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Short-term impact of exposure to ambient air volatile organic compounds on daily clinic visits for urticaria in Kaohsiung, Taiwan

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Abstract

Background: Air volatile organic compounds (VOCs) cause allergic reaction mainly via the respiratory tract or skin.

Objectives: This study aimed to investigate the association between daily visits by patients with urticaria and short-term changes in exposure to ambient air VOCs.

Methods: The dependent variable was information from patients with urticaria at a medical center in Kaohsiung, Taiwan, from 2014/01/01 to 2018/07/31. The multivariable model included one-day average 75th percentile values of air VOCs and meteorologic data retrieved from Taiwan Air Quality Monitoring Network database, and was analyzed using a case-crossover study design and conditional logistic regression.

Results: Total daily clinic visits for urticaria were significantly positively associated with higher levels of 4 VOCs (ethylbenzene, toluene, m-/p-xylene, and o-xylene (adjusted odds ratio (AOR: 1.03–1.28)) on the visit days, and 10 VOC levels on the fourth lag day (benzene, ethylbenzene, toluene, m-/p-xylene, o-xylene, 1,3,5-trimethylbenzene, n-hexane, methylcyclohexane, cyclohexane, and ethylene (AOR: 1.02–3.02)). Analyses of age and gender subgroups revealed that men showed resistance on the visit day, and women, older, and younger patients were more vulnerable. Men were influenced by higher benzene levels (AOR = 1.24) on the fourth lag day. Higher values of more than 6 VOCs on the fourth lag day significantly affected women, younger and older patients (AOR: 1.04–6.5). The most notable VOCs were methylcyclohexane (women AOR = 3.28, younger AOR = 3.82) and 1,3,5-trimethylbenzene (women AOR = 2.77, older AOR = 6.5) on the fourth lag day, which had the lowest concentrations but highest influence.

Conclusion: the concentration of certain air VOCs significantly affected daily visits for urticaria.

Key words: ambient air volatile organic compounds, case-crossover study, short-term impact, urticaria, Kaohsiung, Taiwan

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Introduction

Ambient air volatile organic compounds (VOCs) are air pollutants associated with negative health effects on short- or long-term exposure according to the World Health Organization (WHO) global health observatory data on public health.[1] The United States Environmental Protection Agency (USEPA) has reported increasing evidence of a strong association between ambient air VOCs exposure with respiratory, neurologic, and hematologic diseases.[2]

Urticaria, also known as hives, is a severe pruritic skin disease with extensive transient wheals that appear after short exposure to inducing factors. Recurrence can occur from days to years. Acute onset urticaria with severe pruritus strongly interferes with daily life, and patients tend to seek treatment quickly within days.[3] Previous studies using questionnaires in Europe have reported a lifetime prevalence of urticaria of around 9%.[4] Many possible etiologies should be evaluated for urticaria, and it may be related to food and inhalant allergic reactions, viral infection, medicine, physical factors, emotional stress, environmental factors, air pollution, or weather temperature. However, about 50~80% of patients cannot identify a clear allergen or known inducible etiology.[3,5] A few epidemiological studies have shown the crucial association between air pollution and allergic skin diseases,[6-8] particularly urticaria.[9] Koasha et al.[9] and Szyszkowicz et al.[7] demonstrated that short-term changes in air pollutant exposure within days could affect visits for urticaria, including visit days and lag-day effects, especially a lag of 4 days. In our previous study, exposure to ambient air pollutants on the visit days and after a lag of 1-5 days, including NO_2, CO, O_3, $PM_{2.5}$, and PM_{10}, was important risk factors for patients with urticaria seeking treatment.[10]

VOCs are a large and diverse group of compounds that volatilize into the air at room temperature with a boiling point ≤ 250°C measured at a standard atmospheric pressure of 101.3 kPa according to the definition provided by the WHO.[11,12] Owing to the physical and volatile chemical properties of VOCs, they can spread over long distances from the sites of emission, and be present in the air, water, or on solid surfaces. The mean lifespan of atmospheric VOCs ranges from minutes to months.[13,14]

Toxicokinetic studies in humans and animals detailed on the USEPA IRIS website indicate that lipophilic VOCs can penetrate the skin, nasal mucosa and epithelia of the respiratory tract and the cell membranes in various organs. Lipophilic VOCs are distributed in lipid-rich tissues and blood vessels, such as body fat, the brain, and bone marrow, and they are metabolized in the liver and then eliminated from the body.[2,13,15]

The key symptoms or signs of the effect of exposure to VOCs on the skin include allergic reactions[16] and acute or subacute inflammation-like reactions of the skin and mucous membrane,[11] which resemble the cutaneous signs of urticaria. Rautiainen et al. reported that symptoms such as itch or redness of the face and hands in hospital workers were strongly related to poor indoor air quality, and especially VOC concentrations.[17] Garrido et al. reported that air semi-VOCs could diffuse through the stratum corneum of the skin.[18] Although there is increasing evidence of associations between air VOCs and asthma,[19,20] no previous study has focused on the acute effect of ambient air VOCs on daily clinic visits for urticaria. Therefore, it would be interesting to investigate whether an association exists between air VOCs and urticaria.

