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Effects of ambient benzene and toluene on emergency COPD hospitalizations: A time series study in Hong Kong

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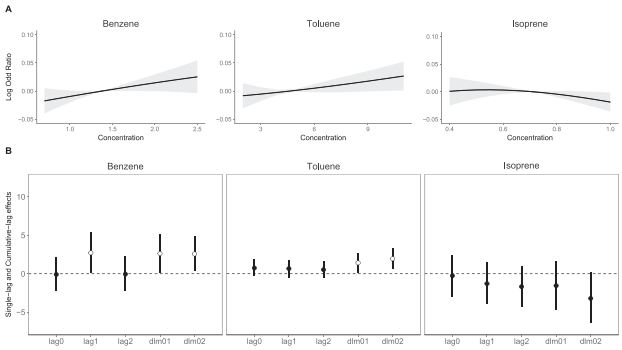
HIGHLIGHTS

- Evidence of ambient benzene and toluene on COPD is insufficient.
- We performed generalized additive distributed lag model to assess short-term effects of ambient benzene and toluene on emergency COPD hospitalizations.
- We observed cumulative effects of daily mean benzene and toluene on emergency COPD hospitalizations up to two days.
- The relation of daily maximum toluene on emergency COPD hospitalizations was stronger in the younger people.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Although numerous studies have demonstrated that the criteria air pollutants increased the risk of exacerbation of chronic obstructive pulmonary disease (COPD), few have explored the effects of ambient benzene and toluene on COPD.
Objective: This study aimed to evaluate the short-term effects of ambient benzene and toluene on emergency COPD (eCOPD) hospitalizations.
Methods: We obtained daily mean and maximum concentrations of benzene and toluene during April 1, 2011 - December 31, 2014 from the Hong Kong Environmental Protection Department, and daily counts of eCOPD hospitalizations from the Hospital Authority. Generalized additive distributed lag models were used to estimate the percentage excess risk (ER%) of eCOPD hospitalizations per interquartile range (IQR) increase in ambient benzene and toluene.
Results: The ER% estimates of eCOPD hospitalizations post cumulative exposure of up to two days were 2.62% (95%CI: 0.17% to 5.13%) and 1.42% (0.16% to 2.69%), for per IQR increase of daily mean benzene (1.4 μg/m^3) and toluene (4.6 μg/m^3), respectively. People below the age of 65 had a significantly higher risk of eCOPD hospitalizations associated with daily maximum toluene than the elderly.
Conclusions: Ambient benzene and toluene might be environmental stressors for acute exacerbations of COPD in the Hong Kong population.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) has contributed to most of the global burden of chronic respiratory diseases (Soriano et al., 2017). In 2015, COPD was the eighth leading cause of disease burden, associated with 2.6% of global disability-adjusted life years (DALYs) and >3 million deaths (Soriano et al., 2017; Wang et al., 2016). In China, COPD was the third leading cause of death in 2013 and claimed >0.9 million deaths (Zhou et al., 2016). The death rate of COPD has increased 11.6% from 1990 to 2015 (Soriano et al., 2017), and COPD was projected to become more prevalent among young adults (Cerveri et al., 2008).

Tobacco smoking has been well recognized as the primary cause of COPD, and air pollution was also found as a risk factor for COPD mortality and morbidity (Vestbo and Mathioudakis, 2018; Wang et al., 2018). Previous studies on the short- and long-term effects of air pollutants on COPD have focused on the criteria air pollutants, including ambient particulate matter, household air pollution, occupational matters, and ozone (Li et al., 2016; Meng et al., 2013; Ni et al., 2015; Qiu et al., 2013; Schikowski et al., 2014; Soriano et al., 2017; Sun et al., 2018), but few have explored the effects of aromatic volatile organic compounds (VOCs), such as benzene and toluene. These hazardous gaseous pollutants coexist with the criteria air pollutants in the ambient environment but received less attention in previous studies.

A few studies have reported adverse respiratory effects of benzene and toluene. Oftedal and colleagues found that ambient benzene and toluene increased the risk of respiratory hospitalizations from 1994 to 1997, but the effect of ambient benzene was not significant after 1997 (Oftedal et al., 2003). A study in Australia and the US also found two or three times higher incidence risks of asthma associated with per 10-unit increase in toluene or benzene, respectively (Arif and Shah, 2007). However, to date, there are no clear and uniform guidelines for the safe range of their ambient concentrations. For example, the annual reference level of ambient benzene is set to 5 and 3 μg/m^3 by the European Union and Japan, respectively, and no reference level is set by the United States and WHO (Kuklinska et al., 2015; Ministry of the Environment, 2014). A few cities had a guideline on the odor threshold of ambient toluene, but not on its safety range.

