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Utilizing daily excessive concentration hours to estimate cardiovascular mortality and years of life lost attributable to fine particulate matter in Tehran, Iran

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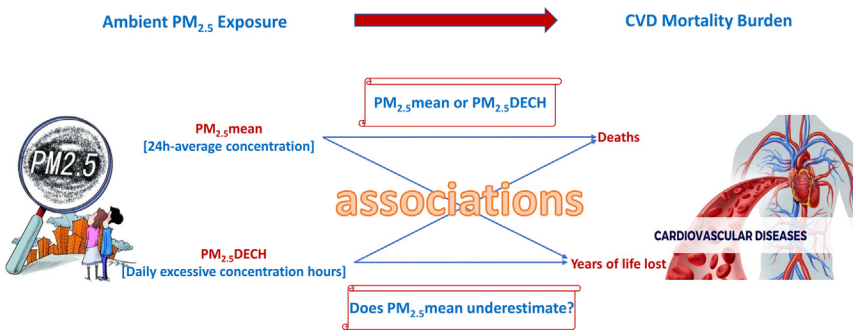
HIGHLIGHTS

- First study to use DECH to evaluate $PM_{2.5}$-attributable CVD mortality burden in Iran.
- Both mortality risk and years of life lost (YLLs) was adopted to assess CVD burden.
- Significant associations between $PM_{2.5}$ and stroke mortality were identified.
- 355 CVD deaths and 9280 YLLs were attributed to $PM_{2.5}$DECH annually in Tehran.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Evidence for associations between fine particulate matter ($PM_{2.5}$) and cardiovascular diseases (CVDs) in Iran is scarce. Given large within-day variations of $PM_{2.5}$ concentration, using the daily mean of $PM_{2.5}$ ($PM_{2.5}$mean) as exposure metric might bias the health-related assessment. This study applied a novel indicator, daily excessive concentration hours (DECH), to evaluate the effect of ambient $PM_{2.5}$ on CVD mortality and years of life lost (YLL) in Tehran, the capital city of Iran.
Methods: Hourly concentration data for $PM_{2.5}$, daily information for meteorology and records of registered cardiovascular deaths from 2012 to 2016 were obtained from Tehran, Iran. Daily excessive concentration hours of $PM_{2.5}$ ($PM_{2.5}$DECH) was defined as daily total concentration-hours exceeding 35 μg/m^3.

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Using a time-series design, we applied generalized linear models to assess the attributable effects of $PM_{2.5}$DECH and $PM_{2.5}$mean on CVD mortality and YLL.
Results: For an interquartile range (IQR) rise in $PM_{2.5}$DECH, total CVD mortality at lag 0–10 days and YLL at lag 0–8 days increased 2.26% (95% confidence interval (CI): 0.85–3.69%) and 23.24 (6.07–40.42) person years, respectively. Corresponding increases were 3.45% (1.44–5.49%) and 35.21 (10.85–59.58) person years for an IQR rise in $PM_{2.5}$mean. Significant associations between $PM_{2.5}$ pollution (i.e., $PM_{2.5}$mean and $PM_{2.5}$DECH) and cause-specific cardiovascular health (i.e., mortality and YLL) were only identified in stroke. Subgroup analyses showed that male and people aged 0–64 years suffered more from $PM_{2.5}$ pollution. Furthermore, we attributed a greater CVD burden to $PM_{2.5}$DECH (1.67% for mortality and 2.67% for YLL) than $PM_{2.5}$mean (0.63% for mortality and 0.70% for YLL) during the study period.
Conclusions: This study strengthened the evidence for the aggravated CVD mortality burden associated with short-term exposure to $PM_{2.5}$. Our findings also suggested that $PM_{2.5}$DECH might be a potential alternative indicator of exposure assessment in $PM_{2.5}$-related health investigations.

1. Introduction

The Global Burden of Disease Study (GBD) estimated that cardiovascular diseases (CVDs) caused 17.8 million deaths in 2017, making it the primary mortality risk factor globally (GBD Collaborators, 2018). It was estimated that the incidence and the case fatality rates of major cardiovascular events were higher in low- and middle-income countries than those in high-income countries (Finegold et al., 2013; Yusuf et al., 2014). Specifically, growing epidemiological and clinical evidence indicated potential deleterious effects of environmental factors (e.g., temperature, noise and air pollution) on cardiovascular health (Babisch et al., 2005; Brook et al., 2010; Lin et al., 2009; Ran et al., 2018). Ambient fine particulate matter, or particles with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), is one of the principal air pollutants that has been linked to increased risk of cardiovascular morbidity and mortality (Chen et al., 2017b; Dominici et al., 2006; Pope et al., 2006). Numerous epidemiological research from the United States and Europe have established the associations between long- and short-term exposure to $PM_{2.5}$ and a variety of acute and chronic cardiovascular consequences such as increased blood pressure, heart rate fluctuations, ischemic heart disease and stroke (Crouse et al., 2012; Kettunen et al., 2007; Pope et al., 2004; Zanobetti and Schwartz, 2005).

In recent years, Iran has suffered a great CVD mortality burden attributable to $PM_{2.5}$ over the past decade due to rapid industrial development, population explosion and dessert dust storms in Western Asia (Faridi et al., 2018; Khaniabadi et al., 2019). However, available evidence from Iran regarding $PM_{2.5}$-CVD mortality relationships is still relatively limited, and age- and gender-specific findings remain inconsistent (Kermani et al., 2018; Yarahmadi et al., 2018). Besides, most previous studies in Iran investigating $PM_{2.5}$-CVD health relationships used the death counts as the endpoint indicator, which overlooked differences in the life lost from different age groups (Karimi et al., 2019; Khajavi et al., 2019; Miri et al., 2016). In addition to mortality, years of life lost (YLL) is an important complementary index that has been extensively used to evaluate the disease burden locally, regionally, and globally (Fitzmaurice et al., 2017; Fontaine et al., 2003; Huang et al., 2012). YLL takes into consideration the premature deaths and the life expectancy by giving different weights to deaths at different ages (Guo et al., 2013; Liang et al., 2018). In comparison with mortality, YLL is a more sensitive and informative indicator in quantifying premature deaths since it partly resolves the disease effects caused by death numbers alone (Zhang et al., 2017; Zhu et al., 2017). Yet, there have been very sparse studies investigating $PM_{2.5}$-YLL relationships in Iran so far, though YLL contributes valuable age-based perspective for public policy making and health resource allocation (Faridi et al., 2018).

