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Are ambient volatile organic compounds environmental stressors for heart failure?☆

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ABSTRACT

Background: Numerous epidemiological studies have indicated the adverse cardiovascular effects of air pollution on heart failure (HF) risk. However, little data are available directly evaluating the association of ambient volatile organic compounds (VOCs) with HF risk. We aimed to estimate the short-term effects of ambient VOCs on HF emergency hospitalizations in Hong Kong and to evaluate whether the associations were modified by sex and age.

Methods: We collected the daily VOCs concentrations from the Hong Kong Environmental Protection Department between April 2011 to December 2014. HF emergency hospital admission data were obtained from the Hospital Authority of Hong Kong. Generalized additive model (GAM) integrated with the distributed lag model (DLM) was used to estimate the excess risks of HF emergency hospitalizations with ambient concentrations of each VOCs groups – alkane, alkene, alkyne, benzene and substituted benzene.

Results: We observed short-term effects of alkyne and benzene on an increased risk of HF emergency hospitalizations. The cumulative effect over 0–6 lag days (dlm_{0-6}) for an IQR increment of alkyne (1.17 ppb) was associated with 4.2% (95% CI: 1.18%–7.26%) increases of HF emergency hospitalizations, while the corresponding effect estimate over dlm_{0-2} for benzene per IQR (0.43 ppb) was 2.7% (95% CI: 0.39%–5.04%). Each VOCs groups was significantly associated with HF emergency hospitalizations in men.

Conclusions: Ambient volatile organic compounds, particularly alkyne and benzene, were associated with increased risks of heart failure in the Hong Kong population.

1. Introduction

Heart failure (HF) is common, disabling and deadly, accounting for substantial morbidity and mortality (Metra and Teerlink, 2017). The prevalence of HF is ever-increasing and is projected to grow by 25% in the next two decades mainly due to the population aging and the treatment improvement (Heidenreich et al., 2013). Approximately 3 million hospital admissions are primarily or secondarily diagnosed as heart failure annually, and the majority are occurring among people older than 65 years (Mozaffarian et al., 2016). A prospective cohort study in Framingham predicted the lifetime risk for developing HF at age 80 years is 20.2% for men and 19.3% for women (Lloyd-Jones et al., 2002). The prevalence of HF comorbidities, such as chronic kidney disease, atrial fibrillation, diabetes, and hypertension is also increasing, resulting in more severe symptoms and worse prognosis (Ettehad et al., 2016; Komajda and Ruschitzka, 2018; Van Deursen et al., 2014; Zinman et al., 2015). In addition, costs of the treatment of HF are projected to increase by 200% in the next two decades from 2 to 3% currently of the total health-related expenditure in the United States (Heidenreich et al., 2013).

Compared with some well-established risk factors of HF such as hypertension, diabetes, dyslipidemia, obesity, alcohol, and tobacco use, environmental factors might be also linked to increased HF risk but the relevant evidence was still under-researched (Bui et al.,

Abbreviation: HF, heart failure; VOCs, volatile organic compounds; $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone; GAM, generalized additive model; DLM, distributed lag model; IQR, inter-quartile range; ER, excess risk; CIs, confidence intervals.

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2011). Most previous studies reported that some criteria air pollutants such as particulate matter, sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) were associated with increased risk of HF emergency hospitalizations and mortality (Shah et al., 2013). However, the evidence for the association of exposure to some coexisting gaseous pollutants particularly volatile organic compounds (VOCs) with a risk of HF is limited.

VOCs are organic compounds with a high vapor pressure at ordinary temperature, residing in the vapor or particle phase based on the surface constituents and organic properties. Ambient VOCs and VOCs in the particle phase form the dynamic equilibrium, a component of organic aerosol (Mauderly and Chow, 2008). Cardiorespiratory impacts of organic aerosols are widely recognized and acknowledged in previous studies (Mauderly and Chow, 2008), but health effects of ambient VOCs and VOCs in particle phase on circulation system are sparsely documented (Delfino et al., 2010b; Tsai et al., 2010; Ye et al., 2017). Additionally, VOCs may play a role in the development of HF, however, the evidence is insufficient to infer this association, particularly the wide range of compounds of ambient VOCs in urban air (Kioumourtzoglou et al., 2013; Sarnat et al., 2015).

