Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Positive effect of exposure to ambient air volatile organic compounds on clinic visits for atopic dermatitis

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Abstract

Background: Exposure to air pollutants have been associated with exacerbations of atopic dermatitis (AD) symptoms, however, the role of each volatile organic compound (VOC) was rarely investigated.

Objective: This population-based study investigated associations between daily visits for AD at hospitals and exposure to each ambient air VOC in central-southern Taiwan.

Methods: The dependent variable with diagnostic code (ICD-9-CM code 691.8 and ICD-10-CM code L20) retrieved from National Health Insurance Research Database (NHIRD) from 2008/01/01 to 2018/12/31. Independent variables included one-day 75th-percentile value of each VOC and four meteorologic conditions retrieved from Taiwan Air Quality Monitoring Network Databases and four allergic diseases from NHIRD. This multivariable model was analyzed using both case-crossover study (adjusted odds ratio (AOR)) and Poisson model (adjusted relative risk (ARR)).

Results: Two study designs in total and each subgroup showed consistently significantly positive effects of each 12 ambient air VOC, especially highest in 1,3,5-trimethylbenzene and methylcyclohexane. The concentration of each 12 VOC was highly affected the total daily visits (AOR: 1.05-3.58, ARR: 1.03-3.74, $P < 0.001$), particularly highest for 1,3,5-trimethylbenzene (AOR = 3.58, ARR = 3.74, $P < 0.001$) and methylcyclohexane (AOR = 3.55, ARR = 2.13, $P < 0.001$). The results of each VOC were similarly positive in men and women. Children were the most vulnerable on the exposure to methylcyclohexane (AOR = 6.18, ARR = 2.35, $P < 0.001$), and 1,3,5-trimethylbenzene (AOR = 6.08, ARR = 4.62, $P < 0.001$). The results for older adults, adolescents, and younger adults were also significantly higher. In the analysis of five areas, mostly VOCs showed significantly higher effects using two methods.

Conclusions: 12 air VOCs can be considered as risk factors of daily visits for AD.

Key words: ambient air volatile organic compounds, atopic dermatitis, Taiwan National Health Insurance Research Database, Taiwan Air Quality Monitoring Network databases, case-crossover study, Poisson model,

Citation:
Tseng, H. W. (0000). Positive effect of exposure to ambient air volatile organic compounds on clinic visits for atopic dermatitis. *Asian Pac J Allergy Immunol*, 00(0), 000-000.
https://doi.org/10.12932/ap-250224-1796

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Introduction

Increasing evidences has shown an association between air pollution including air volatile organic compounds (VOCs) and atopic dermatitis (AD). AD is one of the most prevalent chronic inflammatory skin diseases characterized by pruritic localized and generalized eczema, often with seasonal fluctuations and a chronic relapsing and remitting courses of more than 6 months.[1] Many patients possibly also have allergic march, including allergic asthma, allergic rhinoconjunctivitis, urticaria, food allergies, and other IgE-mediated immediate hypersensitivity (type 1) allergies.[2] The factors involved in its onset and exacerbation of AD should be considered in clinical practice. In addition to genetic factors, exposure to environmental factors such as allergens, stimuli in the daily environment, meteorologic factors, and life-style factors can increase cutaneous hyperreactivity and exacerbates dermatitis.[1]

VOCs are defined by the World Health Organization (WHO) as compounds with a boiling point of ≤ 250°C measured at a standard atmospheric pressure of 101.3 kPa, and it is a category of many diverse compounds that volatilize into the air at room temperature.[3,4] The vapor and liquid of all VOCs can cause respiratory tract, eye, and skin irritation, drowsiness and dizziness. Toxicokinetic studies in animals and humans on the United States Environmental Protection Agency (USEPA) IRIS websites demonstrated that lipophilic VOCs can pass through the skin barrier, nasal mucosa, and epithelia of the respiratory tract, and then enter the blood stream reaching the cell membranes of distant organs. This lipophilic characteristic cause long-lasting effects on organisms.[5-7]