Besides, previous epidemiological studies mostly reported $PM_{2.5}$-mortality/morbidity associations by using daily average $PM_{2.5}$ as the exposure indicator (Cao et al., 2012; Salimi et al., 2017; Szyszkowicz et al., 2018). This commonly used measurement for $PM_{2.5}$ neglected large variations of air pollutants concentrations within one day, and thus might underestimate the disease burden from air pollution (Lin et al., 2017b). Additionally, a large amount of research observed approximately linear exposure-response relationships between $PM_{2.5}$ and health outcomes (e.g., mortality and YLL), indicating that significant health effects could occur even with relatively low concentrations (Mate et al., 2010; Shi et al., 2016). This, argued by Lin et al., might be partly due to excessive hourly concentrations (Lin et al., 2018b). The perspective was based on the finding that even if daily mean exposure was lower than the standard, hourly concentrations could exceed the guideline in a given day. To better capture the health consequences attributable to air pollution, a novel exposure assessment index named daily excessive concentration hours (DECH) was developed (Lin et al., 2017a). DECH can take into account both hourly concentration variations and extreme conditions (i.e., the concentration of $PM_{2.5}$ is comparatively high) within a day, and may give a more accurate understanding of the cardiovascular burden attributable to short-term exposure to $PM_{2.5}$.

This time-series study evaluated the short-term effects of $PM_{2.5}$ on CVD mortality and YLL in Tehran, Iran, 2012–2016. Subgroup analyses were performed to explore the potential modifying effects of individual-level factors, including gender, age and the specific cause of CVD mortality. We further estimated and compared the CVD mortality burden attributable to $PM_{2.5}$DECH and $PM_{2.5}$mean. Our findings might possess important implications for policy-makers to prompt the air quality regulations and improve health resources relocation in Tehran.

2. Materials and methods

2.1. Study area and population

Tehran (coordinates: 35°31′ to 35°57′ N, 51°04′ to 51°47′ E), the capital city of Iran, has a semi-arid climate with continental climate characteristics and a Mediterranean climate precipitation pattern (Mohammadi et al., 2018). As one of the largest Middle Eastern metropolises, Tehran has undergone expanded population (about 7.51million in 2011 and 7.99 million in 2016, Statistical Center of Iran, https://www.amar.org.ir/), accelerated urbanization and industrialization during the past several decades. In recent years, Tehran has been among one of the most polluted megacities in the world (Karimi et al., 2019). Severe air pollution events frequently occurred in the city due to motorized traffic, industrial

emissions, dust storms and natural gas. Residents of Tehran suffered from high concentrations of ambient air pollution especially in cold seasons that schools and government offices were closed to avoid potential health risks (Faridi et al., 2018).

2.2. Data collection

Daily mortality data of Tehran from January 1, 2012, to December 31, 2016, were obtained from the Municipality Tehran (Behesht-e Zahra organization) (http://www.tehran.ir/). According to the International Classification of Diseases (ICD–10), causes of mortality were coded as follows: cardiovascular disease (ICD–10: I00–I99), ischemic heart disease (IHD, I20–I25), stroke (I60–I69) and sudden cardiac death (SCD, I46). Cardiovascular mortality data were further classified by gender (male and female) and age (0–64 years, 65–74 years, 75+ years).

Air pollution data including $PM_{2.5}$, carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) were collected from Tehran air quality control website (http://airnow.tehran.ir). These items are measured hourly by 22 stations located in different parts of Tehran, and their daily averages were used in subsequent analyses. Daily meteorological data were collected from IRAN Meteorological Organization (IRIMO) (http://www.irimo.ir), including daily average temperature (∘C), relative humidity (%), wind speed (m/s), atmospheric pressure (hPa), precipitation (mm) and sunshine hours (h).

2.3. Calculations of YLL and DECH

Life tables for Iran population from 2012 to 2016 were obtained from the World Health Organization's (WHO) Global Health Observatory (GHO) data, which provided life expectancies at every exact age for both sexes. YLL for each death was calculated by matching age and sex to the life tables, and daily YLL were estimated as the sum for all deaths on the given day (Guo et al., 2013; Zhang et al., 2017). Furthermore, we stratified daily YLL by gender (male, female), age (0–64 years, 65–74 years, 75+ years) and cardiovascular mortality categories (IHD, stroke, SCD). More details are available in our previous publications (Jiao et al., 2019; Zhang et al., 2018).

We adopted DECH as the sum of concentration-hours >35 g/m^3 within one day. 35 $\mu g/m^3$ was chosen as the concentration threshold based on the Clean Air Standards in Iran. For instance, an hour with the concentration of 38 $\mu g/m^3$ contributed 3 concentration-hours to the DECH values, while hours with concentrations lower than or equal to 35 $\mu g/m^3$ contributed zero excessive concentration-hours to the daily total. DECH is calculated by the formula:

$$\mathrm{DECH} = \sum_{i=0}^{23} \Delta c_i$$

$$\Delta c_i = \begin{cases} c_i - 35, & c_i \geq 35 \\ 0, & c_i < 35 \end{cases}$$

where i is the hour time of observation;c_i is the concentration of $PM_{2.5}$ at the hour of observation; Δc_i is the difference between c_i and concentration threshold of 35 $\mu g/m^3$.