The aim of this study was to investigate the potential acute effects of short-term changes in ambient air VOC concentrations and meteorological factors on daily clinic visits for patients with urticaria at a governmental medical center in Kaohsiung City using a case-crossover study design and conditional logistic regression. Subgroup analyses of age and gender were also performed to clarify potential effects.

Methods

Data sources of daily outpatient clinic visits for urticaria

Data of daily outpatient clinic visits for urticaria by adult patients (aged ≥ 20 years) at Kaohsiung Veterans General Hospital were retrospectively obtained from the hospital database from January 1, 2014 to July 31, 2018. Before releasing the data for research, the original identification numbers were anonymized to protect the patients' privacy, and thus the need for informed consent was waived by the Institutional Review Board of the hospital. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 708 and ICD-10-CM code L50 on medical records diagnosed by dermatologist and immunologists were used to identify patients with urticaria. Laboratory tests of these patients, including immunoglobulin E, eosinophil cationic protein, inhalant allergen screen tests, and/or specific allergen tests, were retrieved. These tests can be performed for patients with severe or chronic (> 6 weeks) urticaria under the regulations of the National Health Insurance program in Taiwan.

Study area

The study area was "Kaohsiung City". Kaohsiung City was the second largest city in Taiwan before 2018 and was ranked as the most air-polluted city in Taiwan in 2018 due to the presence of heavy industries, and this status has been sustained for several years.[21] It is located in southwestern Taiwan with a tropical monsoon climate. The north latitude is between 22°28′32″ and 23°28′17″, and east longitude is between 120°10′29″ and 121°02′55″. Patients who lived in Kaohsiung City were included.

Data sources of ambient air VOCs and meteorological conditions

Ambient air pollution data were retrieved from the Taiwan Air Quality Monitoring Network Database (TAQMND), Environmental Protection Administration, Executive Yuan, Taiwan, R.O.C.[22,23] The database includes hourly monitoring data for air pollutant concentrations (parts-per-billion as carbon (ppbC); ppbC = ppb * (number of carbon atoms)) of 54 VOCs from two air quality monitoring stations (Siaugang and Qiaotou) located in the corresponding administrative districts in Kaohsiung City. The 11 VOCs with higher concentrations in ambient air (benzene, ethylbenzene, toluene, m-/p-xylene, o-xylene, 1,3,5-trimethylbenzene, 1,2,4-trimethylbenzene, n-hexane, methylcyclohexane, cyclohexane, and ethylene) and meteorological conditions (weather temperature (°C), humidity (%), wind speed (m /sec), and rainfall (mm/hour)) were analyzed.[22,23]

The Siaugang monitoring station is located in the Siaugang district of Kaohsiung, which is a higher air-polluted area, with an international airport, international harbor, petroleum oil refinery, shipbuilding, steel production corporations, coal-fired power generation plants, and industrial areas. The Qiaotou monitoring station is located in the Qiaotou district that is an area with relatively low air-pollution, lower population density, lower transportation flow, and no industrial areas (**Figure 1**). Districts without VOC monitoring stations were assigned to one of two monitoring stations located in a neighboring district with similar industrial and population characteristics. Each patient's exposure to VOC levels was assigned to the data from one of these two monitoring stations according their recorded districts of residence. The one-day average 75th percentile value of each air pollutant was calculated from 24 hourly data of each date.

Study design and statistical methods:

A case-crossover study design with conditional logistic regression was used to analyze the cross-sectional data. The case-crossover design is an adaptation and realization of a case-control study. In such a design, cases act as their own controls on a set of predefined control days proximate to the time they become cases. To produce unbiased conditional logistic regression estimates, a time-stratified approach was applied to determine controls. The day on which the exposure supposedly affected the patients' health, defined as the clinic visit date for urticaria, was considered the case event day. In the design, the control days were determined as the same weekday of the case event day in other weeks in the same month and year. The daily 75th percentile value of each VOC level on control days on the same weekdays were matched to the daily 75th percentile value of each VOC level on the case event day. Using this strategy, four controls were chosen for each case before and after the case event day symmetrically.[24,25] The effects of 1st-5th lag days with daily 75th percentile value of each air VOC concentration and meteorological data at that lag days were also evaluated.[9]