Hong Kong is an ideal setting for the present study, with metropolitan, dense and aging population as well as heavy traffic. HF cases in Hong Kong are common and progressively increasing, according to the Hospital Authority of Hong Kong (the statutory body for all Hong Kong public hospitals; http://www.ha.org.hk). In 2017, the total numbers of hospitalizations and deaths of HF in Hong Kong reached 20,143, with a 10% increase over the year of 2010 (Hospital Authority, 2017). The objectives of this study were to estimate the short-term exposure to VOCs with HF emergency hospitalizations in a longitudinal time series study with 1371 days in Hong Kong and to evaluate whether the associations were modified by sex and age.

2. Methods

2.1. HF hospital admissions

This study was based on data obtained from the Hospital Authority Corporate Data Warehouse of Hong Kong. The Hospital Authority is the statutory body responsible for all Hong Kong public hospitals, which covers 90% of the hospital beds in the territory. Only emergency hospital admissions for HF as the principal diagnosis (ICD-9: 428) was included in this study. A total of 54,003 emergency hospital admissions for HF (39.4 ± 12.3 admissions per day) were identified from April 2011 to December 2014, about 55.3% (29,890) of whom were female and 44.7% (24,113) were male. The emergency HF admissions by sex and age group (age ≤ 65 and age > 65 years) were also computed.

2.2. Air pollution and meteorological data

Data of ambient VOCs concentrations during the same period were obtained from the Environmental Protection Department (EPD) of Hong Kong. VOCs were monitored in five monitoring stations - Mong Kok (MK), Yuen Long (YL), Hok Tsui (HT), Tung Chung (TC) and the Hong Kong University of Science and Technology (UT), covering Hong Kong Island, Kowloon, and New Territories. Citywide mean concentrations of VOCs were calculated by averaging daily means from all five monitoring stations. Online VOC data were collected from the online VOC analyzers (Syntech Spectras GC 955, Series 600/800, Netherland), which consisted of two sampling systems and two column separating systems: GC1 for the C2-C5 and GC2 for C6-C10, respectively. Both FID (Flame Ionization Detection) and PID (Photoionization Detection) were used to ensure high sensitivity and high selectivity. The GC system collected and analyzed continuously the ambient sample every 30 min, 24 h every day. The analyzers used built-in computerized programs of auto-linearization and auto-calibration. Weekly calibration was also provided by certified calibration gas (NPL span gas, National Physical Laboratory) in advance.

The quality of the real-time data was checked by comparison with canister samples analyzed at UC-Irvine. The measurement precision, accuracy and detection limits of these VOCs varied among species. Briefly, the precision ranged 2.5–20%, the accuracy 1%–10%, and the detection limit 0.002–0.787 ppb. More details about the exposure measurement were reported elsewhere (Feng et al., 2013; Wang et al., 2017). A total of 19 VOCs were monitored at each site, and we calculated average concentrations from the five monitoring sites to estimate the city-wide concentrations. Then, the 19 VOCs were *a priori* categorized into five groups and the sum of each group was used for analysis: alkane (ethane, propane, butane, pentane, hexane, heptane and octane), alkene (ethene, propene, butane, pentene, butadiene, and isoprene), alkyne (ethyne), benzene, and substituted benzene (toluene, ethylbenzene, xylene, and trimethylbenzene) (Ye et al., 2017). The motivation of grouping via chemical structure had the following reasons: 1) pollutants with the same functional structure may result in similar toxicity; 2) pollutants sharing the same functional group may be emitted from the same source or the similar atmospheric process. Twenty-four-hour mean concentrations of $PM_{2.5}$, NO_2, CO and O_3 were collected from ten general stations of EPD from April 1, 2011 to December 31, 2014 (Qiu et al., 2014). Daily relative humidity and average temperature were provided by the Hong Kong Observatory for the same period.