2.4. Statistical analysis

A standard time-series generalized model (GLM) was applied to evaluate the effects of $PM_{2.5}$ on CVD mortality and YLL. Consistent with previous research, daily CVD deaths followed an over-dispersed Poisson distribution, and daily cardiovascular YLL followed a normal distribution (Liang et al., 2018; Lu et al., 2015). Several covariates were adjusted in GLM: (1) a natural cubic smooth function of time with 7 degrees of freedom (df) per year to control for secular trend and seasonality (Chen et al., 2017b); (2) natural cubic smooth (ns) functions with 6 df for the current day's temperature and moving average of 3 days' mean temperature (Lin et al., 2017a); (3) ns functions with 3 df for more meteorological factors such as mean relative humidity (RH), wind speed (WS), sunlight hours (SH), precipitation (Pp) and atmospheric pressure (AP) (Chen et al., 2017a); (4) indicator variable for "day of the week (DOW)" (Guo et al., 2011). The GLM model is expressed as:

$$\begin{aligned} log\left[E\left(\mu_{t1}\right)\right] = {} & \alpha + \beta^* x_t + ns(Time, df = 7\times 5) + ns(Temp_t, df = 6) \\ & + ns(Temp_{1-3}, df = 6) + ns(RH_t, df = 3) + ns(WS_t, df = 3) \\ & + ns(AP_t, df = 3) + ns(SH_t, df = 3) + ns(Pp_t, df = 3) + \gamma^* DOW_t \end{aligned}$$

$$\begin{aligned} E\left(\mu_{t2}\right) = {} & \alpha + \beta^* x_t + ns(Time, df = 7\times 5) + ns(Temp_t, df = 6) \\ & + ns(Temp_{1-3}, df = 6) + ns(RH_t, df = 3) + ns(WS_t, df = 3) \\ & + ns(AP_t, df = 3) + ns(SH_t, df = 3) + ns(Pp_t, df = 3) + \gamma^* DOW_t \end{aligned}$$

where t refers to the day of observation; x_t refers to $PM_{2.5}$mean or $PM_{2.5}$ DECH; $E(\mu_t)$ is the expected daily CVD death counts on day t; *ns ()* refers to the natural cubic splines; β and γ are the regression coefficients, and α is the intercept.

To estimate potential harvesting and cumulative effects of $PM_{2.5}$mean and $PM_{2.5}$DECH, we first used a single-day lag (current day up to the previous 10 days: lag 0–lag 10). As single-day lag models may underestimate the health impacts of $PM_{2.5}$ pollution (Bell et al., 2004), we further applied moving averages of lag 0–1 to lag 0–10 days to perform analyses. To identify vulnerable subpopulations, subgroup analyses were conducted stratified by gender (male, female), age group (0–64 years, 65–74 years, 75+ years) and cardiovascular mortality categories (IHD, stroke, SCD). We then visually checked the linearity of exposure-response curves between $PM_{2.5}$ pollution (i.e., $PM_{2.5}$mean and $PM_{2.5}$DECH) and CVD health (i.e., mortality and YLL) by applying smoothing functions of the natural cubic spline with 3 df (Smargiassi et al., 2009).

We further quantified the CVD mortality burden (i.e., deaths and YLLs) attributable to $PM_{2.5}$ DECH and $PM_{2.5}$mean, respectively (Lin et al., 2016; Lin et al., 2018a). Two indicators, attributable number (AN) and attributable fraction (AF) were applied. First, we calculated attributable number of CVD deaths and YLLs caused by $PM_{2.5}$mean (reference = 35 $\mu g/m^3$) and $PM_{2.5}$DECH (reference = 0 $\mu g/m^3$ * hours) on each day of the whole series, namely AN_i of deaths and YLLs. By summing up AN_i during the whole series, total attributable deaths and YLLs (AN_{total}) can be obtained. Attributable fractions (AF, %) of deaths and YLLs could be provided by the ratios of AN_{total} to the corresponding total number of observed deaths or YLLs.

To test the robustness of our models, we performed several sensitivity analyses by including gaseous pollutants (SO_2, NO_2, CO and O_3) to establish two-pollutant models, and using alternative dfs for smoothing functions of temporal trends (5–9 df/year) and the weather factors (5 and 7 df for temperature and 4 and 5 df for relative humidity).

All analyses were performed using R software (version 3.3.3). The results for $PM_{2.5}$-CVD associations were expressed as the percent increase in daily mortality (%) and absolute changes in YLL (person years) associated with per interquartile range (IQR) increment of $PM_{2.5}$mean and $PM_{2.5}$DECH. The confidence intervals (CIs) were reported at the 95% confidence level. Two-sided statistical tests were conducted, and effects of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Data description

Table 1 summarizes the statistical characteristics of daily CVD deaths and YLLs. A total of 106,180 CVD deaths were recorded during the study period, of which 48.71% aged 75+ years and 56.45% were male. On each day, approximately 58, 10, 18 and 16 deaths were from CVD, stroke, IHD and SCD. Daily mean YLL was 851.3 person years, more than two-thirds of which were contributed by the youngest group (age 0–64 years). The temporal patterns of daily air pollutants and meteorological factors in Tehran, Iran, 2012–2016 were shown in Fig. 1. Time series plots of daily CVD mortality and YLL in the corresponding period were presented in Fig. S1. The overall $PM_{2.5}$mean and $PM_{2.5}$DECH shared similar periodic fluctuation annually, both of which showed an intuitive seasonal pattern with values higher in winter and lower in summer. We observed an increasing trend for daily SO_2, while a decreasing trend for NO_2 during the study period. Summary characteristics of daily air pollutants and meteorological variables were presented in Table S1. Annual average $PM_{2.5}$mean and $PM_{2.5}$DECH were 34.7 μg/m^3 and 172.4 μg/m^3 * hours, respectively (Table S1). Spearman correlation coefficients between air pollutants and meteorological variables were shown in Table S2.

3.2. Associations between air pollution and CVD mortality and YLL

Fig. 2 reveals the exposure-response relationships between $PM_{2.5}$mean, $PM_{2.5}$DECH and CVD mortality, YLL, adjusting for confounders in the time-series analysis. Approximately linear associations between $PM_{2.5}$mean, $PM_{2.5}$DECH and CVD mortality, YLL were observed in the current study. Therefore, we subsequently estimated the effects on mortality and YLL associated with per IQR increase in $PM_{2.5}$mean (IQR = 18.2 μg/m^3) and $PM_{2.5}$DECH (IQR = 216.2 μg/m^3 * hours).