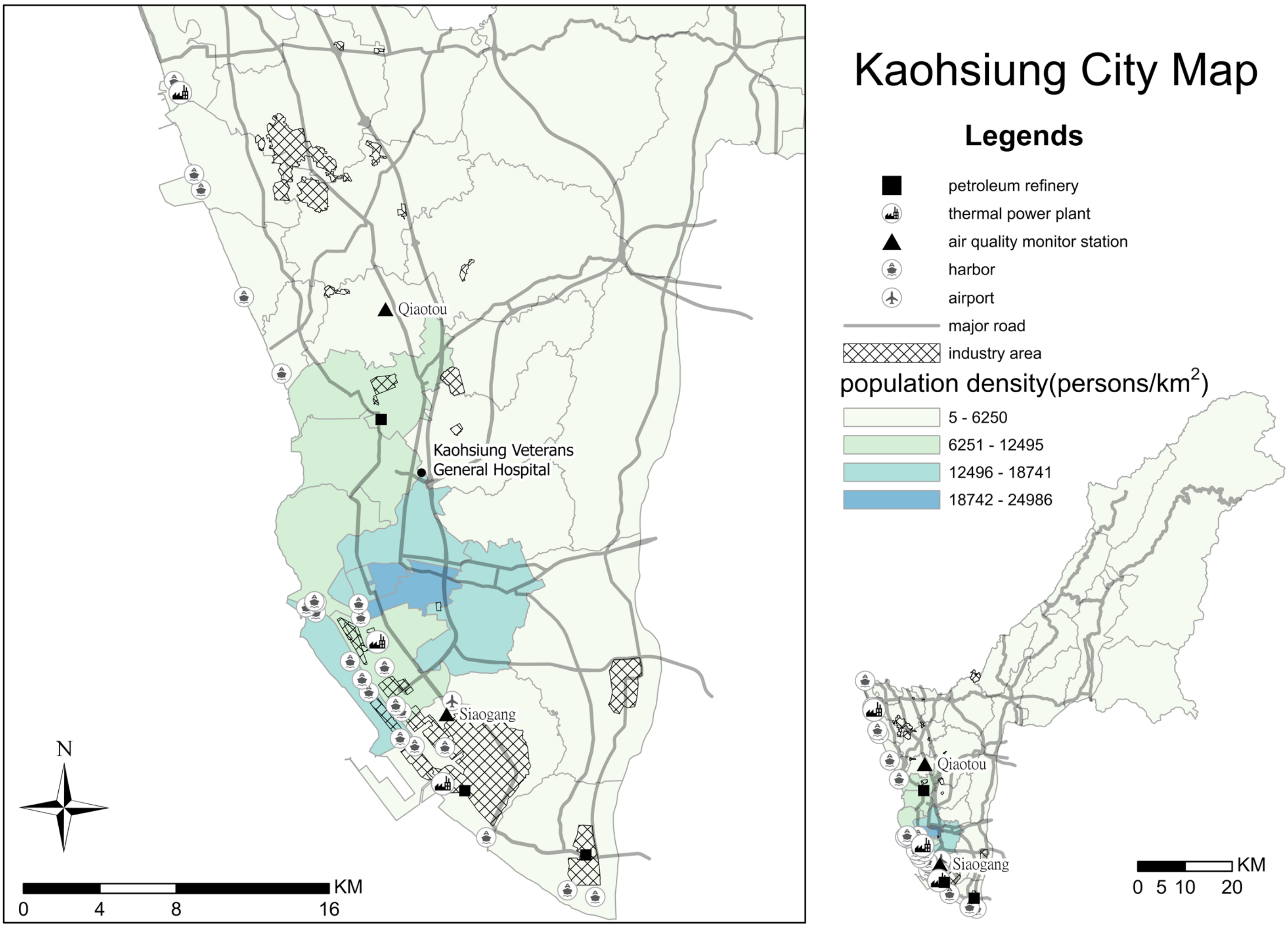

Figure 1. Kaohsiung City map: indicated population densities in districts (persons per square kilometer), the sites of major industrial areas, harbor, international airport, thermal power plants, major traffic roads, 2 monitoring stations (Siaugang & Qiaotou), and Kaohsiung Veterans General Hospital. KM: kilometer. Whole map of Kaohsiung City is shown in the right corner. (ArcGIS Pro Version 2.9)

The univariable model included one kind of VOC. The multivariable model included one kind of VOC and four kinds of meteorological data (weather temperature, humidity, rainfall, and wind speed) as confounding factors for adjustment.

The mathematical formula of the multivariable model is expressed as:

$$logit\ (p) = \beta_{0i} + \beta_1 VOC + \beta_2 weather\ temperature + \beta_3 humidity + \beta_4 rainfall + \beta_5 wind\ speed$$

where p is the probability of daily visits for urticaria,

β_{0i} is the contribution to the logit of all term constants within the i^{th} matching set, for i = 1, …, n subjects,

β denotes the regression coefficients.

The 75th percentile values of each air pollutant concentration and meteorological data are continuous numerical variables in the analysis. The subgroup analyses included gender (men and women) and age (younger patients: age < 65 years, and older patients: ≥ 65 years). The results for the association between daily clinic visits and the one-day average 75th percentile value of each VOC concentration were presented as crude odds ratio (COR) and adjusted odds ratio (AOR), 95% confidence interval (CI), and *P*-value. Statistical significance was defined as a two-tailed *P*-value of < 0.05. Data management and all statistical analyses were performed using Excel (Microsoft Corp., Redmond, WA, version 2019) and IBM SPSS Statistics (IBM Inc., Armonk, NY, version 22). The study design, patient selection, air VOC data, and statistical methods are shown in **Figure 2**. This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (approval no. VGHKS18-CT10-02) and conducted according to the Declaration of Helsinki.

