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Short-term effects of ambient benzene and TEX (toluene, ethylbenzene, and xylene combined) on cardiorespiratory mortality in Hong Kong

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ABSTRACT

Background: Numerous epidemiological and experimental studies have demonstrated the detrimental effects of the criteria air pollutants on population health, including particulate matters, ozone, and nitrogen dioxide. However, evidence on health effects of benzene, toluene, ethylbenzene, and xylene (BTEX in short) is insufficient.

Objectives: The present study aimed to assess the exposure-lag-response relations of ambient BTEX components with cardiorespiratory mortality in Hong Kong population.

Methods: Daily BTEX concentrations from April 2011 to December 2014 were collected from the Hong Kong Environmental Protection Department. Cause-specific mortality records were obtained from the Census and Statistics Department of Hong Kong. Generalized additive model (GAM) integrated with a distributed lag model (DLM) was used to estimate the excess risks of cardiorespiratory mortality associated with the cumulative exposure to benzene and TEX (toluene, ethylbenzene and xylene combined) over 0–9 lag days, while adjusting for time trend, seasonality, weather conditions and calendar effects.

Results: We observed the delayed and distributed lag effects of BTEX components on circulatory mortality. The cumulative exposures over 0–9 lag days for IQR increments of benzene (1.4 μg/m^3) and TEX (7.9 μg/m^3) were associated with 5.8% (95%CI: 1.0% to 10.8%) and 3.5% (95%CI: 1.0% to 6.1%) increases in circulatory mortality, respectively. The effect estimates of benzene and TEX were more delayed than that of $PM_{2.5}$. We didn't observe any significant association of BTEX exposure on total and respiratory deaths.

Conclusions: Short-term elevations in ambient BTEX concentrations may trigger circulatory mortality in Hong Kong population.

1. Introduction

Air pollution has been demonstrated as the largest environmental risk factor of disease and premature deaths worldwide, in which ambient air pollution accounted for 16% of all deaths in 2015 (Landrigan et al., 2017). Extensive epidemiologic and experimental studies have been conducted to evaluate the adverse health effects of criteria pollutants on the whole population (Cao et al., 2012; Chen et al., 2017; Lin et al., 2016; Tao et al., 2012; Zhou et al., 2015). However, knowledge of health impacts of ambient benzene, toluene, ethylbenzene and xylene (BTEX in short) is limited (Oftedal et al., 2003; Smargiassi et al., 2014; Ye et al., 2017). BTEX are the main chemical components of aromatic volatile organic compounds, which have extensive distributions and explicit toxicological materials.

Traffic is the major source of ambient BTEX in some metropolises with advanced de-industrialization, such as Hong Kong (Lee et al., 2002). Because of their special performances, BTEX are widely used in fuel formulation to make reformates, added to aviation and motor fuel to control autoignition under high pressure and hot temperature condition. Over 27.5% of high octane gasoline comprises of BTEX compounds collectively. Most BTEX chemical components in vehicle fuels are released into the air via gasoline evaporation and combustion, contributing approximate 90%–95% anthropogenic ambient BTEX (Bolden et al., 2015). With the rise in city transportation and air transportation tools, health effect of ambient BTEX will become an unavoidable problem and worldwide concern foreseeingly.

Abbreviations: BTEX, benzene toluene ethylbenzene and xylene; TEX, toluene ethylbenzene and xylene; ATSDR, the Agency for Toxic Substance & Disease Registry; HKEPD, the Hong Kong Environmental Protection Department; $PM_{2.5}$, particulate matter with aerodynamic diameter < 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; GAM, generalized additive model; IQR, inter-quartile range; ER, excess risk; CIs, confidence intervals; μg/m^3, micrograms per cubic meter; ppb, part per billion

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Toxicological information on BTEX constituents has been mainly based on studies of indoor environments. Benzene was listed as a Group 1 carcinogen by International Agency for Research on Cancer (IARC) in 1987 (IARC, 1987), and Ethylbenzene was classified as a possible carcinogen to humans (Group 2B) in 2000 (IARC, 2000). All four components had well-documented influences on the central nervous system and immune functions, such as dizziness, atopy, eczema, and asthma (ATSDR, 2004). Furthermore, benzene was also involved in metabolic function, indicating insulin resistance, toluene could result in the birth defect (Bolden et al., 2015). Ethylbenzene and xylene could cause acute eye and skin irritation (Bolden et al., 2015). According to these results from indoor-environment studies, the Agency for Toxic Substance & Disease Registry (ATSDR) set the Minimal Risk Levels (MRLs) at 3 ppb (9.57 μg/m^3), 1000 ppb (3770 μg/m^3), 60 ppb (260.4 μg/m^3) and 50 ppb (246 μg/m^3) for the chronic-duration inhalation of benzene, toluene, ethylbenzene and xylene, respectively (MRLs, 2017), probably based on their neurotoxicity to health human. European Environmental legislation established a thresholds value for benzene of 5 μg/m^3 as an annual average to protect human health (Kuklinska et al., 2015). The guideline was formulated based on the carcinogenicity of long-term exposure to benzene. However, some studies also suggested a harmful impact of short-term exposure to benzene on the cardiorespiratory system (Bolden et al., 2015; Oftedal et al., 2003), probably accelerating acute symptoms to occur for the high-risk population. Relevant guidelines for short-term exposure to ambient BTEX are insufficient.