Fig. 3 illustrates the effects of $PM_{2.5}$mean and $PM_{2.5}$DECH on CVD mortality and YLL across different lag days. The lag pattern was generally similar for CVD mortality and YLL. For single lag days, the associations appeared at lag 1 with the most significant effect, and lasted for two or three days with a decreasing trend. For multiple lag days, the effects of $PM_{2.5}$mean and $PM_{2.5}$DECH on CVD mortality gradually increased from lag 0–1 to lag 0–10 days, with $PM_{2.5}$mean and $PM_{2.5}$DECH along lag 0–10 days found to be most strongly associated with CVD mortality. The corresponding effects of $PM_{2.5}$ on CVD YLL showed an upward trend from lag 0–1 to lag 0–8 days, with the highest effect estimates at lag 0–8 days. Thus, we separately selected lag 0–10 days for CVD mortality, and lag 0–8 days for CVD YLL as the exposure periods to report the subsequent results. Specifically, an IQR increase in $PM_{2.5}$mean was associated with 3.45% (95% CI: 1.44–5.49%) increase in CVD mortality at lag 0–10 days, and 35.21 (95% CI: 10.85–59.58) person years increase in YLL at lag 0–8 days. Corresponding increases for an IQR increase in $PM_{2.5}$DECH were 2.26% (95% CI: 0.85–3.69%) and 23.24 (95% CI: 6.07–42.42) person years (Table 2). Estimated changes of CVD mortality and YLL associated with $PM_{2.5}$mean and $PM_{2.5}$DECH at different exposure days were also shown in Table S3.

Table 1
Descriptive statistics of daily cardiovascular deaths and years of life lost in Tehran, Iran, 2012–2016.

Variables	Mean	SD	Min	Percentile			Max
				P_{25}	P_{50}	P_{75}	
Mortality							
CVD	58.1	10.0	31.0	51.0	58.0	65.0	97.0
Stroke	9.9	4.3	1.0	7.0	9.0	12.0	33.0
IHD	18.1	5.0	4.0	15.0	18.0	21.0	40.0
SCD	16.0	5.2	3.0	12.0	16.0	19.0	39.0
Gender							
Female	24.8	5.7	9.0	21.0	24.0	28.0	47.0
Male	32.8	6.8	10.0	28.0	32.0	37.0	58.0
Age, years							
0–64	18.7	5.2	6.0	15.0	18.0	22.0	43.0
65–74	11.1	3.6	2.0	8.0	11.0	14.0	25.0
75+	28.3	6.1	11.0	24.0	28.0	32.0	53.0
YLL							
CVD	951.3	215.0	381.6	802.0	934.6	1076.6	1975.0
Stroke	167.8	128.8	8.8	90.8	136.5	192.8	916.9
IHD	264.4	90.8	19.9	200.2	255.5	318.6	775.9
SCD	276.2	112.5	32.6	195.4	265.9	341.6	817.4
Gender							
Female	353.6	106.8	82.2	277.9	344.8	418.7	877.1
Male	558.3	153.3	137.0	448.0	545.9	647.6	1423.8
Age, years							
0–64	627.9	194.8	158.0	492.6	603.8	741.9	1548.2
65–74	147.8	48.9	22.6	112.8	143.1	180.2	337.4
75+	175.6	38.9	60.8	147.8	172.0	199.2	337.6

Abbreviations: CVD, cardiovascular disease; IHD, ischemic heart disease; SCD, sudden cardiac death; YLL, years of life lost.

3.3. Subgroup analyses

Table 2 compares the effects of per IQR increase in $PM_{2.5}$mean and $PM_{2.5}$DECH on CVD mortality (lag 0–10 days) and YLL (lag 0–8 days), stratified by gender, age and the specific cause of CVD mortality. Stratified by gender and cause of CVD mortality, statistically significant associations between $PM_{2.5}$ pollution (i.e., $PM_{2.5}$-mean and $PM_{2.5}$DECH) and cardiovascular health (i.e., mortality and YLL) were only identified in male and stroke cases. For example, the ERRs of CVD mortality per IQR increment in $PM_{2.5}$mean and $PM_{2.5}$DECH for stroke was 8.30% (95% CI: 3.65–13.16%) and 5.50% (95% CI: 2.31–8.79%), and for male was 4.68% (95% CI:1.99–7.45%) and 2.93% (95% CI: 1.04–4.85%). For both CVD mortality and YLL, we observed stronger cardiovascular effects in people aged 0–64 years compared with those aged 75+, while no significant effects of $PM_{2.5}$mean and $PM_{2.5}$DECH on people aged 65–74 years. For example, the ERRs of CVD mortality per IQR increment in $PM_{2.5}$mean and $PM_{2.5}$DECH for people aged 0–64 years was 4.16% (95% CI: 0.62–7.81%) and 2.79% (95% CI: 0.31–5.33%), and for people aged 75 + years was 3.53% (95% CI: 0.74–6.39%) and 2.38% (95% CI: 0.42–4.37%).

3.4. Mortality burden attributable to $PM_{2.5}$mean and $PM_{2.5}$DECH

Table 3 estimates the yearly AN and overall AF for CVD mortality at lag 0–10 days, and YLL at lag 0–8 days associated with $PM_{2.5}$-mean and $PM_{2.5}$DECH. Generally, we observed a relatively greater CVD mortality burden attributable to $PM_{2.5}$DECH than $PM_{2.5}$mean. During the study period, approximately 0.63% (95% CI: 0.28–0.98%) CVD deaths (134 cases per year) and corresponding 0.70% (95% CI: 0.23–1.18%) YLLs (2440 person years per year) were attributable to $PM_{2.5}$mean; 1.67% (95% CI: 0.70–2.63%) CVD deaths (355 cases per year) and corresponding 2.67% (95% CI: 0.86–4.48%) YLLs (9280 person years per year) were ascribed to $PM_{2.5}$DECH. People aged 0–64 years contributed more to yearly YLLs (2050 person years) than people aged 75+ (322 person years), suggesting that people dying at younger ages caused greater mortality burden.