This study aimed to estimate the short-term effects of benzene and toluene on emergency COPD (eCOPD) hospitalizations in Hong Kong. A time series modeling approach was adopted, given its advantage of minimizing the confounding effects of time-invariant variables, such as tobacco smoking and socioeconomic status. The findings of this study could provide critical evidence for developing the guidelines for preventing acute exacerbations of COPD associated with environmental risk factors.

2. Materials and methods

2.1. Study area

Hong Kong is a coastal city located on the eastern side of the Greater Bay Area of China. Hong Kong has a typical subtropical climate and one of the highest population density city in the world, with a population of over 7.3 million in a residential and commercial area of 1104 km^2. The standardized death rate of Hong Kong in 2016 is approximate 5.6 per 1000 population (with 7.5 in men and 5.3 in women) (Census and Statistics Department, 2016). The major air pollutants in Hong Kong are the criteria air pollutants and ambient VOC. The latter is mainly derived from road transport and non-combustion sources such as volatilization of gasoline (Hong Kong Environmental Protection Department, 2015).

2.2. eCOPD hospitalizations

Daily data of emergency hospitalizations from April 1, 2011 to December 31, 2014 were obtained from the Hospital Authority which manages 42 public hospitals in Hong Kong and provides over 90% of hospital beds for local residents (Tian et al., 2017). Daily counts of eCOPD hospitalizations were retrieved by the International Classification for Diseases version 9 (ICD-9) codes of 491, 492 and 496 as the primary discharge diagnosis. Informed consent from each patient was exempted by the ethical committee of the University of Hong Kong, because only aggregated data were used in this study.

2.3. Air pollution and meteorological data

We obtained daily concentrations of ambient benzene and toluene from the Hong Kong Environmental Protection Department (HKEPD), a government-run ambient monitoring network. The geographic locations of five monitoring stations at Mong Kok (MK), Tung Chung (TC), Hok Tsui (HT), Yuen Long (YL) and the Hong Kong University of Science and Technology (UT) are shown in Fig. S1. We also obtained daily concentrations of isoprene, which were used as negative control in this study, from the same five monitoring stations. Isoprene is assumed harmless to human health since it is naturally generated by some tree species. Detailed information about exposure measurements has been reported elsewhere (Feng et al., 2013; Ran et al., 2018a; Wang et al., 2017). Briefly, the online GC-FID analyzer (Syntech Spectras GC 955, Series 600/800, Netherland) was used to continually record benzene and toluene concentrations at 30-min epoch. Built-in computerized programs of QC systems were used, such as auto-linearization and auto-calibration. Weekly calibrations were performed by NPL standard gas (National Physical Laboratory, Teddington, Middlesex, UK). The precision and accuracy of benzene were controlled under 5% and 2%, toluene were 3% and 1%, respectively (Feng et al., 2013; Wang et al., 2017). The detection limit 0.0191, 0.0263 and 0.0279 μg/m^3 for benzene, toluene, and isoprene, respectively. Daily (24-hour) mean and maximum concentrations of benzene were calculated for each station, and subsequently averaged to represent the citywide exposure. Similar calculations were repeated for toluene and isoprene. Daily mean concentrations of $PM_{2.5}$, NO_2, and O_3 of ten general fixed-site monitoring stations were obtained from HKEPD during the study period (Liang et al., 2018), and daily mean temperature and relative humidity were provided from the Hong Kong Observatory.

Table 1
Descriptive statistics for emergency COPD hospitalizations, VOCs, criteria air pollutants and weather factors in Hong Kong during 2011 to 2014.

	Mean	SD	P_{25}	P_{50}	P_{75}	IQR
Emergency hospitalizations (counts)						
Total COPD	54.8	13.9	44.0	53.0	64.0	20.0
Female	8.5	3.6	6.0	8.0	11.0	5.0
Male	46.3	12.0	37.0	45.0	54.0	17.0
Age < 65	6.2	2.6	4.0	6.0	8.0	4.0
Age ≥ 65	48.6	13.0	39.0	47.0	57.0	18.0
Volatile organic components (μg/m^3)						
Benzene (daily mean)	1.3	1.0	0.4	1.1	1.8	1.4
Benzene (daily max)	3.4	3.9	1.5	2.4	3.9	2.5
Toluene (daily mean)	5.1	4.7	2.0	3.5	6.6	4.6
Toluene (daily max)	23.8	32.0	9.9	14.7	25.1	15.2
Isoprene (daily mean)	0.8	0.5	0.4	0.7	1.1	0.7
Isoprene (daily max)	3.5	2.8	1.4	2.8	4.9	3.5
Means of other air pollutants (μg/m^3)						
$PM_{2.5}$	30.5	17.1	16.4	27.2	40.2	23.8
NO_2	64.4	19.5	50.7	61.6	74.6	24.0
O_3	38.1	22.2	19.6	32.6	52.4	32.8
Weather conditions						
Temp (°C)	23.8	5.2	19.8	25.1	28.3	8.5
RH (%)	78.7	10.4	74.0	79.0	86.0	12.0

Abbreviations: COPD, chronic obstructive pulmonary disease; VOC, volatile organic compounds; P_{25}, 25th percentile; P_{50}, 50th percentile; P_{75}, 75th percentile; $PM_{2.5}$, particulate matter with aerodynamic diameter < 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; Temp, temperature; RH, relative humidity; max, maximum.