Hong Kong is a representative city for most metropolises, with advanced de-industrialization, dense and aging population, as well as heavy traffic. It is an ideal field for studying the health effects of ambient BTEX. In the present study, we aimed to examine the short-term effects of ambient benzene and TEX (toluene, ethylbenzene, and xylene combined) constituents on both respiratory and circulatory mortality in Hong Kong's population via distributed lag modeling. The results of our study can contribute to the enrichment of basic materials for guideline formulation about ambient BTEX concentrations.

2. Materials and methods

2.1. Study area

Hong Kong is an autonomous territory on the eastern side of the Pearl River estuary in East Asia, located in the subtropical climate zone. With over 7.34 million inhabitants in a territory 1104 km^2, the population density of Hong Kong is over 6780 people per square kilometer. The age-standardized death rate in Hong Kong was about 3.0 per 1000 population, lower than the 7.1 per 1000 population in whole China in 2015 (HealthyHK, 2016). Ambient volatile organic compounds (VOC) is mainly derived from non-combustion sources (volatilization of gasoline) and road transport (Hong Kong Environmental Protection Department, 2015).

2.2. Environmental data

Air pollution data from April 1, 2011 to December 31, 2014 were obtained from the Hong Kong Environmental Protection Department (HKEPD), a government-run ambient monitoring network. BTEX components were monitored in five monitoring stations, Yuen Long (YL), Tung Chung (TC), Mong Kok (MK), Hok Tsui (HT) and the Hong Kong University of Science and Technology (UT), covering Hong Kong Island, Kowloon and the New Territories (Fig. 1). The on-line GC-FID analyzer (Syntech Spectras GC 955, Series 600/800, Netherland) was used to collect BTEX speciation data continuously with a time resolution of 30 min, which contained two separate systems for detection of C_2–C_5 and C_6–C_{10} hydrocarbons, respectively (Feng et al., 2013; Ling et al., 2013). In terms of the quality assurance and control (QA/QC), it used built-in computerized programs of QC systems such as auto-linearization and auto-calibration. Weekly calibrations were performed by NPL standard gas (National Physical Laboratory, Teddington, Middlesex, UK). Generally, the detection limits of the target BTEX ranged from 0.006 ppb (0.0191 μg/m^3 for benzene) to 0.009 ppb (0.0443 μg/m^3 for xylene), and both precision and accuracy of each species were lower 5% (**Table S1**) (Feng et al., 2013; Wang et al., 2017). Daily 24-h mean concentrations of benzene, toluene, ethylbenzene, m-/p-xylene, and o-xylene were computed from the 30-min resolution data for each station. We combined m-/p-xylene and o-xylene concentrations into total xylene, and then combined toluene, ethylbenzene and xylene as the total TEX concentration (TEX in short hereafter) because of the instrumental analysis challenges in separating these compounds, and their similar emission sources as well as toxicological properties. BTEX concentrations from the five stations were averaged to represent the territory-wide exposure. Daily 24-hour mean concentrations of fine particulate matter, nitrogen dioxide (NO_2) and ozone (O_3) were obtained from ten general fixed-site air quality monitoring stations of Hong Kong (Liang et al., 2018). The collection and validation of the data quality for criteria air pollutants followed closely with USEPA guidelines. Both the accuracy and precision were within the control limit of ± 10% (Hong Kong Environmental Protection Department, 1996). Meteorological data, daily relative humidity and mean temperature were obtained from the Hong Kong Observatory.

2.3. Total and cause-specific mortality

The Census and Statistics Department provided daily mortality data of the entire population in Hong Kong. Natural deaths (ICD-10: A00-R99), respiratory diseases (ICD-10: J00-J99) and circulatory diseases (ICD-10: I00-I99) were coded the 10th revisions of the International Classification of Diseases (ICD-10). No informed consent from individual subjects was provided since only aggregated data were used in this study.

2.4. Statistical modeling

Generalized additive Poisson models (GAM) integrated with distributed lag models (DLM) were used to fit the association between air pollution and risk of cardiorespiratory mortality (Zanobetti, 2000). Simple B-spline smooth functions were used to filter out the seasonal pattern and long-term trend in daily mortality, and to control for the non-linear effect of temperature and relative humidity (Mann et al., 2002). Referring to previous studies, we selected a priori model specification, with 7 degrees of freedom per year for time trend, 3 degrees of freedom for relative humidity and daily mean temperature (Qiu et al., 2012; Zanobetti and Schwartz, 2008). Calendar effects, such as public holidays and days of the week (DOW) were set as dummy variables.

We conducted distributed lag model (DLM) to pre-build the exposure-lag-response relations for both pollutants and temperature, which was integrated into the GAM as a *cross-basis* function to account for the potential distributed and lagged effect of pollution and temperature on mortality flexibly (Gasparrinia et al., 2010). We used second-degree polynomials to constrain the smooth shape of the distributed lags (Costa et al., 2016). The detail of the model specifications please refer to supplementary materials. In a preliminary test, we found the cumulative effects of BTEX reached a maximum when days of lag were extended to around 9 or 10, which was similar with the result from a previous study focusing on other air pollutants (Costa et al., 2016). We hence calculated distributed lag effects over 0–9 lag days for BTEX components, and computed cumulative effects over different lag periods, 0–4 and 5–9 lag days, to represent the relatively acute and delayed effects respectively. Temperature-lag-mortality association was suggested being considered when estimating the pollutant-mortality association (Kim et al., 2017), so we also used DLM to control temperature with the same temporal matrix as benzene (lags of 0–9 days). With the same statistical methods for testing the effects of BTEX on mortality, we tested the association of isoprene and $PM_{2.5}$ with