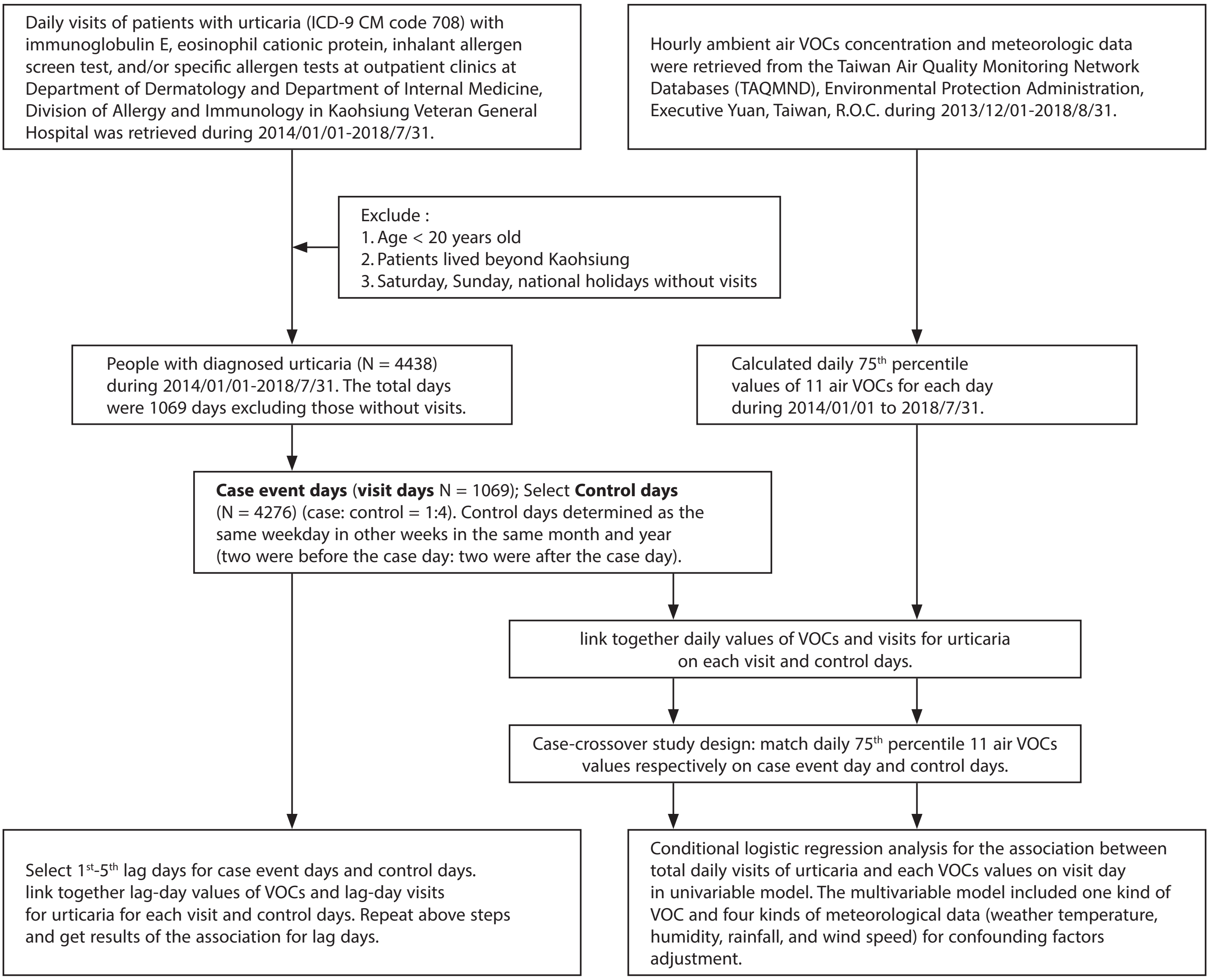

Figure 2. Flowchart of study design, patient selection, air VOCs data, statistical methods of this case-crossover study.

Results

Demographic characteristics, air VOCs, and meteorological data

The number of daily visits ranged from 1-16 per day (median 4). There were a total of 4438 visits from January 1, 2014 to July 31, 2018 (men: 1431, women: 3005, unclassified gender: 2; age ≥ 65 years: 684, age < 65 years: 3754) after excluding those with a diagnosis other than urticaria.

The characteristics of the 11 ambient air VOCs and meteorological data in Kaohsiung City are listed in **Table 1**. A comparison of the VOC values between Siaugang and Qiaotou monitoring stations showed that most values (the 50^{th}, 75^{th} percentile and maximum) of each VOC at Siaugang were higher than those at Qiaotou.

To investigate the probability of certain VOCs being emitted simultaneously, Pearson's correlation analysis of each air pollutant at the same monitoring station during 2014-2018 revealed that certain VOCs were highly positively correlated (coefficient r ≥ 0.7, $P < 0.001$), indicating that they might be emitted simultaneously (for example, ethylbenzene and xylene isomers, toluene and xylene isomers, benzene and ethylbenzene, ethylbenzene and toluene, methylcyclohexane and n-hexane).

Pearson's correlation analysis of the values of the same VOC between Siaugang and Qiaotou monitoring stations showed that toluene was highly correlated in Siaugang and Qiaotou (r = 0.75, $P < 0.001$). Certain VOCs in Siaugang and Qiaotou were moderately positively correlated (0.5 < r < 0.68, $P < 0.001$) (for example, benzene, ethylbenzene, (m-/p- and o-) xylene, methylcyclohexane, and 1,3,5-trimethylbenzene). It is possible that these VOCs, especially toluene, could have spread over a long distance from Siaugang to Qiaotou.