Table 2
Spearman correlation coefficients between volatile organic components, criteria air pollutants, and weather factors.

	Benzene	Toluene	Isoprene	$PM_{2.5}$	NO_2	O_3	Temp	RH
Benzene	1.000	–	–	–	–	–	–	–
Toluene	0.823	1.000	–	–	–	–	–	–
Isoprene	−0.570	−0.404	1.000	–	–	–	–	–
$PM_{2.5}$	0.735	0.610	−0.349	1.000	–	–	–	–
NO_2	0.621	0.651	−0.317	0.757	1.000	–	–	–
O_3	0.345	0.180	−0.239	0.622	0.369	1.000	–	–
Temp	−0.761	−0.570	0.792	−0.484	−0.427	−0.182	1.000	–
RH	−0.274	−0.197	−0.026	−0.474	−0.347	−0.460	0.055	1.000

Abbreviations: $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; Temp, temperature; RH, relative humidity.

2.4. Statistical modeling

A generalized additive distributed lag model with the quasi-Poisson family was used to estimate the risk of eCOPD hospitalizations associated with benzene and toluene (Gasparrini et al., 2010; Zanobetti, 2000). Natural spline smooth functions were used to filter out the secular trend and seasonality in daily counts, and to control the non-linear effects of temperature and relative humidity (Gasparrini et al., 2015). Model specifications were selected from previous time series studies: 8 degrees of freedom per year for time trend and seasonality; 3 degrees of freedom for relative humidity, current day mean temperature as well as the previous three days' moving average (Qiu et al., 2013; Tian et al., 2017). Weekday and holiday effects were controlled by adding the dummy variables of day-of-week (DOW) and public holidays (Holidays) in our model.

A distributed lag model (DLM) was used to establish the exposure-lag-response relationship between ambient VOCs and eCOPD hospitalizations (Gasparrini et al., 2010). The single lag linear effects of benzene