2.3. Statistical modeling

Generalized additive Poisson models (GAM) with distributed lag models (DLM) were applied to estimate the associations between ambient VOCs (alkane, alkene, alkyne, benzene and substituted benzene) and the HF emergency hospitalizations. We used cubic basis splines to filter out long-term trends and seasonal patterns and the non-linear effect of relative humidity (*Humid*$_0$) (Mann et al., 2002). Public holiday (*Holiday*) and days of the week (*DOW*) were also adjusted in the model. We chose *a priori* model specifications with 8 degrees of freedom (*df*) per year for time trend and seasonality and 3 df for daily mean temperature and relative humidity based on previous studies. Public holidays and DOW were treated as dummy variables (Tian et al., 2017, 2015).

DLM was used to pre-build the exposure-lag-response relations for both pollutants and temperature (Gasparrini, 2011; Gasparrinia et al., 2010). Second-degree polynomials were used to constrain the smooth shape of the distributed lags of VOCs variables for computing less-noise results (Costa et al., 2017; Zanobetti et al., 2002). We calculated cumulative effects for each VOC groups over lag 0–6 days ($dlm_{06} = e^{IQR*(\beta_{lag_0}+\beta_{lag_1}+\ldots\beta_{lag_6})}$), and computed the acute effect over lag 0–2 days as well as the delayed effect over lag 3–6 days, respectively. We also used DLM model to control temperature with the same temporal matrix as VOCs to eliminate residual confounding of temperature-lag-response (Kim et al., 2017; Ye et al., 2017). As positive controls (Shah et al., 2013), we estimated the associations of $PM_{2.5}$, NO_2, O_3, and CO with emergency hospital admissions for HF. The model can be specified as follows:

$$\begin{aligned}\log(E(Y)) &= \alpha + \beta_{1,l} \times Var_{t,l} + bs(t, df \\ &= 8/year*no.of\ years) + bs(Humid_0, df \\ &= 3) + +\beta_{2,l} \times Temp_{t,l} + \beta_3 \times DOW + \beta_4 \times Holiday\end{aligned} \quad (1)$$

Here, $E(Y)$ means the expected daily counts of HF hospitalizations on day t; $bs(.)$ indicates the basis spline; β_i indicates regression coefficients; $\beta_{i,l}$ represents the coefficient for matrix; $Var_{t,l}$, matrix obtained by applying the DLM to pollutants; $Temp_{t,l}$, matrix to temperature; l, the lag days. The Residual and partial autocorrelation function (PACF) figures were plotted to check the potential discernible pattern and autocorrelation of the model.

Stratification analyses by sex and age were conducted to identify the susceptible subpopulations. The statistical significances of the differences between subgroups were tested via using the formula: $(\beta_1 - \beta_2)\pm 1.96\sqrt{SE_1^2 + SE_2^2}$, where β_1 and β_2 are the estimates for the comparable subgroups, SE_1 and SE_2 are their corresponding standard errors (Schenker and Gentleman, 2001). We conducted several sensitivity analyses to ascertain the robustness of the associations: 1) further controlling for $PM_{2.5}$, NO_2 CO, and O_3 each at time in the two-pollutant models; 2) maximum lag days for temperature in DLM were adjusted up to 13 and 20, respectively since cold temperature effects lasted for a few weeks (Kim et al., 2017; Tian et al., 2016).

The risk estimates were reported as the percentage excess risk (ER%) changes in HF emergency hospital admissions per interquartile range (IQR) increment of VOCs concentrations and corresponding 95% confidence intervals (CIs). $ER\% = (RR - 1) \times 100\%$. The null hypothesis was rejected for values of $p < 0.05$ for parameters of quasi-Poisson regression. All analyses were achieved in environment R 3.3.2 version with 'dlnm' package.