Associations between the total daily visits for urticaria and values of air VOCs on the visit and lag days

Significant positive associations were found between the total daily visits and higher values of the VOCs on the visit days (**Table 2**), including ethylbenzene (AOR = 1.24, 95%CI: 1.05–1.47), toluene (AOR = 1.03, 95%CI: 1.01–1.06), m-/p-xylene (AOR = 1.09, 95%CI: 1.03–1.17), and o-xylene (AOR = 1.28, 95%CI: 1.06–1.55); and a significant negative association was found with higher rainfall (AOR = 0.98, 95%CI: 0.97–0.99).

Analysis of the effect of VOC values on lag days showed significant positive influences particularly on the fourth lag day (**Table 2**). Total daily visits for urticaria was significantly positively associated with higher weather temperature (AOR = 1.02, 95%CI: 1.002–1.03), and higher levels of the following 10 VOCs: benzene (AOR = 1.15, 95%CI: 1.02–1.28), ethylbenzene (AOR = 1.27, 95%CI: 1.08–1.51), toluene (AOR = 1.03, 95%CI: 1.008–1.05), m-/p-xylene (AOR = 1.12, 95%CI: 1.04–1.2), o-xylene (AOR = 1.41, 95%CI: 1.15–1.72), 1,3,5-trimethylbenzene (AOR = 2.21, 95%CI: 1.06–4.6), n-hexane (AOR = 1.13, 95%CI: 1.02–1.26), methylcyclohexane (AOR = 3.02, 95%CI: 1.48–6.14), cyclohexane (AOR = 1.13, 95%CI: 1.0004–1.27), and ethylene (AOR = 1.02, 95%CI: 1.002–1.03).

Table 1. The concentrations of air volatile organic compounds and meteorological data of quartiles from two monitoring stations at Siaugang and Qiaotou during 2014/01/01-2018/07/31.

	50^{th} percentile		75^{th} percentile		maximum	
	Siaugang	Qiaotou	Siaugang	Qiaotou	Siaugang	Qiaotou
benzene	0.50	0.49	0.98	0.78	52.98	30.75
ethylbenzene	0.30	0.29	0.56	0.47	27.90	3.44
toluene	2.48	2.35	4.86	4.44	192.78	73.84
m-/p-xylene	0.91	0.83	1.66	1.41	46.11	17.13
o-xylene	0.41	0.35	0.67	0.58	13.21	5.81
1,3,5-trimethylbenzene	0.07	0.07	0.14	0.11	2.70	3.12
1,2,4-trimethylbenzene	0.39	0.27	0.59	0.44	25.80	10.81
n-hexane	0.27	0.35	0.55	0.64	75.35	6.01
methylcyclohexane	0.09	0.07	0.16	0.12	4.91	2.86
cyclohexane	0.13	0.10	0.33	0.20	9.48	7.44
ethylene	1.82	1.85	4.12	3.05	238.69	1213.51
temperature (°C)	27	26.1	29.75	29	37	36
humidity (%)	73.5	76	81	84	100	99
rainfall (mm)	0	0	0.2	0.2	82	56
windspeed (m/sec)	1.8	2.15	2.725	3.35	14	15

Concentration of each volatile organic compound: parts per billion (ppb),
°C: degree of Celsius; m/sec: meter per second; mm: millimeter

Table 2. The odds ratios between total daily clinic visits for urticaria and the daily average 75th percentile values of each volatile organic compound on the visit days and fourth lag days.

	visit days			the fourth lag days		
	AOR	95%CI	*P* value	AOR	95%CI	*P* value
benzene	1.03	0.93-1.15	0.55	**1.15**	**1.02-1.28**	**0.02**
ethylbenzene	**1.24**	**1.05-1.47**	**0.01**	**1.27**	**1.08-1.51**	**0.005**
toluene	**1.03**	**1.01-1.06**	**0.003**	**1.02**	**1.008-1.05**	**0.008**
m-/p-xylene	**1.09**	**1.03-1.17**	**0.007**	**1.12**	**1.04-1.2**	**0.002**
o-xylene	**1.28**	**1.06-1.55**	**0.01**	**1.41**	**1.15-1.72**	**0.001**
1,3,5-trimethylbenzene	1.85	0.91-3.77	0.09	**2.21**	**1.06-4.6**	**0.04**
1,2,4-trimethylbenzene	1.08	0.96-1.2	0.18	1.16	0.93-1.44	0.18
n-hexane	1.008	0.90-1.13	0.89	**1.13**	**1.02-1.26**	**0.02**
methylcyclohexane	1.78	0.88-3.59	0.11	**3.02**	**1.48-6.14**	**0.002**
cyclohexane	0.91	0.79-1.04	0.17	**1.13**	**1.0004-1.27**	**0.049**
ethylene	0.995	0.98-1.008	0.45	**1.02**	**1.002-1.03**	**0.02**

AOR: adjusted odds ratio; CI: confidence interval
AOR: the multivariable model included one kind of VOC and temperature, humidity, rainfall, and windspeed
Statistical significance: a two-tailed *P*-value of < 0.05.

Table 3. The odds ratios in age and gender subgroups between daily clinic visits for urticaria and daily average 75th percentile values of each volatile organic compound on the visit days.