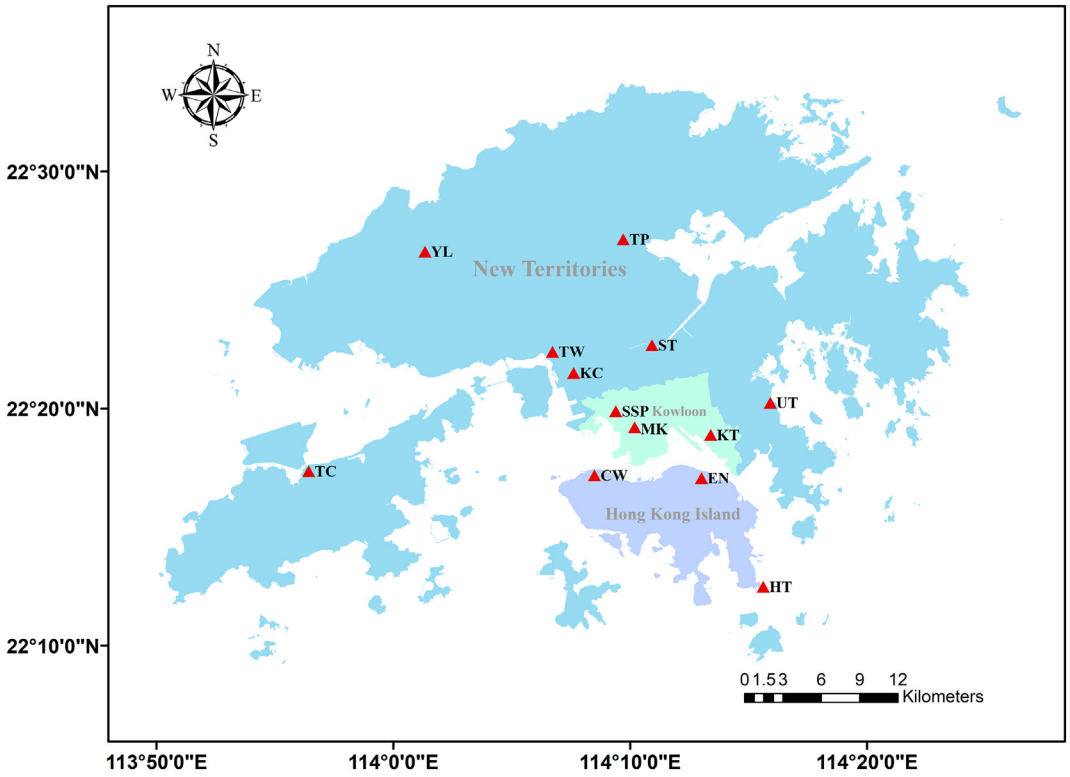

Fig. 1. Hong Kong map showing the monitoring stations for ambient BTEX components, $PM_{2.5}$, NO_2 and O_3. The five monitoring sites for ambient benzene and TEX are: YL, TC, MK, HT and UT. The ten monitoring sites for $PM_{2.5}$, NO_2 and O_3 are: YL, TP, ST, TW, KC, SSP, KT, CW, EN and TC.

mortality. These extra tests were intended to examine the specificity of the associations for causal inference (Lipsitch et al., 2010; Lumley and Sheppard, 2000). Isoprene was measured by the same on-line VOC analyzer and in the same five monitoring sites as for BTEX. We expected to observe a null association between cardiovascular mortality and isoprene, a presumably harmless compound emitted from certain tree species, and positive association between cardiovascular mortality and $PM_{2.5}$ which demonstrated the clear detrimental effect on the cardiovascular system (Atkinson et al., 2014). Plots of single-day lag and cumulative effect estimates were drawn to show the distributions of lag effects for benzene, TEX, isoprene and $PM_{2.5}$. The residuals of the model were checked for potential discernible pattern and autocorrelation by means of residual plot and partial autocorrelation function (PACF).

Sensitivity analyses were conducted to test the robustness of the association: 1) varying the degrees of freedom from 7 to 4 and 12 per year, respectively, to control for long-term trend and seasonality; 2) adjusting temperature by more rigorous control with 21 lag days (Kim et al., 2017; Tian et al., 2016); 3) excluding the data from HT monitoring site which locates in a remote area, and using the other four stations to compute the daily mean BTEX exposure; 4) further adjusting for other traffic-related air pollutants: nitrogen dioxide (NO_2) and ozone (O_3), respectively, with the same temporal matrix over lag 0–9 days.

The risk estimates were reported in terms of the percentage excess risk (ER%) changes in cause-specific mortality per interquartile range (IQR) increment of BTEX concentrations and corresponding 95% confidence intervals (CIs) (Tian et al., 2017). All regression analyses were achieved by R 3.3.2 version using 'dlnm' package, and variable-lag matrices of temperature and BTEX components were generated by 'crossbasis' function in 'dlnm' package.