3. Results

Table 1 shows the descriptive statistics on HF hospitalizations, ambient VOCs, other air pollution and weather conditions. Daily 24-h mean concentrations (corresponding IQRs) were 14.88 ppb (5.80 ppb) for alkane, 4.01 ppb (1.13 ppb) for alkene, 2.42 ppb (1.17 ppb) for alkyne, 0.40 ppb (0.43 ppb) for benzene, and 2.42 ppb (1.94 ppb) for substituted benzene. Mean concentrations of $PM_{2.5}$, NO_2, O_3, and CO were 30.5 $\mu g/m^3$, 64.4 $\mu g/m^3$, 38.1 $\mu g/m^3$, and 773.9 $\mu g/m^3$, respectively. The daily mean temperature was 23.8 °C and relative humidity was 78.7%. Fig. 1 provides the daily variation as well as long-term trend and seasonal pattern of each VOCs groups and the emergency hospital admissions for HF during the study period. Both HF emergency hospitalizations and ambient VOCs' concentrations had regular periodicities, approximately higher in winter and lower in summer.

Table 2 presents the percentage excess risks of HF emergency hospitalizations per IQR increments of ambient VOCs and other criteria air pollutants. For the cumulative risk estimate over 0–6 lag days (dlm_{0-6}), a 1.17 ppb increase in ambient alkyne was associated with a 4.2% (95% CI: 1.18%–7.26%) increase in HF emergency hospitalizations. The cumulative risk estimate over 0–2 days (dlm_{0-2}) of benzene was also statistically significant: an IQR increment of benzene (0.43 ppb) was associated with a 2.7% (95% CI: 0.39%–5.04%) increase of HF emergency hospitalizations. The associations of $PM_{2.5}$, NO_2, O_3, and CO with the HF emergency hospitalizations were observed within 2 previous days. The HF risk estimates for benzene were significant within 2 previous days while those for alkyne were significant on the same day or within 6 previous days (Fig. 2).

Table 3 summarizes the results of stratified analyses by sex and age. We observed a statistically significant association of each VOCs groups on HF emergency hospitalizations in men than on women. Percentage excess risks per IQR increases of alkyne and benzene on HF emergency admissions in men were 7.8% (95% CI: 3.31%–12.46%) and 6.7% (95% CI: 1.93%–11.68%), respectively. We did not observe any significant associations in women. For the stratified analyses by age group, the association of each VOCs groups with HF showed no significant difference between younger and older groups.

The results of sensitivity analyses show that the these estimated associations varied slightly after further adjustment for traffic-related air pollutants (NO_2 and O_3, respectively) in the two-pollutant models. Estimates were also similar after controlling for temperature effects with lag days up to 14 and 21, respectively. However, risk estimates for VOCs changed after adjustment for $PM_{2.5}$ in the bi-pollutant models, especially for benzene which was found to be inversely correlated with HF risk (Figure S1, Table S3).

4. Discussion

In this longitudinal time series study with 1371 days, we found that exposure to short-term ambient VOCs, particularly alkyne and

Table 1
Descriptive statistics for daily emergency hospital admissions for heart failure, 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
Daily emergency hospital admission (counts per day)								
Heart failure	39.4	12.3	15	31	37	46	102	15
Female	21.8	7.3	6	17	20	26	56	9
Male	17.6	6.5	4	13	16	21	46	8
Age ≤ 65	5.0	2.4	0	3	5	6	15	3
Age > 65	34.4	11.4	11	26	32	41	94	15
Ambient VOCs (ppb)								
Alkane	14.88	4.83	4.42	11.66	14.29	17.46	35.54	5.80
Alkene	4.01	1.03	1.68	3.37	3.86	4.49	8.34	1.13
Alkyne	2.42	0.86	0.54	1.78	2.34	2.94	6.70	1.17
Benzene	0.40	0.31	0.04	0.13	0.33	0.56	2.15	0.43
Substituted benzene	2.42	2.05	0.25	1.12	1.66	3.06	15.99	1.94
Other pollutants ($\mu g/m^3$)								
$PM_{2.5}$	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
CO	773.9	220.2	337.4	608.6	736.3	902.0	1676.3	293.4
Weather conditions								
Temperature (°C)	23.8	5.2	8.4	19.8	25.1	28.3	31.8	8.5
Relatively humidity (%)	78.7	10.4	29.0	74.0	79.0	86.0	99.0	12.0

Abbreviations: SD, standard deviation; Max, maximum; Min, minimum; IQR, interquartile range; VOC, volatile organic compounds; P_{25}, 25th percentile; P_{50}, 50^{th} percentile; P_{75}, 75th percentile; $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone; ppb, part per billion.