According to the USEPA and WHO, exposure to all VOCs on the skin can cause allergic reactions, and acute or subacute inflammation-like reaction of the skin and mucous membrane.[3,8] Evidence from animal models, *in vitro* experiments, case-control, and cohort studies suggests that indoor and outdoor air pollution exposure may cause allergic inflammation and worsen the symptoms of AD.[9,10] In addition, airborne pollutants have been shown to have a destructive effect on skin barrier integrity, and to be involved in various pathophysiological mechanisms, including oxidative damage, immune stimulation, and propagation of the itch–scratch cycle.[11] Total VOCs are among the aggravating factors of atopic dermatitis,[12] asthma, and urticaria,[13] and as supported by Kim et al, who demonstrated that symptoms of AD were influenced by outdoor and indoor air pollution, including VOCs.[14-16] However, the role of each VOC was rarely investigated.

The aim of this study was to investigate the potential acute effects and short-term changes in 12 ambient air VOC concentrations on daily clinic visits in patients with AD in central and southern Taiwan. This population-based nationwide study used data from the Taiwan National Health Insurance Research Database (NHIRD) with two study designs, a case-crossover study design with conditional logistic regression, and a Poisson model with Poisson regression. Subgroups analyses of age, sex, and areas were also performed.

Methods

Data sources of daily outpatient clinic visits for AD

Data of daily outpatient clinic visits for patients with AD of any age at institutions, including local hospitals, regional hospitals, and medical centers, were retrospectively obtained from the NHIRD from January 1, 2008 to December 31, 2018. The NHIRD can represent the nearly entire population of Taiwan. Before data from the NHIRD are released for research, the original identification numbers are anonymized to protect the patients' privacy, and thus the need for informed consent was waived by the Institutional Review Board. International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification codes (ICD-9-CM code 691.8 and ICD-10-CM code L20) were used to identify patients with AD. The definition of an AD case required an AD diagnosis confirmed three or more times in an outpatient department within 1 year by dermatologist, rheumatologist, and pediatrist. These diagnostic codes and definition have been applied in previous studies using the NHIRD.[17] The event date for the patients in the AD cohort was defined as the date of the diagnosis of AD.

Study areas

The study areas were Kaohsiung City, Tainan City, Yunlin County, Changhua County, and Taichung City in central-southern Taiwan (**Figure 1**). Kaohsiung City, Taichung City, and Tainan City were the second, third, and fifth largest cities in Taiwan with high-density populations before 2018, respectively.[18] These areas had been recorded as the higher air pollution levels in central and southern Taiwan in 2018, and also for several years before this.[19] From Kaohsiung to Taichung, the north latitude is between 22°28′32″ and 24°26′38″, and east longitude is between 120°03′54″ and 121°29′55″. The patients whose registered National Health Insurance address was in the listed cities or counties were included.

Data sources of ambient air VOCs and meteorological conditions

Ambient air pollution data were retrieved from the Taiwan Air Quality Monitoring Network Databases (TAQMND), Environmental Protection Administration, Executive Yuan, Taiwan, R.O.C.[20,21] which was transformed to Ministry of Environment since August 2023. The database provided hourly monitoring data for concentrations (parts-per-billion as carbon (ppbC); ppbC = ppb * (number of carbon atoms)) of VOCs from air quality monitoring stations for photochemicals. The 12 ambient air VOCs with higher concentrations (benzene, ethylbenzene, toluene, m-/p-xylene, o-xylene, 1,3,5-trimethylbenzene, 1,2,4-trimethylbenzene, isopentane, n-pentane, n-hexane, methylcyclohexane, and cyclohexane) were analyzed.[20,21] The one-day average 75th-percentile value of each VOC that was calculated from the 24-hourly data of each date was chosen for analysis.