	AOR	95%CI	*P* value	AOR	95%CI	*P* value
	Men subgroup			Women subgroup		
benzene	0.89	0.72-1.09	0.27	1.1	0.97-1.26	0.15
ethylbenzene	1.16	0.86-1.56	0.34	**1.29**	**1.04-1.58**	**0.02**
toluene	1.03	0.99-1.07	0.16	**1.04**	**1.009-1.06**	**0.007**
m-/p-xylene	1.08	0.96-1.21	0.17	**1.1**	**1.02-1.19**	**0.02**
o-xylene	1.22	0.88-1.7	0.23	**1.31**	**1.04-1.66**	**0.02**
1,3,5-trimethylbenzene	1.06	0.3-3.69	0.92	**2.45**	**1.02-5.88**	**0.04**
1,2,4-trimethylbenzene	1.02	0.83-1.26	0.83	1.11	0.97-1.26	0.14
	Age ≥ 65 years			Age < 65 years		
benzene	0.83	0.62-1.11	0.21	1.08	0.95-1.21	0.23
ethylbenzene	1.37	0.94-1.98	0.09	**1.23**	**1.01-1.49**	**0.04**
toluene	1.05	0.997-1.12	0.06	**1.03**	**1.006-1.05**	**0.01**
m-/p-xylene	**1.17**	**1.004-1.35**	**0.04**	**1.08**	**1.007-1.16**	**0.03**
o-xylene	1.53	0.97-2.42	0.07	**1.25**	**1.01-1.54**	**0.04**
1,3,5-trimethylbenzene	1.71	0.27-10.63	0.57	1.91	0.88-4.15	0.1
1,2,4-trimethylbenzene	1.33	0.79-2.25	0.28	1.07	0.95-1.2	0.25

AOR: adjusted odds ratio; CI: confidence interval
AOR: the multivariable model included one kind of VOC and temperature, humidity, rainfall, and windspeed
Statistical significance: a two-tailed *P*-value of < 0.05.

Subgroup analysis by gender on the visit and lag days

Regarding gender subgroup analysis, in the women subgroup on the visit days (**Table 3**), daily visits for urticaria was significantly positively associated with higher levels of 5 VOCs (ethylbenzene (AOR = 1.29, 95%CI: 1.04-1.58), toluene (AOR = 1.04, 95%CI: 1.009-1.06), m-/p-xylene (AOR = 1.1, 95%CI: 1.02-1.19), o-xylene (AOR = 1.31, 95%CI: 1.04-1.66), and 1,3,5-trimethylbenzene (AOR = 2.45, 95%CI: 1.02-5.88)), and significantly negatively associated with a higher level of rainfall (AOR = 0.98, 95%CI: 0.96–0.99).

On the fourth lag days (**Table 4**), higher weather temperature (AOR = 1.02, 95%CI: 1.002–1.04)) and the following 8 VOCs significantly positively affected women: ethylbenzene (AOR = 1.44, 95%CI: 1.17–1.78), toluene (AOR = 1.04, 95%CI: 1.01–1.07), m-/p-xylene (AOR = 1.16, 95%CI: 1.07–1.26), o-xylene (AOR = 1.53, 95%CI: 1.2–1.96), 1,3,5-trimethylbenzene (AOR = 2.77, 95%CI: 1.12–6.82), methylcyclohexane (AOR = 3.28, 95%CI: 1.36–7.88), cyclohexane (AOR = 1.17, 95%CI: 1.01–1.35), and ethylene (AOR = 1.02, 95%CI: 1.002–1.03).

In the men subgroup, daily visits for urticaria was not associated with levels of 11 VOCs on the visit days (**Table 3**). On the fourth lag days (**Table 4**), men were significantly positively affected by higher benzene levels (AOR = 1.24, 95%CI: 1.02–1.5). Men showed greater resistance to VOCs exposure and meteorological factors.

Table 4. The odds ratios in age and gender subgroups between daily clinic visits for urticaria and daily average 75th percentile values of each volatile organic compound on the fourth lag days.