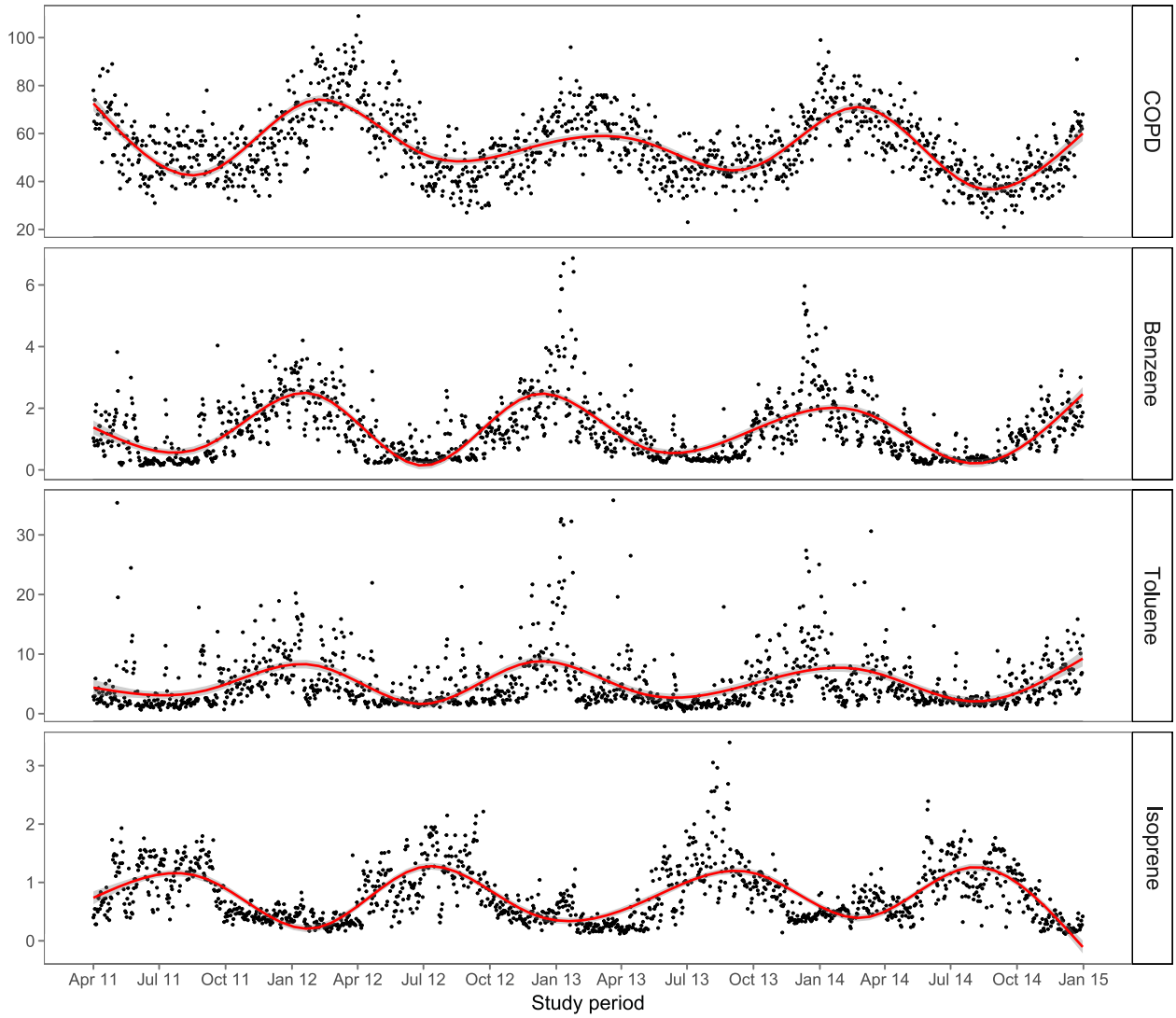

Fig. 1. Time series plots of daily number of eCOPD hospitalizations and daily mean concentrations of ambient benzene, toluene, and isoprene. The unit of eCOPD hospitalizations is count per day, the units of benzene, toluene and isoprene are μg/m^3. Red lines are the natural spline smooth lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and toluene on eCOPD hospitalizations were estimated for the current day and up to the preceding two days (lag_0 to lag_2). The cumulative 1-day and 2-day lag effects (dlm_{01}, dlm_{02}) were fit by an unconstrained DLM (Schwartz, 2000; Tian et al., 2015). Given the photochemical reaction between VOCs and ozone and the potential relation of ozone on COPD mortality, we also adjusted for the potential confounding of ozone by adding daily mean ozone concentration with the same temporal matrix as organic variables in our model (Ling, 2013; Qiu et al., 2013). The discernible pattern and autocorrelation were checked by residual and partial autocorrelation function (PACF) figures. A typical model is as follows:

$$\log(E(Y)) = \alpha + s(t, df = 8/year * no.of\ years) + s(Humid_0, df = 3) + s(Temp_0, df = 3) + s(Temp_{13}, df = 3) + \beta_1 DOW + \beta_2 Holiday + \beta_{3,l} O_3 + \beta_{4,l} Var$$

Here, $E(Y)$ represents the expected daily counts of eCOPD hospitalizations on day t; s(.) denotes cubic splines for nonlinear variables; β_i are regression coefficients; $\beta_{i,\,l}$ are coefficients for matrices; *Var* are VOC variables; $Humid_0$ denotes the daily mean relative humidity; $Temp_0$ denotes the daily mean temperature; $Temp_{13}$ denotes the moving average of temperature in the preceding three days; *DOW* is the dummy variable for days of the week.

Sex- and age-stratified analyses were performed to identify susceptible subpopulations. We tested the statistical significance of age and gender differences (male vs female, aged <65y vs ≥65y), by calculating: $(\beta_1 - \beta_2) \pm 1.96\sqrt{SE_1^2 + SE_2^2}$ (Ran et al., 2018b; Schenker and Gentleman, 2001). To ensure the robustness of effect estimates, we also conducted the following sensitivity analyses: 1) daily mean concentrations of $PM_{2.5}$ (or NO_2) were added into the model; 2) ambient ozone concentration was adjusted with the maximum lagged days extending to a week; 3) temperature was controlled with the maximum lagged days extending to one and two weeks; 4) the degree of the freedom for the time trend was changed from 8 per year to 4 and 12 per year (Kim et al., 2017; Tian et al., 2016).

The percentage excess risk (ER%) changes and corresponding 95% confidence intervals (CIs) of eCOPD hospitalizations per interquartile range (IQR) increase of benzene and toluene concentrations were chosen as the risk estimates: ER (%) = (RR - 1) × 100%. All analyses were conducted using the 'mgcv' and 'dlnm' packages in the R software (3.3.2 version).