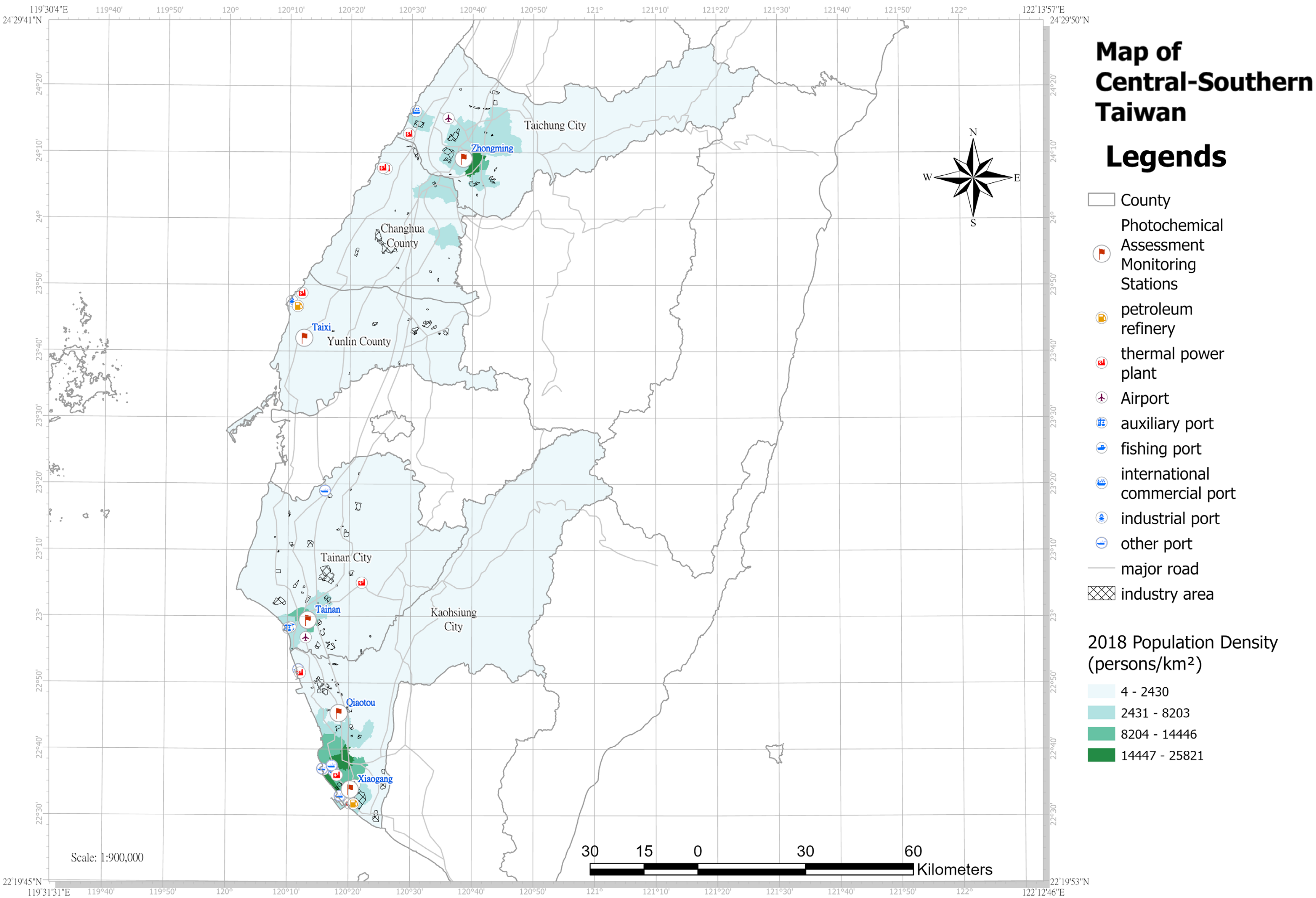

Figure 1. Map of Central-Southern Taiwan (Kaohsiung City, Tainan City, Yunlin County, Changhua County, and Taichung City): indicating population densities in districts (persons per square kilometer), the sites of major industrial areas, ports, international airport, thermal power plants, major traffic roads, monitoring stations. KM: kilometer. (ArcGIS Pro Version 3.1.1)

Regarding the monitoring stations for photochemicals in 5 areas, two monitoring stations were located in the administrative districts of Siaugang and Qiaotou in Kaohsiung City. These stations are representative as a highest and lowest air-polluted areas, respectively, in Kaohsiung City. Tainan monitoring station is located at Chungci district at Tainan City. Taici monitoring station is located at Taici district near Mailiao at Yunlin County. The above monitor stations were all established before January 2008. Zongming monitor station was established on 2011/11/1 and was located at Nantun District at Taichung City. Air VOC data for Changhua County were recorded by a moving monitoring truck, and dates without air pollutants data in Changhua County were excluded. Therefore, the data periods recorded for Changhua County and Taichung City were shorter.