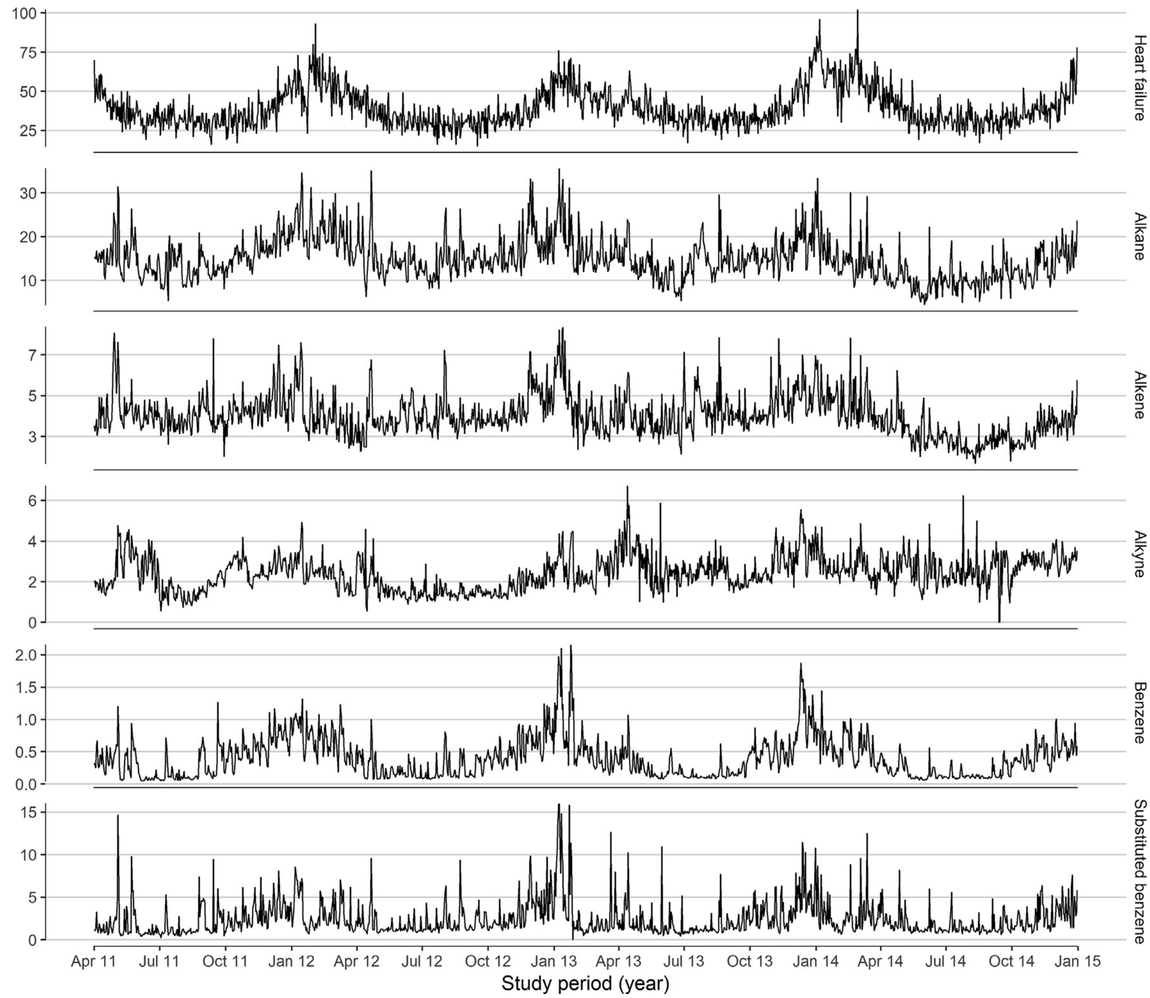

Fig. 1. Time series plots of the daily emergency hospitalizations for heart failure and ambient VOCs. The unit of each VOC group is parts per billion (ppb), and the unit of emergency hospitalizations for heart failure is count per day.