3. Results

3.1. Data description

A total of 162,312 natural deaths were recorded in our study population during the study period (April 1, 2011 to December 31, 2014), with mean cases of 118.4 per day. Thereinto, deaths of respiratory and circulatory diseases accounted for 21.4% (25.3 cases per day) and 23.1% (27.4 cases per day), respectively. The daily 24-hour mean concentrations of benzene, TEX and isoprene were 1.4 μg/m^3, 7.9 μg/m^3, and 0.7 μg/m^3. Mean concentrations of $PM_{2.5}$, NO_2 and O_3 were 30.5 μg/m^3, 64.4 μg/m^3 and 38.1 μg/m^3. The daily mean temperature was 23.8 °C and the relative humidity was 78.7% in study period in Hong Kong (Table 1).

Fig. 1 shows the distribution of monitoring sites in Hong Kong. There were five monitoring sites for ambient BTEX, three (YL, TC, and UT) distributed in New Territories, one (MK) in Kowloon and one (HT) in Hong Kong Island. The long-term trends and seasonality of both ambient BTEX components and cardiorespiratory mortalities are reflected by time-series plots of daily variation (Fig. 2). Annual periodicity was observed in these time series of pollutants and health outcomes. Higher concentrations of ambient BTEX occurred in winter and lowers occurred in summer. Cardiorespiratory deaths also began to increase in October, reaching maximum level in January or February, followed by a decreasing trend which reached a minimum level around September. We further analyzed the Spearman correlation among pollutants and weather factors. There was a strong correlation between benzene and TEX, with a Spearman correlation coefficient (ρ) of 0.803 ($P < 0.01$). Benzene was highly correlated with $PM_{2.5}$ ($\rho = 0.735$, $P < 0.01$) but moderately correlated with NO_2 ($\rho = 0.621$, $P < 0.01$) and O_3 ($\rho = 0.345$, $P < 0.01$). $PM_{2.5}$ was highly correlated with NO_2 ($\rho = 0.757$, $P < 0.01$) in Table 2 and **Table S2**.

Table 1
Descriptive statistics for daily total and cause-specific mortality, ambient VOC components, air pollutants, and weather conditions in Hong Kong, 2011–2014 (n = 1371 days).

	Mean	SD	Min	P_{25}	P_{50}	P_{75}	Max	IQR
Population mortality (counts per day)								
Total deaths	118.4	16.6	72.0	107.0	116.0	128.0	186.0	21.0
Respiratory deaths	25.3	6.9	8.0	20.0	25.0	30.0	50.0	10.0
Circulatory deaths	27.4	7.1	10.0	22.0	26.0	31.0	56.0	9.0
VOC components (μg/m^3)								
Benzene	1.3	1.0	0.1	0.4	1.1	1.8	6.9	1.4
TEX	8.9	8.2	0.9	3.7	5.8	11.6	63.8	7.9
Isoprene	0.8	0.5	0.1	0.4	0.7	1.1	3.4	0.7
Other pollutants (μg/m^3)								
$PM_{2.5}$	30.5	17.1	5.2	16.4	27.2	40.2	116.9	23.8
NO_2	64.4	19.5	17.2	50.7	61.6	74.6	161.5	24.0
O_3	38.1	22.2	4.5	19.6	32.6	52.4	131.5	32.8
Weather conditions								
Temperature (°C)	23.8	5.2	8.4	19.8	25.1	28.3	31.8	8.5
Relative humidity (%)	78.7	10.4	29.0	74.0	79.0	86.0	99.0	12.0

Abbreviations: VOC, volatile organic compounds; SD, standard deviation; Min, minimum; Max, maximum; IQR, interquartile range; P_{25}, 25th percentile; P_{50}, 50th percentile; P_{75}, 75th percentile; TEX, toluene, ethylbenzene and xylene Combined; $PM_{2.5}$, particulate matter with aerodynamic diameter < 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone.

3.2. Associations of BTEX with cardiorespiratory mortality

Exposure-response curves between BTEX and cardiovascular mortality were approximately linear at ambient BTEX levels (**Fig. S1**). We observed the distributed lag effects of both benzene and TEX on circulatory deaths. The cumulative effects over 0–9 lag days for IQR increments of benzene (1.4 μg/m^3) and TEX (7.9 μg/m^3) was associated with 5.8% (95%CI: 1.0% to 10.8%) and 3.5% (95%CI: 1.0% to 6.1%) increases of circulatory mortality, respectively (Table 3). Compared with the acute effect of $PM_{2.5}$ observed over 0–4 lag days, the effects of both benzene and TEX on circulatory deaths were relatively delayed, resulting 4.1% and 2.9% increments of mortality over 5–9 lags days respectively (Table 3). We didn't observe the significant associations of BTEX components with total and respiratory mortality. We also obtained positive relations of IQR increments of $PM_{2.5}$ and NO_2 on circulatory pre-deaths over ten days of cumulative exposure, and only observed acute impacts of ozone on total deaths.

Single-day effects and cumulative effects over 0–9 lag days for both benzene and TEX were shown, with isoprene as the negative control and $PM_{2.5}$ as the positive control (Fig. 3). We observed the delayed effect of benzene on circulatory deaths occurred on 6–7 lag days, and TEX on 6–9 lag days. The cumulative effects of benzene and TEX increased along the lags and were significant after the 8 lag days. We also observed a significant effect for $PM_{2.5}$ on circulatory mortality and no impacts of isoprene (Fig. 3). Fig. 4 presents the sensitivity analyses for the cumulative ER% of ambient BTEX and $PM_{2.5}$ over 0–9 lag days (dlm_{0-9}) on cardiovascular mortality. S1 and S2 are the results of models with 4 degrees of freedom per year and 12 degrees of freedom per year to control time trend respectively. S3 represents results of 0–21 lag days' temperature adjustment. S4 and S5 show results of models with further adjustment for NO_2 and O_3 respectively. S6 means the cumulative effects when removing the data from HT. These sensitivity analyses show that the effect estimates of both benzene and TEX on cardiovascular deaths changed slightly after modifying the degrees of freedom for time trend, controlling temperature over 0–21 lag days, and traffic-related co-pollutant adjustment, suggesting the robustness of the detected associations. The effect of $PM_{2.5}$ was also robust to time