3. Results

A total of 75,113 episodes of eCOPD hospitalizations were recorded during April 1, 2011 to December 31, 2014, and 84.5% occurred in men. Overall average of daily mean and maximum concentrations during the study period was 1.4 and 2.5 μg/m^3 for benzene, 4.6 and 15.2 μg/m^3 for toluene, 0.7 and 3.5 μg/m^3 for isoprene. For the criteria air pollutants, overall average of daily mean concentrations was 23.8 μg/m^3 for $PM_{2.5}$, 24.0 μg/m^3 for NO_2, and 32.8 μg/m^3 for O_3. Daily mean temperature and relative humidity had an average of 8.5 °C and 12.0% (Table 1).

High correlations were found between ambient benzene and toluene ($\rho = 0.823$), $PM_{2.5}$ and NO_2 ($\rho = 0.757$), ambient benzene and $PM_{2.5}$ ($\rho = 0.735$). The correlation coefficients between the other pollutants and weather variables ranged from low to moderate (Table 2). Daily number of eCOPD hospitalizations had a peak in winter and a trough in summer. A similar seasonal pattern was observed in ambient benzene and toluene, but not in isoprene (Fig. 1).

Exposure-response curves show a positive linear relationship between benzene, toluene, and eCOPD hospitalizations, but isoprene had a negative relationship with eCOPD (Fig. 2A). The IQR increase of daily mean benzene (1.4 μg/m^3) and toluene (4.6 μg/m^3) in the preceding two days was associated with 2.57% (95% CI: 0.33% to 4.86%) and 1.95% (95% CI: 0.65% to 3.26%) excess risk of eCOPD hospitalizations, respectively (Table 3, Fig. 2B). The cumulative 1-day lag effects of ambient mean benzene and toluene were 2.62% and 1.42% respectively (Table 3).