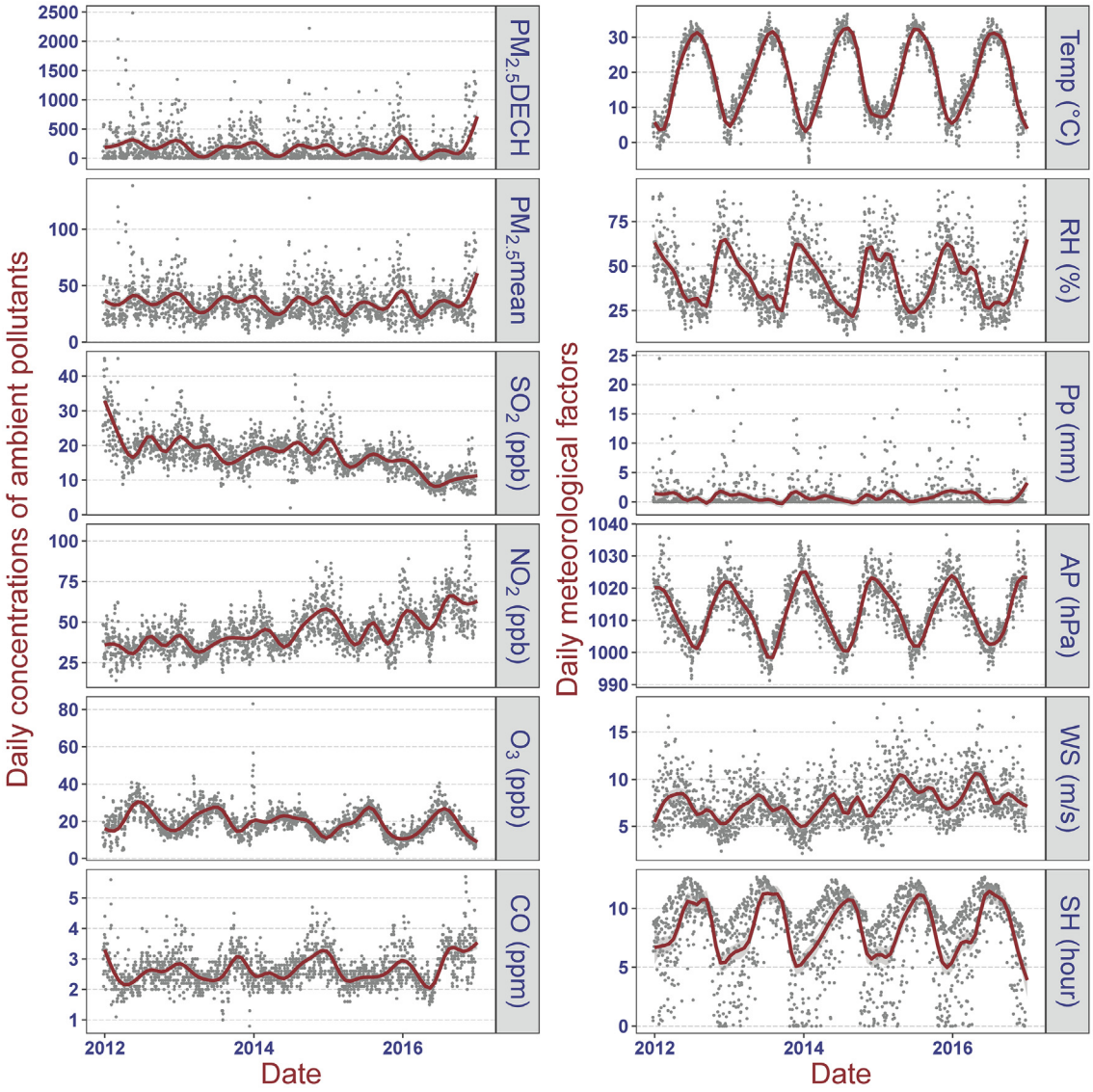

Fig.1. Time series of daily air pollutants and meteorological factors in Tehran, Iran, 2012–2016. Abbreviations: Temp, daily mean temperature; RH, relative humidity; Pp, precipitation; AP, atmospheric pressure; WS, wind speed; SH, sunshine hour.

3.5. Sensitivity analyses

Sensitivity analyses showed that the estimated associations of CVD mortality and YLL with exposure to $PM_{2.5}$DECH than $PM_{2.5}$-mean changed a little when adopting two-pollutant models (Tables S4 & S5). Also, $PM_{2.5}$-associated estimates were generally stable in our study regarding gender and age-specific analyses in the two-pollutant models. Furthermore, the results remained robust to additional adjustment of degrees of freedom of temporal trends (5–9/year), mean temperature (4–5) and relative humidity (4–5) (Table S6).

4. Discussion

This is the first study to use $PM_{2.5}$DECH as the exposure metric to evaluate the impacts of $PM_{2.5}$ on cause-specific CVD mortality and YLL in Iran. Evidence gained in the current study showed that rises in both $PM_{2.5}$DECH and $PM_{2.5}$mean were significantly associated with increased CVD mortality and YLL. For cause-specific CVD mortality, only deaths from stroke were found to be associated with $PM_{2.5}$ pollution. Compared with the most elderly (age 75+ years) and female, younger people (age 0–64 years) and males appeared to be more susceptible. We further obtained a relatively greater CVD mortality burden attributable to $PM_{2.5}$DECH than $PM_{2.5}$mean. These findings may possess important implications for public agencies of Tehran to prompt the process of clean air action plans and health resource relocation.

While previous epidemiological studies widely reported adverse health effects by using daily mean concentration of air pollutants as the exposure index (Ran et al., 2018a; Zhong et al., 2018), an increasing number of research noticed that significant within-day concentration variations might bias the health-related assessments (Lin et al., 2017b; Lin et al., 2018b). To better capture the health impacts of air pollution, recent studies focused on hourly variations of air pollutants (Bhaskaran et al., 2011; Sullivan et al., 2005), and conceived a series of novel exposure indicators, such as hourly peak concentration, hourly mean concentration and daily excessive concentration hours (Chen et al., 2019; Lin et al., 2017a; Lin et al., 2017b; Lin et al., 2018b). In several prior research, $PM_{2.5}$-DECH has been well implemented with advantages (Lin et al., 2017a; Lin et al., 2018b). Compared with $PM_{2.5}$mean, $PM_{2.5}$DECH is more informative by fully considering the large variations of