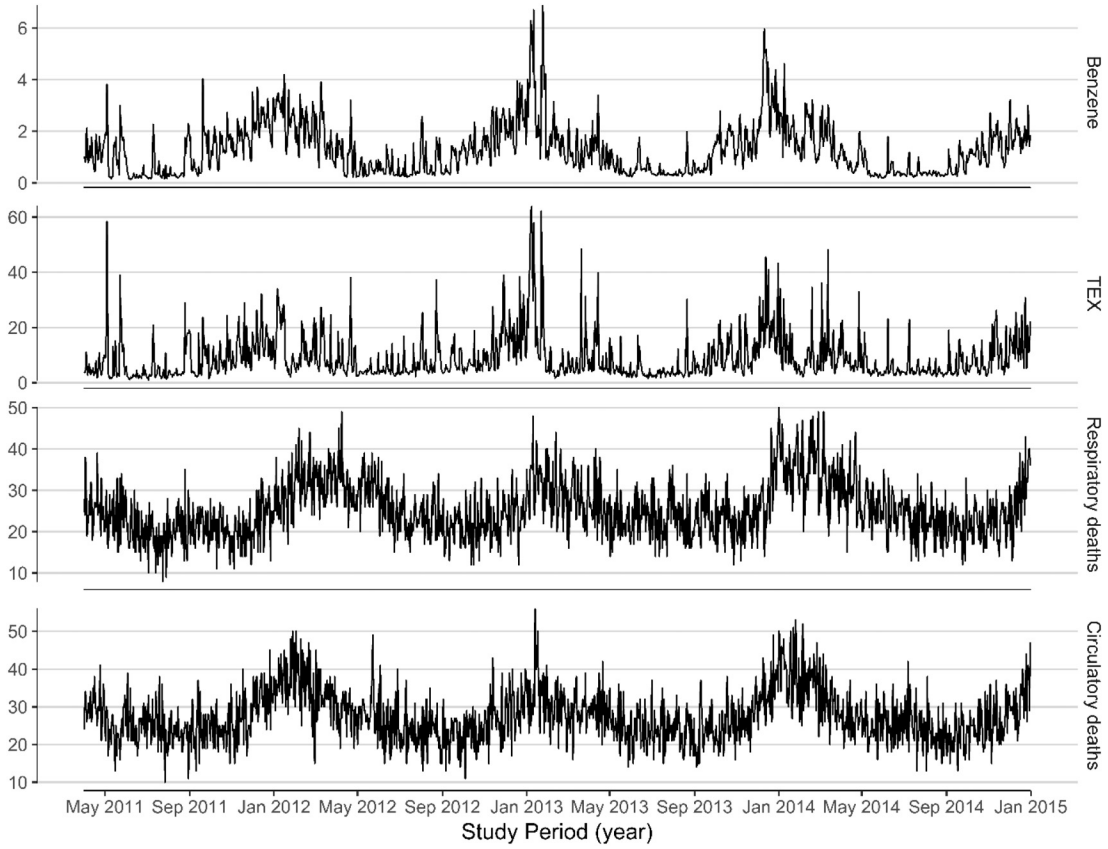

Fig. 2. Time series plots of the daily mean ambient Benzene, TEX and cardiorespiratory mortality in Hong Kong population, 2011–2014. The units of Benzene and TEX are μg/m^3, and units for cardiorespiratory death are counts per day.

Table 2
Spearman correlation coefficients between BTEX components, traffic-related pollutants and weather conditions in Hong Kong, 2011–2014 (n = 1371 days).

	Benzene	TEX	Isoprene	$PM_{2.5}$	NO_2	O_3	Temperature	Humidity
Benzene	1.000	–	–	–	–	–	–	–
TEX	0.803	1.000	–	–	–	–	–	–
Isoprene	−0.570	−0.355	1.000	–	–	–	–	–
$PM_{2.5}$	0.735	0.584	−0.349	1.000	–	–	–	–
NO_2	0.621	0.638	−0.317	0.757	1.000	–	–	–
O_3	0.345	0.151	−0.239	0.622	0.369	1.000	–	–
Temperature	−0.761	−0.532	0.792	−0.484	−0.427	−0.182	1.000	–
Humidity	−0.274	−0.185	−0.026	−0.474	−0.347	−0.460	0.055	1.000

Abbreviations: BTEX, benzene, toluene, ethylbenzene and xylene; TEX, toluene, ethylbenzene and xylene Combined; $PM_{2.5}$, particulate matter with aerodynamic diameter < 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone.