	AOR	95%CI	*P* value	AOR	95%CI	*P* value
	Men subgroup			Women subgroup		
benzene	**1.24**	**1.02-1.5**	**0.03**	1.1	0.96-1.27	0.16
ethylbenzene	1.03	0.77-1.38	0.83	**1.44**	**1.17-1.78**	**0.001**
toluene	1.01	0.97-1.06	0.5	**1.04**	**1.01-1.07**	**0.007**
m-/p-xylene	1.03	0.91-1.17	0.66	**1.16**	**1.07-1.26**	**0.001**
o-xylene	1.18	0.82-1.68	0.37	**1.53**	**1.2-1.96**	**0.001**
1,3,5-trimethylbenzene	1.36	0.38-4.9	0.64	**2.77**	**1.12-6.82**	**0.03**
1,2,4-trimethylbenzene	1.19	0.83-1.72	0.35	1.13	0.87-1.48	0.36
n-hexane	1.16	0.96-1.41	0.13	1.12	0.98-1.28	0.08
methylcyclohexane	2.55	0.76-8.57	0.13	**3.28**	**1.36-7.88**	**0.008**
cyclohexane	1.04	0.83-1.29	0.75	**1.17**	**1.01-1.35**	**0.03**
ethylene	1.01	0.99-1.03	0.4	**1.02**	**1.002-1.03**	**0.03**
	Age ≥ 65 years subgroup			Age < 65 years subgroup		
benzene	**1.31**	**1.02-1.68**	**0.03**	1.1	0.97-1.25	0.14
ethylbenzene	1.53	0.97-2.4	0.07	**1.24**	**1.03-1.48**	**0.02**
toluene	**1.06**	**1.001-1.11**	**0.046**	1.02	0.999-1.05	0.06
m-/p-xylene	**1.21**	**1.01-1.45**	**0.04**	**1.1**	**1.02-1.19**	**0.02**
o-xylene	**1.76**	**1.06-2.92**	**0.03**	**1.34**	**1.08-1.68**	**0.008**
1,3,5-trimethylbenzene	**6.5**	**1.13-37.28**	**0.04**	1.76	0.78-3.98	0.17
1,2,4-trimethylbenzene	**1.95**	**1.17-3.26**	**0.01**	1.03	0.81-1.32	0.78
n-hexane	1.005	0.72-1.27	0.77	**1.17**	**1.04-1.31**	**0.009**
methylcyclohexane	0.92	0.16-5.26	0.92	**3.82**	**1.75-8.31**	**0.001**
cyclohexane	0.91	0.65-1.27	0.57	**1.17**	**1.03-1.33**	**0.02**
ethylene	1.02	0.99-1.05	0.25	**1.01**	**1.0002-1.03**	**0.046**

AOR: adjusted odds ratio; CI: confidence interval
AOR: the multivariable model included one kind of VOC and temperature, humidity, rainfall, and windspeed.
Statistical significance: a two-tailed *P*-value of <0.05.

Subgroup analysis by age on the visit and lag days

Regarding age subgroup analysis, in the younger subgroup (age < 65 years) on the visit days (**Table 3**), daily visits for urticaria was significantly positively associated with higher levels of 4 VOCs (ethylbenzene (AOR = 1.23, 95%CI: 1.01–1.49), toluene (AOR = 1.03, 95%CI: 1.006–1.05), m-/p-xylene (AOR = 1.08, 95%CI: 1.007–1.16), o-xylene (AOR = 1.25, 95%CI: 1.01–1.54)), and significantly negatively associated with a higher level of rainfall (AOR = 0.98, 95%CI: 0.97–0.99).

On the fourth lag days (**Table 4**), higher weather temperature (AOR = 1.02, 95%CI: 1.002–1.04) and the following 7 VOCs significantly positively affected younger patients: ethylbenzene (AOR = 1.24, 95%CI: 1.03–1.48), m-/p-xylene (AOR = 1.1, 95%CI: 1.02–1.19), o-xylene (AOR = 1.34, 95%CI: 1.08–1.68), n-hexane (AOR = 1.17, 95%CI: 1.04–1.31), methylcyclohexane (AOR = 3.82, 95%CI: 1.75–8.31), cyclohexane (AOR = 1.17, 95%CI: 1.03–1.33), ethylene (AOR = 1.01, 95%CI: 1.0002–1.03).

In the older patient subgroup (age ≥ 65 years), daily visits for urticaria was significantly positively associated with an increased level of m-/p-xylene (AOR = 1.17, 95%CI: 1.004–1.35) on the visit days (**Table 3**). They were significantly negatively associated with higher levels of rainfall (AOR = 0.94, 95%CI: 0.90–0.98), and windspeed (AOR = 0.81, 95%CI: 0.70–0.93) on the visit days. On the fourth lag days (**Table 4**), the following 6 VOCs significantly positively affected the older subgroup: benzene (AOR = 1.31, 95%CI: 1.02–1.68), toluene (AOR = 1.06, 95%CI: 1.001–1.11), m-/p-xylene (AOR = 1.21, 95%CI: 1.01–1.45), o-xylene (AOR = 1.76, 95%CI: 1.06–2.92), 1,3,5-trimethylbenzene (AOR = 6.5, 95%CI: 1.13–37.28), and 1,2,4-trimethylbenzene (AOR = 1.95, 95%CI: 1.17–3.26)).

The daily clinic visits for urticaria in all patients, and in the age and gender subgroups on visit days were not significantly associated with the levels of benzene, 1,2,4-trimethylbenzene, n-hexane, methylcyclohexane, cyclohexane, and ethylene. No significant associations for the 11 VOCs were found on the 1st, 2nd, 3rd and 5th lag days.

Discussion

The major anthropogenic contributors to air VOCs in Kaohsiung City include petroleum and natural gas extraction, petroleum oil refineries, the burning of fossil fuels in heavy industrial areas, coal-fired power generation plants, steel production, ships and airplanes at the international harbor and airport, pollutants leakage during industrial production processes, and the use of pesticides in agriculture.[26] VOCs may contribute to the formation of ground-ozone and $PM_{2.5}$ in urban and suburban areas.[27,28] High population density with a total population of about 2.77 million in Kaohsiung,[26,29] and high traffic flow are also contributing factors.

Aromatic VOCs (benzene, toluene, ethylbenzene, and xylenes isomers, jointly known as BTEX), have been found to be the most abundant VOCs in the environment in urban and suburban areas, and are key indicators of main VOCs exposure that have been studied for association with the development and exacerbations of asthma and allergy.[13,30] The USEPA IRIS database provides reference concentrations for inhalation exposure of VOCs that can cause critical human/animal health effects, including hematological, neurological, and developmental effects.[2] However, the reference concentrations for allergic reaction have not previously been reported.