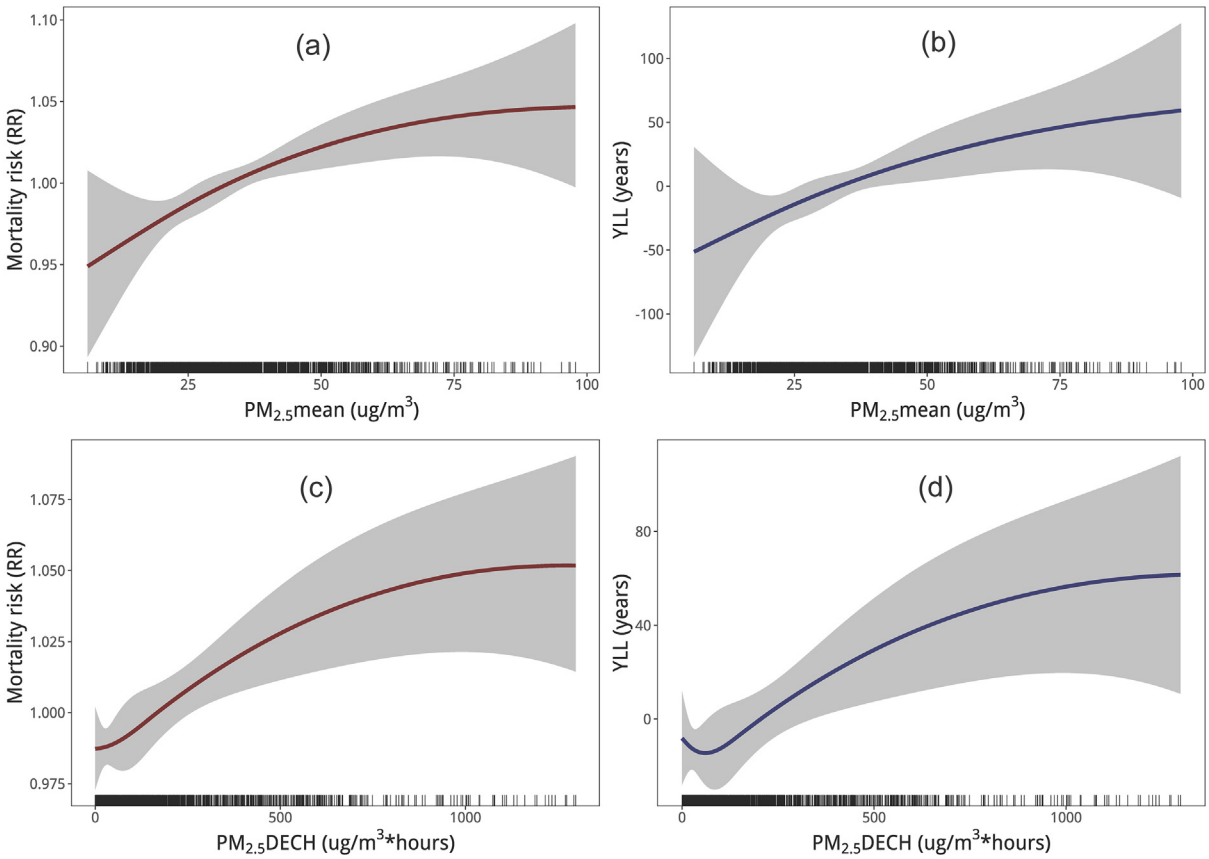

Fig.2. Dose-response curves for $PM_{2.5}$mean, $PM_{2.5}$DECH and CVD mortality, YLL in Tehran, Iran, 2012–2016. A natural spline smoother with 3 df was applied. The continuous bold red and blue lines refer to the effect estimates, and the boundaries of the shaded parts refer to the 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

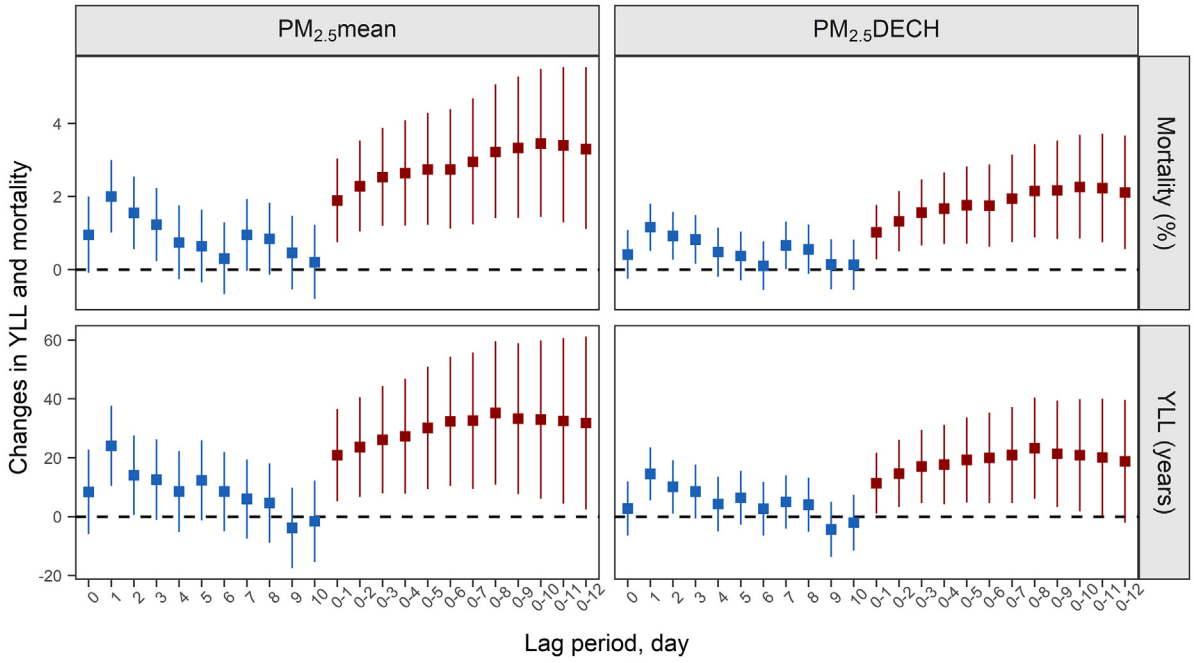

Fig.3. Estimated changes with 95% confidence intervals of CVD mortality (%) and YLL (years) associated with per IQR increase in $PM_{2.5}$mean and $PM_{2.5}$DECH at different exposure days in Tehran, Iran, 2012–2016.

Table 2
Estimated changes with 95% confidence intervals (CIs) of CVD mortality (%) and YLL (years) associated with per IQR increase in $PM_{2.5}$mean and $PM_{2.5}$DECH.