Table 3
The association of Benzene and TEX exposure with total and cardiorespiratory mortality (percent excess risk per IQR increase of pollutant).[a]

	Total deaths	Respiratory deaths	Circulatory deaths
Benzene			
dlm_{0-4}[b]	−0.8 (−2.2, 0.7)	−1.9 (−5.0, 1.4)	1.6 (−1.5, 4.8)
dlm_{5-9}[c]	0.5 (−1.0, 1.9)	0.7 (−2.4, 4.0)	4.1 (1.0, 7.4)[e]
dlm_{0-9}[d]	−0.3 (−2.5, 1.9)	−1.1 (−5.8, 3.8)	5.8 (1.0, 10.8)[e]
TEX			
dlm_{0-4}	0 (−0.9, 0.8)	0.9 (−0.9, 2.7)	0.6 (−1.1, 2.4)
dlm_{5-9}	0.2 (−0.6, 1.1)	0.1 (−1.6, 1.9)	2.9 (1.1, 4.6)[e]
dlm_{0-9}	0.2 (−1.0, 1.4)	1.0 (−1.5, 3.6)	3.5 (1.0, 6.1)[e]
Isoprene			
dlm_{0-4}	0.1 (−2.0, 2.3)	−2.6 (−7.1, 2.1)	4.0 (−0.7, 9.0)
dlm_{5-9}	−1.1 (−3.1, 1.0)	1.2 (−3.3, 6.0)	−1.8 (−6.2, 2.8)
dlm_{0-9}	−1.0 (−4.0, 2.2)	−1.4 (−8.0, 5.7)	2.2 (−4.6, 9.5)
$PM_{2.5}$			
dlm_{0-4}	0.9 (−0.3, 2.1)	−0.3 (−2.9, 2.4)	2.9 (0.3, 5.6)[e]
dlm_{5-9}	1.0 (−0.1, 2.2)	1.4 (−1.0, 3.9)	1.7 (−0.7, 4.1)
dlm_{0-9}	1.9 (0.3, 3.6)[e]	1.1 (−2.5, 4.9)	4.6 (1.0, 8.3)[e]
Other pollutants			
NO_2 (dlm_{0-9})	1.0 (−0.9, 2.9)	1.2 (−2.9, 5.5)	4.3 (0.2, 8.6)[e]
O_3 (dlm_{0-9})	2.6 (0.2, 5.0)[e]	−1.4 (−6.4, 3.9)	0.9 (−4.1, 6.1)

Abbreviations: TEX, toluene, ethylbenzene and xylene Combined; IQR, interquartile range; $PM_{2.5}$, particulate matter with aerodynamic diameter < 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone.

[a] Time-series study using GAM distributed lag model adjusting temperature, relative humidity, public holidays and days of week and effect estimates are percent excess risk (ER%; 95%CI).

[b] Cumulative effect over 0–4 lag days.

[c] Cumulative effect over 5–9 lag days.

[d] Cumulative effect over 0–9 lag days.

[e] Statistically significant effect estimates.

trend modification, longer temperature and O_3 adjustment, but decreased moderately with the adjustment for NO_2 in a co-pollutant model (Fig. 4, Table 2).

4. Discussion

In this time series study, we assessed the short-term effects of benzene and TEX over ten lag days on cardiorespiratory mortality. Significant delayed effects of benzene and TEX on premature circulatory deaths were found. We didn't observe the significant associations of both benzene and TEX with total and respiratory mortality. The associations of BTEX with circulatory deaths were robust by modifying the degrees of freedom for time trend, rigorous controlling for temperature or adjustment for traffic-related co-pollutants. We also found detrimental impacts of $PM_{2.5}$ and NO_2 on circulatory mortality and harmful effect of O_3 on total deaths. Consistency between our study and the previous studies in the results about $PM_{2.5}$, NO_2 and O_3 (Metzger et al., 2004), also showed the reliability of the model we used.

This is the first study to assess the health effects of BTEX components using Hong Kong monitored data. A few previous epidemiological studies of outdoor benzene exposure and circulatory diseases generated inconsistent findings. A case-crossover study detected an association of benzene with myocardial infarction (Bard et al., 2014). Another study on personal exposures of children with asthma observed a null association between industrial benzene exposure and cardiovascular function. Actually, the design of the study was very different from our operation. It focused on the personal exposure of children with asthma while we observed the whole population. It only chose the indices of circulatory function much relevant to asthma, blood pressure and heart rate, which were not efficient indices for cardiovascular death (Smargiassi et al., 2014). A study from the US used three different analytic approaches in time-series framework to estimate the acute cardiorespiratory effects of ambient VOC groups (Ye et al., 2017), while no association was found between aromatic group and emergency department visits for cardiovascular diseases or asthma. Another study, examining the chemical properties of air pollutants and cause-specific hospital admissions in Atlanta of the US, didn't find the significant associations of aromatics with cardiorespiratory diseases neither (Suh et al., 2013). However, considering the aromatic hydrocarbons also contained some other chemical components besides BTEX components, the up-mentioned two studies were not precise enough for examining the potential effect of ambient BTEX exposure on the circulatory system. A study from Norway reported the significant associations of benzene on respiratory diseases, but the mixed findings were observed when examining the associations in two different time periods (Oftedal et al., 2003). The reason could be the residual confounding since they did not consider the exposure-lag-response effect of temperature and their control of temperature was not tight enough. Few studies revealed significant harmful effects of ambient TEX exposure on both respiratory and circulatory system, probably because of their weaker toxicity than benzene.

