2017). Another possibility is the misclassification of real exposure to $PM_{2.5}$. For instance, in China, women are more likely to wear face masks and on average spend less time outdoors, compared to men (Li and Tilt 2019). This might have resulted in an attenuated effect of $PM_{2.5}$ in women, compared to men.

Except for the known advantages of ecological studies as have been discussed extensively (Grant 2009; Levin 2006; Wilson et al. 2005), the major advantage of our study is the application of CGAM in analysis, which is also the novelty of the work, i.e., the methodology used rather than the findings concerning the air pollution-mortality association based on the relatively old and limited data. Generalized additive models (GAM) have been widely implemented in time-series studies to explore the relationship between environmental factors and health outcomes because they can control for seasonal trends and nonlinear modification effects of multiple variables, adding to the fact that they are more maneuverable than full-parameter alternatives, generalized linear models (Dehghan et al. 2018; Thelen et al. 2013). The GAM uses local regression, smoothing splines with the local scoring algorithm, penalized smoothing splines, or smoothness selection by criteria such as the generalized cross-validation to fit the nonlinear associations. The traditional GAM only assumes the smoothness of the nonlinear associations; however, cannot restrict their shape. In contrast, the CGAM is a more comprehensive framework over the GAM that incorporates shape or order constraints. As a shape constrained additive model, the CGAM can contain multiple shape constrained and unconstrained terms as well as shape constrained multidimensional smooths (see Fig. 1). The approach allows user to specify constrained splines to fit the components for continuous predictors, and various types of orderings for the ordinal predictors. In addition, the user may also specify parametrically modeled covariates, which facilitates efficient estimation of smoothing parameters as an integral part of model estimation and numerically robust algorithms (Liao and Meyer 2019; Pya and Wood 2015).

Nevertheless, this study also has several limitations. First, as an ecological study, exposure to $PM_{2.5}$ was assessed at the population level, which might have led to aggregation bias. Only daily average $PM_{2.5}$ concentrations from one air monitoring station were used in our study, which could not reflect the variation in the $PM_{2.5}$ concentrations between the districts of Shanghai and during a day, therefore potential bias in effect estimates due to measurement error could not be excluded in the current study. Second, as an inherent limitation of the ecological studies, personal demographics such as occupation and lifestyle factors (e.g., amount of time spent outdoors) could not be incorporated in the analysis and might have biased the effect estimates of exposure to $PM_{2.5}$. Third, although we adjusted for population smoking prevalence and its interaction with $PM_{2.5}$ in the analysis, this information is not on an individual level. Other than smoking, we had little information on other potential factors, such as education and socioeconomic levels, comorbidities, and access to health services. Fourth, we only analyzed the short-term (up to 2 weeks) effects in the current study; however, when we look at all nonaccidental deaths only a subset of diseases would be influenced by the particulate matter. Therefore, a further cause-specific analysis deserves in the future using up to date data that allow for adjusting for more potential confounder. In addition, this study was conducted in Shanghai, one of the most developed cities with the highest life expectancy in China, which limits the generalizability of the findings to other parts of China.

Conclusions

This methodological paper demonstrates the usefulness of CGAM in nonlinear exposure-response air pollution and health studies. Compared to men, exposure to $PM_{2.5}$ pollution was associated with a smaller risk increase in nonaccidental mortality in women, in Shanghai, China, after adjusting for weather types, population level smoking prevalence, and interaction between the smoking prevalence and $PM_{2.5}$ exposure. The underlying mechanisms of the sex difference of $PM_{2.5}$ on death need further investigation.

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Data availability The use of the data was under the agreement between the Institute of Environmental Medicine, Karolinska Institutet, Sweden and the Shanghai Municipal Center for Disease Control and Prevention within a bilateral collaboration framework. The data were not publicly available but may be available upon reasonable request and with permission of the SCDC (xiatian@scdc.sh.cn).

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval This study is an ecological and observational study, based on the data from population-based registers in Shanghai. No personal identification was disclosed in our data. The study was approved by the Ethical Review Committee of the SCDC (approval number: SCDC2016-08).

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Code can be shared upon request.

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