Variables	$PM_{2.5}$mean		$PM_{2.5}$DECH	
	Estimate (95% CI)	*P value*	Estimate (95% CI)	*P value*
Mortality (%)				
CVD	**3.45 (1.44–5.49)**	**0.001**	**2.26 (0.85–3.69)**	**0.002**
Stroke	**8.30 (3.65–13.16)**	**<0.001**	**5.50 (2.31–8.79)**	**0.001**
IHD	−0.26 (−3.79 to 3.40)	0.888	0.10 (−2.42 to 2.69)	0.963
SCD	4.02 (−0.09 to 8.30)	0.056	2.20 (−0.69 to 5.17)	0.138
Gender				
Female	2.08 (−0.85 to 5.10)	0.166	1.55 (−0.53 to 3.66)	0.145
Male	**4.68 (1.99–7.45)**	**0.001**	**2.93 (1.04–4.85)**	**0.002**
Age, years				
0–64	**4.16 (0.62–7.81)**	**0.021**	**2.79 (0.31–5.33)**	**0.028**
65–74	1.86 (−2.57 to 6.50)	0.416	0.94 (−2.20 to 4.18)	0.336
75+	**3.53 (0.74–6.39)**	**0.013**	**2.38 (0.42–4.37)**	**0.017**
YLL (years)				
CVD	**35.21 (10.85–59.58)**	**0.005**	**23.24 (6.07–40.42)**	**0.008**
Stroke	**27.83 (16.35–39.30)**	**<0.001**	**19.31 (11.22–27.40)**	**<0.001**
IHD	−1.97 (−12.97 to 9.02)	0.725	0.09 (−7.66 to 7.83)	0.983
SCD	5.20 (−8.15 to 18.55)	0.445	−1.51 (−7.90 to 10.92)	0.753
Gender				
Female	11.31 (−1.8 to 24.42)	0.091	7.69 (−1.55 to 16.93)	0.103
Male	**25.07 (6.89–43.25)**	**0.007**	**15.77 (2.95–28.60)**	**0.016**
Age, years				
0–64	**28.90 (5.70–52.09)**	**0.015**	**19.65 (3.30–36.01)**	**0.019**
65–74	0.98 (−5.04 to 6.99)	0.751	0.18 (−4.05 to 4.42)	0.932
75+	**5.34 (0.84–9.84)**	**0.020**	**3.41 (0.23–6.58)**	**0.036**

Abbreviations: IQR, interquartile range; DECH, daily excessive concentration hours; CVD, cardiovascular disease; IHD, ischemic heart disease; SCD, sudden cardiac death; YLL, years of life lost.
Note: Bold font face indicates a statistically significant result ($p < 0.05$). Estimates for CVD mortality and YLL were at lag 0–10 and lag–8 days, respectively.

air pollution within one day, and thus may better reflect the actual exposure levels. In addition, focusing on extreme conditions of air quality (i.e., hours with $PM_{2.5}$ concentrations higher than the standards), $PM_{2.5}$DECH may be more sensitive in identifying the health effects of population exposure to different pollution levels. Our study calculated $PM_{2.5}$DECH by adopting the concentration threshold of $PM_{2.5}$ from Clean Air Standards in Iran, the findings of which may have great implications to the decision criteria to enhance the ambient air pollution monitoring system in Iran. Other methods can also be applied to determine the value of the concentration threshold such as referring to the performance of specific statistical models. More population-based studies in various regions using their specific air pollution threshold are recommended, and future studies are required to further explore the determination of the concentration threshold of air pollution.

In the current study, we found that both short-term exposure to $PM_{2.5}$mean and $PM_{2.5}$DECH were positively associated with CVD mortality, and their results were relatively consistent. This finding confirmed that $PM_{2.5}$DECH might be an alternative exposure indicator for $PM_{2.5}$mean. However, very limited epidemiological studies adopted DECH as the exposure indicator to investigate the association between air pollution and adverse health outcomes (Lin et al., 2017b; Lin et al., 2018b), and thus direct comparisons for our results regarding $PM_{2.5}$DECH are restricted. Generally, the findings of our results were consistent with most of the previous research (Lee et al., 2015; Mate et al., 2010; Pascal et al., 2014). Investigations from developed countries have demonstrated that exposure to $PM_{2.5}$ could trigger relatively acute cardiovascular mortality after a few hours to days (Pope et al., 2006; Brook et al., 2010). In recent years, a mounting of studies conducted in

Table 3
The yearly attributable number and overall attributable fraction of cardiovascular mortality and YLL due to $PM_{2.5}$mean and $PM_{2.5}$DECH in Tehran, Iran, 2012–2016.

Variables	$PM_{2.5}$mean		$PM_{2.5}$DECH	
	AN (n, 95% CI)	AF (%, 95% CI)	AN (n, 95% CI)	AF (%, 95% CI)
Mortality				
CVD	134 (60–207)	0.63 (0.28–0.98)	355 (148–559)	1.67 (0.70–2.63)
Male	105 (50–159)	0.88 (0.42–1.33)	265 (110–415)	2.21 (0.92–3.47)
0–64 years	57 (15–99)	0.84 (0.22–1.44)	159 (41–272)	2.32 (0.60–3.98)
75+ years	69 (18–118)	0.66 (0.17–1.14)	181 (41–318)	1.75 (0.40–3.08)
Stroke	68 (40–95)	1.89 (1.12–2.63)	181 (105–253)	5.01 (2.91–7.02)
YLL				
CVD	2440 (784–4097)	0.70 (0.23–1.18)	9280 (2981–15579)	2.67 (0.86–4.48)
Male	1836 (603–3070)	0.90 (0.30–1.50)	6983 (2293–11673)	3.42 (1.12–5.72)
0–64 years	2050 (472–3628)	0.89 (0.21–1.58)	7794 (1794–13794)	3.40 (0.78–6.01)
75+ years	322 (17–628)	0.50 (0.03–0.98)	1226 (63–2388)	1.91 (0.10–3.72)
Stroke	2081 (1299–2863)	3.40 (2.12–4.67)	7914 (4940–10887)	12.91 (8.06–17.76)

Abbreviations: DECH, daily excessive concentration hours; CVD, cardiovascular disease; YLL, years of life lost; AN, attributable number; AF, attributable fraction.
Note: Estimates for CVD mortality and YLL were at lag 0–10 and lag–8 days, respectively.