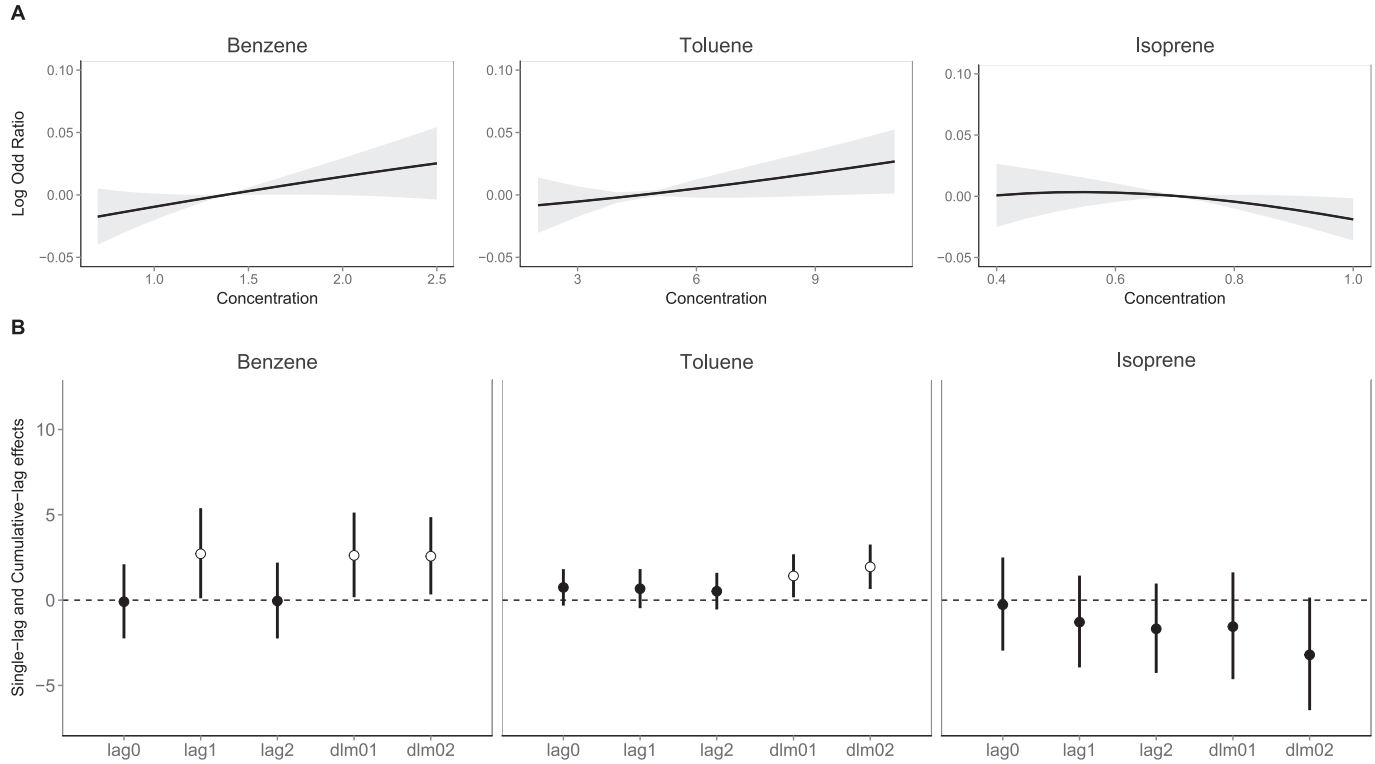

Fig. 2. Exposure-response relationships and percent excess risks of ambient benzene, toluene and isoprene on eCOPD hospitalizations. **A**, the exposure-response relationships of ambient benzene, toluene and isoprene on the COPD outcome. **B**, the single and cumulative effects. Lag_0, lag_1 and lag_2 are the single effects of the current day and the preceding 1–2 days. dlm_{01} and dlm_{02} are the cumulative1-day and 2-day lag effects.

Table 3
Percent excess risk (ER%) in emergency COPD hospitalizations associated per IQR increase of daily mean and maximum ambient benzene, toluene and isoprene in the different lag days.

	lag_0^a	dlm_{01}^b	dlm_{02}^c
Daily mean			
Benzene	−0.09 (−2.24, 2.10)	2.62 (0.17, 5.13)*	2.57 (0.33, 4.86)*
Toluene	0.74 (−0.32, 1.82)	1.42 (0.16, 2.69)*	1.95 (0.65, 3.26)*
Isoprene	−0.27 (−2.96, 2.50)	−1.55 (−4.63, 1.63)	−3.20 (−6.45, 0.15)
Daily maximum			
Benzene	−0.12 (−0.83, 0.60)	0.14 (−0.69, 0.98)	0.57 (−0.24, 1.38)
Toluene	0.20 (−0.22, 0.62)	0.29 (−0.23, 0.82)	0.39 (−0.19, 0.98)
Isoprene	0.33 (−1.38, 2.06)	−1.27 (−3.31, 0.81)	−1.87 (−4.01, 0.31)

[a]Effect at the same day. [b]Cumulative effect over 0–1 lagged day. [c]Cumulative effect over 0–2 lagged day. *Statistically significant.
Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease.

The risk estimates of daily mean isoprene and daily maximum concentrations of all the VOCs were not significant (Table 3). Fig. 2B shows the ER% estimates of the single lag and cumulative lag effects of ambient mean benzene, toluene and isoprene on eCOPD hospitalizations. In addition to the significant cumulative l-day and 2-day lag effect estimates, a significant association between ambient benzene and eCOPD hospitalizations on the one lag day. None of the single and cumulative lag effects of the negative control isoprene was significant.

The positive association of ambient mean benzene and toluene with eCOPD hospitalizations were observed only in men but not in women, although the difference was not statistically significant. The ER% estimate of daily maximum toluene was higher in the younger age group than in the older (4.29% vs 1.66% for benzene, and 2.10% vs 0.18% for toluene, respectively) (Table 4). The results of sensitivity analyses showed that the association between ambient benzene/toluene and eCOPD hospital admissions was robust when changing the degrees of freedom and increasing the lag days of ozone and temperature effects. However, the cumulative 2-day lag effect estimates of benzene and toluene were moderately sensitive to the adjustment of $PM_{2.5}$ or NO_2 as a confounder in the model (Fig. 3).

4. Discussion

This study is among the first to estimate the short-term effects of ambient benzene and toluene on eCOPD hospitalizations. We conducted a population-based time series study with a quasi-Poisson regression, controlling for the temperature, relative humidity, time trend, and calendar effects meanwhile. We also controlled for ozone concentration in the model since it is strongly associated with the ambient VOCs and the health outcome. We found significant short-term effects of ambient benzene and toluene on eCOPD hospitalizations, suggesting that VOCs could be the potential environmental stressors for acute exacerbations of COPD.

Our results are consistent with previous studies on the adverse effects of benzene on respiratory diseases. Hirsch and the colleagues found a positive association between ambient benzene and occurrence of bronchitis and cough of the Germany children (Hirsch et al., 1999). Another study in London showed a latent role of benzene on childhood wheezy episodes (Buchdahl et al., 2000). The adverse association between ambient benzene and asthma was also reported in Germany and Australia (Nicolai et al., 2003; Rumchev, 2004). Previous findings of toluene were less consistent in literature. A study in Australia found that the risk of asthma doubled when ambient toluene increased 10 $\mu g/m^3$, but studies in London and Los Angeles failed to observe any significant associations (Buchdahl et al., 2000; Delfino et al., 2003; Rumchev, 2004). Another study in human volunteers found that exposure to toluene was associated with deterioration of lung function (Yoon et al., 2010).