Hematologic toxicity, Neurotoxicity and immunologic toxicity of benzene had been well-revealed in previous studies, and their biological mechanisms were documented and discussed detailedly in many vivo experiments (ATSDR, 2005). However, Bio-mechanism information of benzene and TEX group on the circulatory system was not mentioned sufficiently. Two points could be deduced based on some known findings: first, the harmful effects of benzene on nervous, endocrine and immunological systems were clear (ATSDR, 2005), so the inhale benzene could be possible to accelerate circulatory death by homeostasis disturbance and immune collapse; second, some metabolites such as phenol, benzene oxide and benzoquinones, had latent cardiovascular toxicities via mucosa irritation of blood vessels and oxidative stress damage (Henderson et al., 1989; Medinsky et al., 1989), which could aggravate patients' circulatory burdens.

Compared with $PM_{2.5}$, the delayed effects of ambient BTEX components on circulatory mortality were interesting. We observed the more acute effect of $PM_{2.5}$ over 2–6 lag days but a relatively delayed effect of BTEX over 6–9 lag days. The premature circulatory deaths

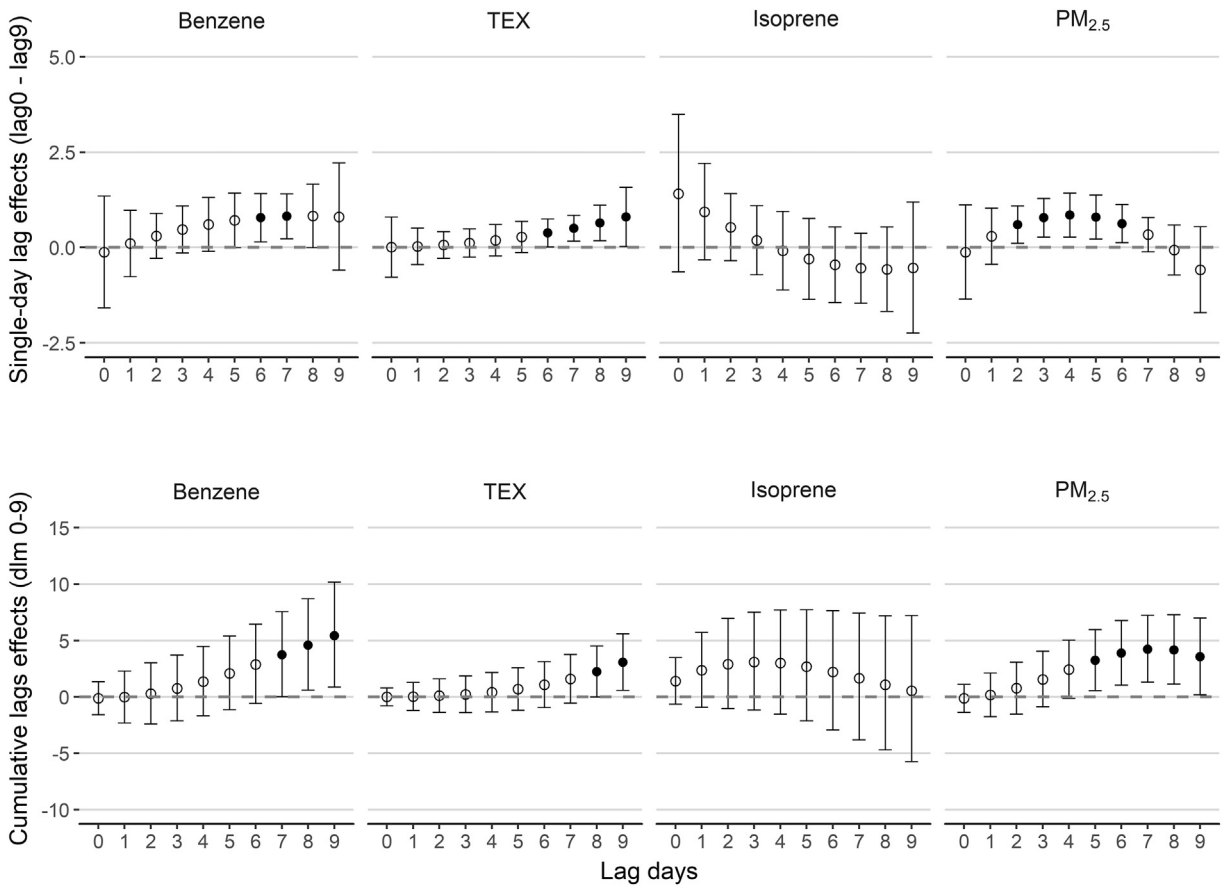

Fig. 3. Lag distributions of both single-day effects and cumulative effects for Benzene, TEX combined, Isoprene and $PM_{2.5}$ on circulatory mortality. dlm_{0-9} stands for the cumulative effect with lags of 0–9 days; ER% is the percentage of the excess relative risk; solid dots represent statistically significant results and hollow dots are statistically non-significant.

could be caused primarily by disturbing hemostasis and destroying the immune defense, rather than simple mucosa or vascular irritation, so relatively longer time for sustaining effects could be necessary for this indirect process. Although inhalational BTEX components would be metabolized timely in the liver and eliminated from the body, the previous studies showed that there was still a smaller portion remaining in adipose tissues and was slowly eliminated (Löf et al., 1993). To some extent, internal BTEX components could be enriched in adipose tissues, like some environmental estrogens (EEs), and after long time accumulation, concentrations of internal BTEX components could break through a certain threshold to harm the human body. Furthermore, internal BTEX components, distributed to tissues, were also dependent on the perfusion rate of the tissue by blood, hence circulatory system was a severely afflicted target (ATSDR, 2005). Finally, it was revealed by in vivo studies that internal benzene tended to generate more putative toxic metabolites at low doses than at high doses. Specifically, benzene could be metabolized to phenol then converted to hydroquinone at low doses, while at high doses, benzene inhibited phenol metabolism to hydroquinone directly (Zhang et al., 2005). Concentrations of ambient BTEX components were undoubtedly at a low level, hence longer-time accumulation might result in the enrichment of some internal putative toxic metabolites, such as phenol, and it was hard to exclude their harmful effects on circulatory system in this complex metabolic system.