Table 2
Percent excess risk (ER%) in emergency hospital admissions for heart failure associated with an IQR increases in ambient VOCs' and other air pollutants' concentrations over different lag periods.[a]

	dlm_{0-2}[b]	dlm_{3-6}[c]	dlm_{0-6}[d]
Ambient VOCs			
Alkane	1.3 (−0.55, 3.22)	1.1 (−0.90, 3.20)	2.5 (−0.22, 5.22)
Alkene	0.5 (−1.19, 2.17)	0.8 (−0.95, 2.59)	1.3 (−1.04, 3.66)
Alkyne	2.6 (0.45, 4.72)#	1.6 (−0.78, 3.97)	4.2 (1.18, 7.26)#
Benzene	2.7 (0.39, 5.04)#	0.3 (−2.12, 2.80)	3.0 (−0.19, 6.31)
Substituted benzene	0.7 (−0.53, 1.95)	0.4 (−1.01, 1.73)	1.1 (−0.67, 2.81)
Other air pollutants			
$PM_{2.5}$	3.6 (1.55, 5.63)#	3.7 (1.76, 5.66)#	7.4 (4.74, 10.11)#
NO_2	1.3 (−0.56, 3.17)	3.9 (2.12, 5.64)#	5.2 (2.78, 7.69)#
CO	2.8 (0.67, 5.03)#	0.6 (−1.74, 2.93)	3.4 (0.32, 6.60)#
O_3	1.8 (−0.66, 3.85)	3.5 (1.26, 5.76)#	5.1 (2.06, 8.25)#

Abbreviations: IQR, interquartile range; $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone.
#Statistically significant effect estimates.
[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 0–2 lag days.
[c] Cumulative effect over 3–6 lag days.
[d] Cumulative effect over 0–6 lag days.

benzene, were associated with HF emergency hospitalizations in a potential sex-different manner. However, we did not observe the differences between the association of VOCs and HF emergency hospitalization among younger and older groups. These results implicated that ambient VOCs may be the potential environmental risks for heart failure in Hong Kong population.

Non-combustion, particularly gasoline evaporation, and road transport are the two major sources of ambient VOCs in Hong Kong (Lee et al., 2002). Benzene and substituted benzene are widely added in fuels of aviation and motor to avoid auto-ignition under soaring temperature and pressure condition. They comprise over 27.5% of the constituents of high octane gasoline and are released to the atmosphere by gasoline evaporation as well as incomplete combustion (Bolden et al., 2015). For other hydrocarbons, alkane, alkene and alkyne groups, vehicular emissions are also the main source in urban and sub-urban of Hong Kong. Petrol evaporation, solvent usage, and industrial emission also play important roles. Biofuel/biomass burning is the priority source of ambient VOCs in the rural area, but it just contributes a small fraction of total ambient VOC levels (Guo et al., 2007).

We observed a consistent association between short-term exposure to some air pollutants ($PM_{2.5}$, NO_2, CO, and O_3) and heart failure which has been widely demonstrated in previous studies: Shah et al. did a meta-analysis summarizing 35 time-series and cross-over studies, and found that carbon monoxide (CO), sulfur dioxide (SO_2), NO_2, $PM_{2.5}$, and PM_{10} were all associated with HF hospitalization (Shah et al., 2013). $PM_{2.5}$ constituents