To date, the biological mechanism behind the adverse effects of benzene and toluene remains unclear. Previous studies suggested that COPD patients often have weak defenses to the oxidative stress generated after exposure to ambient benzene and toluene, hence having a high risk of COPD (Garçon et al., 2006). A more recent study also reported an association between the VOCs' metabolites and biomarkers of oxidative stress, and lung function (Yoon et al., 2010). Experimental studies also found that inhaled benzene and toluene could trigger both local and systematic inflammation response, which resulted in an acute exacerbation of COPD (Andersen et al., 2011; Hogg and Van Eeden, 2009). Deterioration of symptoms for patients with COPD could be irritated by the series of inflammation. Another possible explanation could be that inhaled benzene and toluene chemicals were more likely trapped in the respiratory tracts of COPD patients as compared to those of healthy people (Martins et al., 2012).

In sensitivity analyses, adding $PM_{2.5}$ and NO_2 as covariates in the model substantially attenuated the effect estimates of VOCs. This is not surprising since $PM_{2.5}$ contained both organic and inorganic compounds, some of which could be the chemical reaction products of ambient VOCs (Delfino et al., 2010; Pope et al., 2004). However, we did not consider the mediation effect of $PM_{2.5}$ in this study, because it has been shown that adjustment for mediators might cause biased effect estimates due to over-adjustment (Schisterman et al., 2009). We also found the single lag effect estimates of benzene and toluene on eCOPD hospital admissions were more clear than of $PM_{2.5}$ (Fig. S3). Hence we believe that the adverse effects of benzene and toluene are unlikely solely attributable to $PM_{2.5}$. In fact, there are plenty of experimental studies that have demonstrated the detrimental role of benzene and toluene on the respiratory epithelial cells (Bolden et al., 2015). Similarly, the modifying effect of NO_2 we found in this study could be just due to its strong correlation with $PM_{2.5}$ ($\rho = 0.757$).

We found higher risk estimates of toluene and benzene in people younger than 65 years than in elderly, despite that only the former was significant. We hypothesized that younger people might have higher exposure to ambient benzene and toluene in their working environment, because these VOCs are mainly derived from some non-combustion sources, especially gasoline evaporation and volatilization of industrial organic matters. However, our results need cautious interpretations due to small number of daily counts of eCOPD hospitalizations (daily average 6.2 in the study period), which might have resulted in low statistic power in this age group.

Table 4
The cumulative 2-day lag effects (dlm_{02}) of benzene, toluene and isoprene on emergency COPD emergency hospitalizations in different sex and age.

	Women	Men	P	Age < 65	Age ≥ 65	P[a]
Daily mean						
Benzene	2.66 (−2.43, 8.01)	2.54 (0.10, 5.04)	0.968	5.25 (−1.00, 11.90)	2.26 (−0.09, 4.65)	0.394
Toluene	2.29 (−0.68, 5.36)	1.87 (0.46, 3.30)	0.805	4.29 (0.70, 8.01)	1.66 (0.30, 3.04)	0.187
Isoprene	−3.32 (−10.73, 4.70)	−3.18 (−6.70, 0.48)	0.974	−5.68 (−13.74, 3.13)	−2.86 (−6.29, 0.70)	0.545
Daily maximum						
Benzene	0.81 (−1.03, 2.68)	0.52 (−0.36, 1.41)	0.782	1.88 (−0.40, 4.21)	0.42 (−0.42, 1.27)	0.244
Toluene	0.73 (−0.63, 2.11)	0.33 (−0.31, 0.97)	0.604	2.10 (0.52, 3.70)	0.18 (−0.43, 0.80)	0.027
Isoprene	−0.62 (−5.57, 4.60)	−2.11 (−4.43, 0.27)	0.602	−3.74 (−9.17, 2.01)	−1.64 (−3.90, 0.68)	0.496

[a] $P > 0.05$ means non-significant difference.