Study design and statistical methods

Two study designs and analyses were executed, including both a case-crossover study with conditional logistic regression and a Poisson model with Poisson regression. The flowchart of this study design, patient selection, VOCs data collection was present on **Figure 2**. The subgroups analyses included gender (men and women), age (children: < 12 years of age; adolescents: 12-19 years; younger adults: 20-64 years; and older adults: ≥ 65 years), and 5 areas (Kaohsiung City, Tainan City, Yunlin County, Changhua County, and Taichung City).

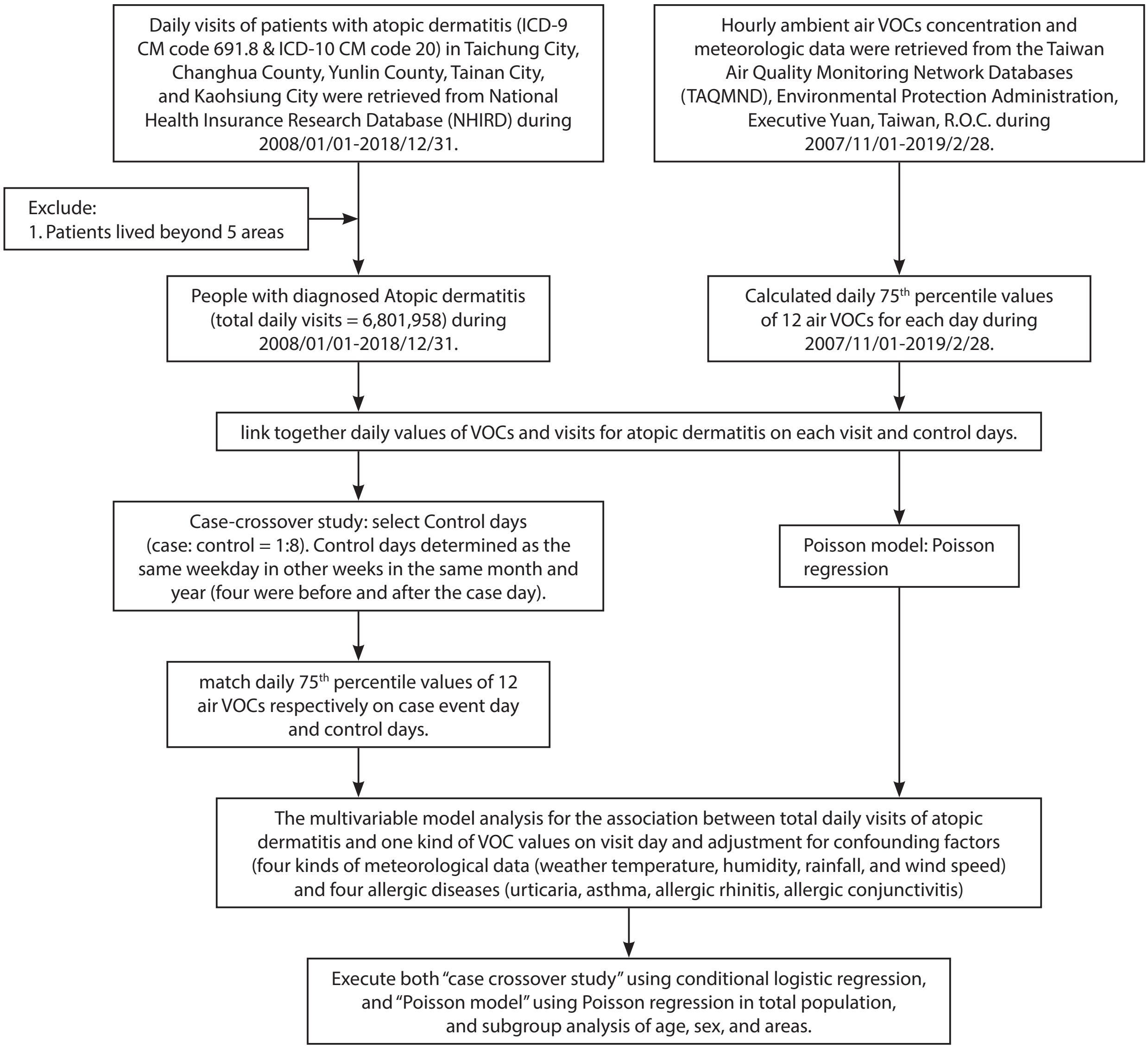

Figure 2. Flowchart of this study design, including both case-crossover study and Poisson model, patient selection, air VOCs data, statistical methods.