developing countries such as China, Thailand and Iran, presented evidence regarding short-term $PM_{2.5}$-CVD mortality relationships (Karimi et al., 2019; Pinichka et al., 2017; Shang et al., 2013). The putative biological mechanisms suggested that soluble components of $PM_{2.5}$ could penetrate pulmonary epithelium into the circulation and interact with lung receptors, which might lead to the instability of a vascular plaque or arrhythmias. In addition, less acute cardiac effects from several hours to weeks could be attributable to $PM_{2.5}$s ability to activate hemostatic pathways, impairing vascular function, and accelerating atherosclerosis (Brook et al., 2004). As for specific causes of CVD mortality, we observed significant effects of $PM_{2.5}$ on stroke deaths, which was in line with previous studies investigating the impacts of $PM_{2.5}$ on cause-specific mortality (Kettunen et al., 2007; Shah et al., 2015). A systematic review including 6.2 million stroke events across 28 countries found that with per 10 $\mu g/m^3$ increase in $PM_{2.5}$, the risk of stroke mortality and hospital admissions increased 0.3%, indicating that $PM_{2.5}$ was a serious environmental risk factor for stroke events (Shah et al., 2015). However, we did not observe statistically significant impacts of $PM_{2.5}$ on IHD and SCD. The results were partly inconsistent with epidemiological research from Tehran evaluating long-term health impacts of $PM_{2.5}$ from 2006 to 2015, which indicated that IHD deaths accounted for most mortality attributable to $PM_{2.5}$ (Faridi et al., 2018). The underlying reasons for the inconsistency remain uncertain, and more studies are warranted to clarify the discrepancy.

Stratified analyses by gender showed that statistically significant effects of all-cause CVD mortality only existed in males. Gender heterogeneity on the fatal CVD impact of $PM_{2.5}$ pollution was also observed in previous research (Clougherty, 2010). While a number of investigations were in agreement with our results (Chen et al., 2018a), numerous prior researchers reported opposite findings that females had a higher risk of CVD mortality due to $PM_{2.5}$ (Franklin et al., 2007; Ostro et al., 2008). This discrepancy might be explained by several potential differences between males and females, such as smoking status, socio-economic status and stress experiences (Chen et al., 2018b; Guo et al., 2013; Seeman et al., 2002). Additionally, men are more likely to have outdoor jobs and may expose to air pollution more frequently. The findings of sex patterns are still unclear and need further investigations.

It is a widely accepted knowledge that elderly population is more susceptible to environmental risk factor, and a large number of epidemiological studies using death counts as endpoint indicator have confirmed this perspective (Chen et al., 2017b; Franklin et al., 2007). However, our results showed relatively smaller effect estimates for people aged 75+ than the younger age group (age 0–64 years) in Tehran, which might be the result of harvesting effects. Additionally, younger people (age 0–64 years) in the current study had higher YLL risk compared with the more elderly (age 75+), which was in line with a retrospective regression analysis from Beijing, the capital city of China (Guo et al., 2013). These findings, contrary to the commonsense view, indicated that giving the same weight to deaths at different ages might underestimate the actual burden of air pollution on younger people. Therefore, as a more informative and comprehensive metric, YLL can serve as an alternative indicator to quantify premature death and evaluate the mortality burden.

In terms of the absolute death counts value and relative mortality proportion, attributable number and fraction can provide more straightforward information for public health policy making compared with relative risk or odds ratio (Wang et al., 2018). Our results showed that Tehran bore a great CVD mortality burden ascribed to ambient $PM_{2.5}$ pollution. In addition, we obtained a relatively larger CVD mortality burden attributable to $PM_{2.5}$DECH (1.67% (95% CI: 0.70–2.63%) CVD deaths) than $PM_{2.5}$mean (0.63% (95% CI: 0.28–0.98%) CVD deaths), indicating that using $PM_{2.5}$mean might underestimate the deleterious health effects of ambient $PM_{2.5}$. Subgroup analyses by age showed that younger people (age 0–64 years) contributed more to YLL than the most elderly (age 75+). Besides, due to a great CVD mortality burden of males and people dying from stroke, public agencies of Tehran should attach much importance to these vulnerable populations.

Some limitations of our research should be considered. First, we used the concentration threshold of Iran's Clean Air Standards to calculate $PM_{2.5}$DECH rather than referring the threshold estimated by model analyses, which might bias the cardiovascular effect assessments. Second, we used the outdoor 24-hour average concentration of air pollutants, which overlooked the people's time-activity pattern and indoor-outdoor air quality exchange in different locations (Lin et al., 2018a). Third, as other studies in this field, we used fixed-site monitoring data rather than individual levels, which might lead to some degrees of exposure misclassification and greater heterogeneity of the results (Zeger et al., 2000).

5. Conclusions

This time-series study found that short-term exposure to ambient $PM_{2.5}$ was significantly associated with increased risk of CVD mortality and YLL in Tehran. Significant associations between $PM_{2.5}$ pollution (i.e., $PM_{2.5}$mean and $PM_{2.5}$DECH) and cause-specific cardiovascular health (i.e., mortality and YLL) were only identified in stroke. Subgroup analyses showed that male and younger people were more susceptible to the high concentration of $PM_{2.5}$. Additionally, we observed a larger cardiovascular mortality burden attributable to $PM_{2.5}$DECH than $PM_{2.5}$mean, indicating that DECH might be an alternative exposure metric in health-related assessments. Our findings may provide valuable information for Iran's public agencies to make a sustainable air pollution control policy and protect the potential vulnerable population.

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Author Contributions

Yunquan Zhang conceived and designed the experiments; Fatemeh Mayvaneh, Mohammad Baaghideh, Alireza Entezari, and Yunquan Zhang collected and cleaned the data; Yunquan Zhang, Dieyi Chen, Qianqian Xiang, Anqi Jiao, and Faxue Zhang performed the data analysis; Dieyi Chen, Yunquan Zhang, and Fatemeh Mayvaneh drafted the manuscript; Hung Chak Ho, Kejia Hu, Gongbo Chen, Qi Zhao, and Shengzhi Sun helped revise the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare they have no competing financial interests.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2019.134909.

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