Yoshida et al. investigated the amounts of several selected aromatic hydrocarbons to evaluate their inhalation toxicokinetics in rats in a closed chamber, and extrapolated values to estimate the absorbed values in car drivers. Their analysis showed that BTEX, trimethylbenzene, n-hexane, and styrene were absorbed in rats.[31]

In a mice model, aromatic compounds, and especially m-xylene, and trimethylbenzene, that were applied to the earlobes of BALB/c mice caused apparent thymic stromal lymphopoietin production which resulted in exacerbations of allergic inflammations.[32] Elevations in T-helper-2-initiating cytokines, including thymic stromal lymphopoietin, have been reported in lesional skin from patients with chronic spontaneous urticaria.[33] Exposure to VOCs has been shown to provoke skin wheal responses through histamine release, and increased plasma levels of substance P, vasoactive intestinal peptide, and nerve growth factor in patients with self-reported multiple chemical sensitivity.[34] Exposure to high concentrations of VOCs might impair the normal skin barrier function.[35]

In this study, certain VOCs affected both the visit days and fourth lag days, including toluene, ethylbenzene, and xylene. It is possible that these VOCs not only directly caused skin inflammation, but that they could also cause skin inflammation through allergic mechanisms. In those affected only on the fourth lag day but not on visit days, it is possible that the reactions were through allergic (sensitization) mechanisms, and that the period for inducing urticaria symptoms and exacerbations was 4 days. The most notable finding was that even though the air levels of methylcyclohexane and 1,3,5-trimethylbenzene were lowest among the 11 VOCs, they showed the most significant AORs. The women-to-men ratio was 2.43:1 in the younger subgroup and 1.02:1 in the older subgroup, and this may explain why the types of VOCs with statistical significance were similar in the women and younger subgroups.

The one-day 75th percentile values of the VOCs were not as high as their reference concentrations in the IRIS database, although the episodic maximum values were quite high in the TAQMND. An important characteristic of urticaria is that episodes usually occur at "lower" exposure values in patients with urticaria than in the general population. However, causality cannot be inferred in a case-crossover study, and further investigation are needed on whether urticaria attacks could be induced or just exacerbated by VOCs.

Meteorological factors such as heavy rainfall and stronger wind speed on the visit days would decrease the air concentration of VOCs. Previous studies have demonstrated that air VOCs can be scavenged by rain droplets. Heavy rainfall and stronger wind speed on the visit days significantly reduced the number of patients visiting the hospital.

In addition, higher weather temperatures on the fourth lag days affected the daily visits for urticaria in all patients, women, and younger subgroups.[10] Higher weather temperatures enhance physiological functions such as sweating and skin capillary dilatation, and then subsequently enhance air VOCs permeation through skin or alveoli and accelerate sensitization. However, further studies are needed to investigate the mechanisms.

The limitations of this observational study include information bias, selection bias, and measurement errors. Despite these limitations, the strengths of this study include accurate records, case-crossover design, lag-day effect, and adjustments for confounders. Information bias may have been caused by patients being unable to remember the exact dates of acute urticaria attacks. Selection bias may have been caused by recruitment of the study subjects from one medical center rather than the general population, which may have led to underestimation of the number of daily clinic visits. Potential errors in exposure measurements may also have occurred as the concentrations of the ambient air VOCs were measured at two fixed outdoor monitoring stations in Kaohsiung. Although measurement errors were unavoidable, the measurement data for each patient were classified according to the nearest corresponding monitoring stations to their home districts to estimate their exposure levels. Data of diagnosis codes and districts of residence are more accurate in medical center records than those in local clinic records. The effects of the available confounders, meteorological factors, were minimized by statistical adjustments in the same model during the multivariable analysis. Compared to Poisson regression, the strength of a case-crossover study design is that it is likely to result in small bias and minimal autocorrelation in individuals' exposure among the case and referent days. It is usually used in studies on the effect of short-term change in air pollutants exposure on health.

Conclusion

Total daily clinic visits for urticaria was significantly positively associated with higher levels of 4 VOCs (ethylbenzene, toluene, m-/p-xylene, and o-xylene) on the visit days, and 10 VOCs on the fourth lag day (benzene, ethylbenzene, toluene, m-/p-xylene, o-xylene, 1,3,5-trimethylbenzene, n-hexane, methylcyclohexane, cyclohexane, and ethylene). Subgroup analyses showed that men were not affected on the visit days but were influenced by higher benzene levels on the fourth lag day. The women and younger subgroups were affected by higher levels of 4 VOCs on the visit days (ethylbenzene, toluene, m-/p-xylene, and o-xylene). The lag effects of more than 6 VOCs on the fourth lag day were significantly higher in women, younger and older patients. The most notable VOCs were methylcyclohexane and 1,3,5-trimethylbenzene, which had the lowest values but highest influence.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability

The datasets from Taiwan Air Quality Monitoring Network Database are open database. The number of clinic visits data are available from Kaohsiung Veterans General Hospital, but not publicly available.

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