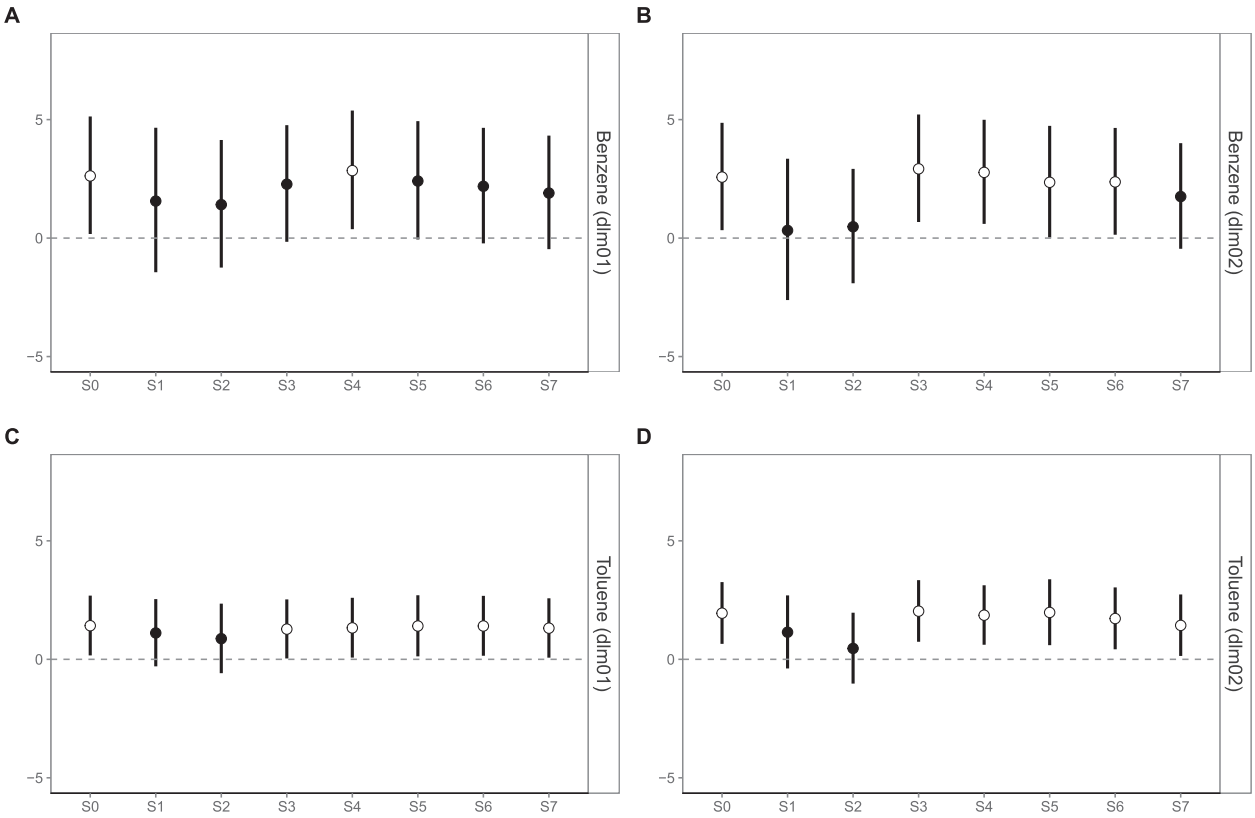

Fig. 3. Sensitivity analyses showing the cumulative1-day and 2-day lag effects of ambient benzene and toluene on eCOPD hospitalizations. S0, results from the main model; S1, daily mean $PM_{2.5}$ was added in the model; S2, daily mean NO_2 was added in the model; S3, ozone was adjusted with the maximum lagged day extending to a week; S4 and S5, the degree of the freedom for the time trend changed from 8 to 4 and 12; S6 and S7, the lag days of temperature increased from three days to seven and fourteen days. **A**, the cumulative 1-day lag effect of benzene; **B**, the cumulative 2-day lag effect of benzene; **C**, the cumulative 1-day lag effect of toluene; **D**, the cumulative 2-day lag effect of toluene.

There are caveats in our study. First, the ecological study design of this study does not allow us to establish the causal relationship of ambient benzene and toluene on eCOPD hospitalizations. Daily exposure of VOCs in the Hong Kong population was measured by the average of daily mean and maximum concentrations from five monitoring sites, which inevitably reduced the variations of individual exposure and led to misclassification. Hence our estimates tend to underestimate the true effects. Nevertheless, these conservative estimates still demonstrated the significant association between VOCs and eCOPD hospitalizations. Second, we found a high correlation between ambient benzene and toluene (Table 2). The toxicities of benzene have been widely demonstrated but the evidence is still limited for toluene. Further studies are warranted to confirm whether the effect of toluene on eCOPD hospitalizations is just a surrogate effect of benzene and the outcome. Third, we aggregated daily number of eCOPD hospitalizations according to primary discharge diagnosis. But some patients might have been admitted due to other comorbidities or had sought medical care in private sectors.

5. Conclusions

In conclusion, the short-term increase of ambient benzene and toluene could trigger events of the eCOPD hospitalizations in Hong Kong population. Our finding suggested that ambient benzene and toluene might be environmental stressors for acute exacerbation of COPD. Further investigations are warranted, especially those with individual exposure data, in order to establish the adverse effects of VOCs and elucidate the underlying biological mechanism.

Disclosure

The authors declare no competing financial 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.scitotenv.2018.12.015.

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