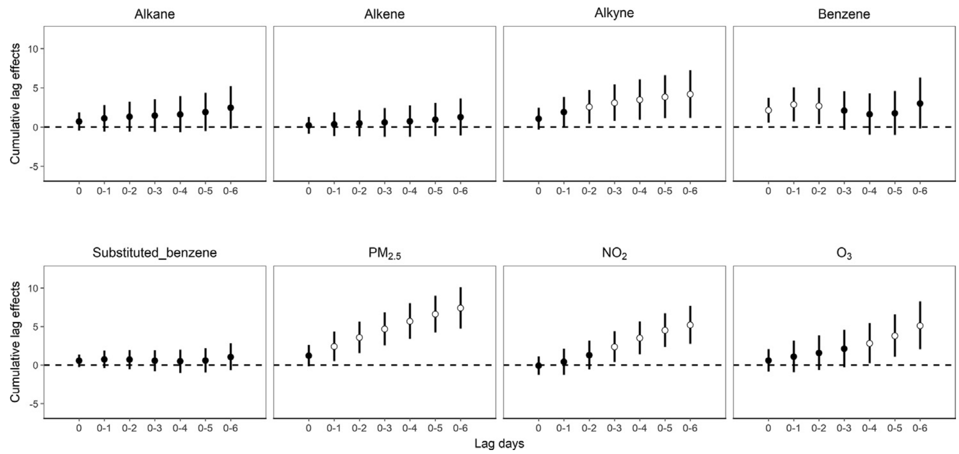

Fig. 2. Cumulative effects distributed over 0–6 lag days for ambient alkane, alkene, alkyne, benzene, substituted benzene and traffic-related air pollutants on emergency hospitalizations for heart failure. $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 µm; NO_2, nitrogen dioxide; O_3, ozone. The black dots are not statistically significant, and the white dots are statistically significant. Error bars represent confidence intervals.

Table 3
Cumulative effects over 0–6 lag days ($dlm_{0\text{-}6}$)[a] of ambient VOCs on the emergency hospital admissions for HF by sex and age group.[d]

Ambient VOCs	Sex			Age		
	Female	Male	P[‡]	≤65	>65	P[c]
Alkane	0.5 (−2.88, 4.09)	4.8 (0.87, 8.95)	0.049[b]	0.8 (−6.13, 8.22)	2.7 (−0.18, 5.63)	0.312
Alkene	−0.9 (−3.83, 2.19)	4.0 (0.52, 7.51)	0.017[b]	2.0 (−4.12, 8.59)	1.2 (−1.31, 3.70)	0.591
Alkyne	1.3 (−2.51, 5.26)	7.8 (3.31, 12.46)	0.015[b]	5.0 (−2.88, 13.42)	4.1 (0.85, 7.34)	0.587
Benzene	0.1 (−4.01, 4.30)	6.7 (1.93, 11.68)	0.020[b]	6.5 (−2.19, 15.89)	2.5 (−0.87, 6.04)	0.793
Substituted benzene	−0.43(-2.67, 1.86)	2.8 (0.31, 5.42)	0.031[b]	1.8 (−2.96, 6.69)	1.0 (−0.87, 2.83)	0.618

[a] Cumulative effect over 0–6 lag days.
[b] Statistically significant effect estimates.
[c] P-value<0.05 means significant difference.
[d] 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).

were also associated with HF hospital admission, especially organic and elemental carbon (Metzger et al., 2004). To our best knowledge, there have been a few reports in the literature about the cardiovascular effects of ambient VOCs. Ye and his colleagues found some hydrocarbon groups, especially alkenes and alkynes might trigger the emergency department visits for cardiovascular diseases (Ye et al., 2017). And we documented the association of ambient benzene and TEX (toluene, ethylbenzene, and xylene) with cardiovascular mortality in a previous study (Ran et al., 2018). In the present study, we further reported the associations of ambient benzene and alkyne with specific diseases of the cardiovascular system.