Previous studies demonstrated longer effects of cold temperature on cardiovascular diseases (Tian et al., 2016), and suggested that a long-structure of temperature would confound the pollution-lag-response relationship (Kim et al., 2017). Therefore, we controlled temperature with the same temporal matrix as benzene and TEX group (over 0–9 lag days) and tested the robustness by controlling temperature with 21 lag days. Compared with previous air pollution studies controlling temperature with the current day and moving average of previous three days (Peng et al., 2008; Qiu et al., 2012), the sufficient control of temperature in this study should be a strength which made our findings more conservative and convincible. Meanwhile, some limitations should also be noted: First, we used data from available monitoring stations to estimates the city-wide population exposures. Although all the five sites had a certain representativeness for different exposure conditions, exposure misclassification was inevitable while estimating the population exposure level. Ecological fallacy could not be eliminated effectively in time-series study, based on aggregated measures of exposures and outcomes. Second, although we had controlled the widely accepted confounders in our model, including temperature, relative humidity and calendar effects, there were still some un-measured time-varying confounders which could not be controlled. Third, we only observed the circulatory effects of BTEX components in this study, the cause-specific health outcomes and the short-term effects of other chemical components of VOCs will be further examined in the future studies.

5. Conclusions

In conclusion, short-term elevation in ambient BTEX levels might trigger events of premature circulatory deaths in Hong Kong population, and the effects may be more delayed compared with the estimate of $PM_{2.5}$. The findings may contribute to more angles for the detrimental effects of traffic-related air pollution on human health. However, association does not mean causation. Merely modeling the

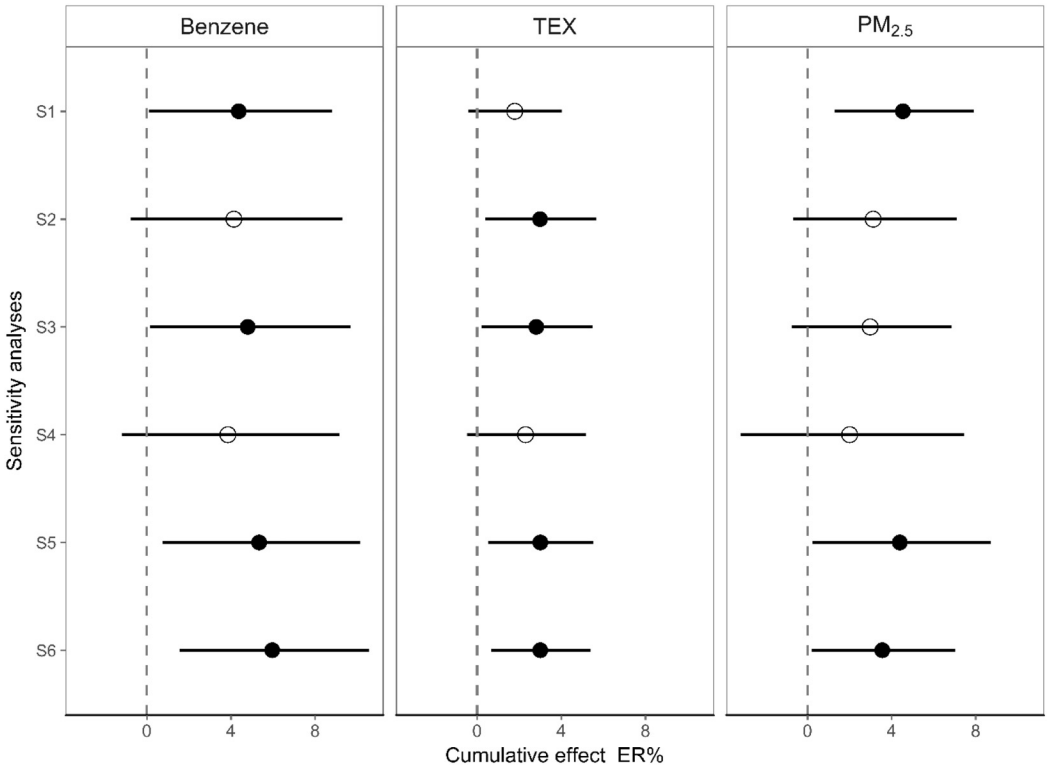

Fig. 4. Sensitively analyses to show the cumulative effects of Benzene, TEX combined and $PM_{2.5}$ on circulatory mortality with lags of 0–9 days. S1–4 degrees of freedom per year; S2–12 degrees of freedom per year; S3 - temperature over 0–21 lag days; S4 - further adjust NO_2; S5 - further adjust O_3; S6 - remove the data from HT; solid dots represent significant results and hollow dots are not significant.

association is deficient because of the possible inequality between association and causality. Yet when there is limited background knowledge about certain surprising associations at extremely low ambient concentrations, we depend mostly on the available data to cautiously infer cause-effect relationships. Certainly, further individual-level and mechanistic studies should be designed and conducted to substantiate our findings.

Declarations of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.04.049.

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