Considering the possibility that these VOCs were surrogates for other criteria air pollutants, we conducted sensitivity analyses controlling for other air pollutants in the two-pollutant models. The robustness of the associations was obtained between each VOCs groups and HF admissions with adjustment for NO_2, CO or O_3. However, we observed the inversed association between VOCs and HF emergency hospitalizations when adjusting $PM_{2.5}$ in the bi-pollutant model. The counter-intuitive founding could be generated by the mediator-outcome confounding. That is conditioning on the mediator may introduce a spurious association between the mediator-outcome confounder and the exposure (Richiardi et al., 2013). Some secondary organics in $PM_{2.5}$ were derived from VOCs and thus may mediate the VOC effects on HF (Delfino et al., 2010a; Pope and Dockery, 2006). Adjustment for the mediators may generate the confounding between the VOCs and the mediator-outcome confounders, such as major ions, metals, and metalloids, which may result in a false conclusion. This is similar to the birth weight paradox, where the spuriously inverse association of maternal smoking on infant mortality was observed in children with low birthweight. The reason was that conditioning on low birthweight introduced a relationship between the maternal smoking and the mediator-outcome confounder, such as birth defect, and the generated confounder (birth defect) might result in the counter-intuitive association between maternal smoking and infant mortality (Hernández-Díaz et al., 2006). As one of the sensitivity analyses, longer maximum lag days' control for temperature did not change the risk estimates substantially.

The adverse association between ambient VOCs and HF emergency hospitalizations appeared to be stronger in men than in women. The different exposure profile might be a result of the differential excess risks across sex. Traffic is the main source of ambient VOCs in Hong Kong (Lee et al., 2002). Men are exposed to higher levels of VOCs than women since most drivers are men. Furthermore, cigarette smoking is a non-negligible source of ambient VOC exposure besides traffic pollution. Among the daily cigarette smokers, 83.9% were males and 16.1% were females (Hong Kong Census and Statistics Department, 2017). Because of the weakened immunological and circulatory systems, smokers might be more sensitive to environmental stressors, such as $PM_{2.5}$ (Pope et al., 2004), and ambient VOC. An Asian population study showed the effects of nitrogen dioxide and particulate matter on cardiac insufficiency, hypertension, and myocardial infarction, which were greater for males than for females (Ye et al., 2001). However, the gender difference in the association between air pollution and cardiovascular diseases was not consistent in the literature (Colais et al., 2012), and needs further investigation.

Most emergency events in patients with HF patients are because of acute decompensated HF and dysrhythmias, with increasing demand on the heart, such as increased heart rate, where filling pressure and blood pressure, can result in acute decompensated HF (Dunlay et al., 2009). Exposure to primary organic carbon from traffic source can increase the blood pressure significantly as well as heart rate due to metabolic dysfunction, and thereby potentially deteriorate the acute decompensation (Delfino et al., 2010b). Some emergency hospitalizations are due to coexisting pulmonary diseases, such as chronic obstructive pulmonary disease and asthma. According to epidemiological and toxicological materials, benzene is widely associated with types of respiratory hypoxia and diseases (Bolden et al., 2015), but there is no direct record about the respiratory effect of the ambient alkyne. Studies provided evidence that both primary and secondary organic aerosols could generate or aggravate the systemic inflammations (Delfino et al., 2010a), and neurotoxic and immunetoxic impacts of benzene and substituted benzene are also acknowledged (Bolden et al., 2015). Inflammatory simulation, homeostasis disturbance, and immune collapse can morbidly increase heart rate or blood pressure and hence result in acute HF hospitalizations.

Caution should be exercised in inferring causality between HF hospitalizations and ambient VOCs. First, we grouped VOCs by functional structure since some commonalities were related to structure, such as source and toxicity. Nevertheless, toxicities of pollutants might still differ even if they shared the similar structure. Second, we identified patients using hospitalization records with HF as the primary diagnosis and HF as a comorbidity was not included in the analysis. Third, the mere association disclosed by regression modeling was not equivalent to causality. Evidence on biological plausibility of these associations is still weak, especially for alkyne. Finally, the time series study is still an ecological study and the associations observed at aggregate levels do not necessarily imply individual level relationships (Greenland, 2001).

In conclusion, short-term ambient VOCs elevation might trigger emergency hospitalizations for heart failure in the Hong Kong population. The heart failure risk estimates associated with VOCs were stronger in men than in women. Our findings suggest that ambient VOCs might be an environmental stressor for heart failure of Hong Kong population. Further mechanistic studies and personal-exposure designs should be performed to substantiate the findings.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.envpol.2018.07.086.

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