Poisson regression uses Poisson distribution that fits count data well, such as attendance counts on different days. The case-crossover design is an adaptation of both case-control design and crossover design that it employs persons' exposed periods as controls. The case event day was considered as the day on which the exposure supposedly affected the patients' health, and defined as the clinic visit date for AD. Controls were matched to case periods by the same weekday of the case event day, in that the control days were determined as the same weekday in other weeks in the same month and year. Using this strategy, eight controls for each case were selected, with four (the 1st, 2nd, 3rd, and 4th same weekday) before and four after the case day match for the day of the week in one month, respectively.[22-24]

The multivariable model included one kind of VOC, four kinds of meteorological data (weather temperature (°C), humidity (%), wind speed (m /sec), and rainfall (mm/hour)), and four allergic diseases (urticaria (ICD-9-CM code 708 and ICD-10-CM code L50), asthma (ICD-9-CM code 493 and ICD-10-CM code J45), allergic rhinitis (ICD-9-CM code 477 and ICD-10-CM code J30), and allergic conjunctivitis (ICD-9-CM code 372.14 and ICD-10-CM code H10.45)). Meteorological data and allergic diseases were as confounding factors for adjustment. The adjustment for comorbidities of allergic diseases was based on the concept of atopic march.[25] The results for the associations between daily clinic visits and one-day 75th-percentile value of each VOC concentration and available confounding factors were presented as adjusted odds ratio (AOR) in conditional logistic regression, adjusted relative risk (ARR) in Poisson regression, 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 SAS, version 9.4 (SAS Institute, Cary, NC).

Ethical approval

This study was approved by the Institutional Review Board of China Medical University Hospital (approval no. CMUH109-REC2-031(CR3)) and conducted according to the Declaration of Helsinki.

Results

Demographic characteristics, air VOCs, and meteorological data

There was a total of 6,801,958 visits from January 1, 2008 to December 31, 2018 (men: 3,322,321 (48.8%), women: 3,479,637 (51.2%); children: 3,176,354 (46.7%), adolescents: 289,246 (4.3%), younger adults: 2,619,566 (38.5%), older adults: 716,792 (10.5%)). Children with AD was the predominant population. The mean values of 12 ambient air VOCs in total five areas are listed in **Table 1**.

Associations between the total daily visits for AD and values of air VOCs on the visit days on all areas.

Consistently significantly positive associations were found between the total daily visits and higher values of the 12 VOCs on the visit days in both statistical methods (**Table 2**) (conditional logistic regression: AOR: 1.05-3.58, Poisson regression: ARR: 1.03-3.74, *P* < 0.001), especially strong for 1,3,5-trimethylbenzene (AOR = 3.58, ARR = 3.74, *P* < 0.001) and methylcyclohexane (AOR = 3.55, ARR = 2.13, *P* < 0.001).

Table 1. The concentrations of air volatile organic compounds of quartiles on event days of total five areas.

Air VOCs	minimum	50th-percentile	75th-percentile	maximum
benzene	0.093	0.408	0.553	1.723
toluene	0.367	2.636	3.484	9.011
ethylbenzene	0.064	0.231	0.291	0.673
m-/p-xylene	0.140	0.718	0.910	4.422
o-xylene	0.070	0.279	0.352	0.954
1,3,5-trimethylbenzene	0.028	0.076	0.091	0.333
1,2,4-trimethylbenzene	0.068	0.246	0.300	1.535
isopentane	0.274	1.050	1.260	3.335
n-pentane	0.149	0.507	0.620	2.233
n-hexane	0.089	0.342	0.436	1.493
methylcyclohexane	0.030	0.097	0.119	0.563
cyclohexane	0.055	0.149	0.192	0.505

Concentration of air volatile organic compounds (VOCs): parts per billion (ppb)

Table 2. The adjusted odds ratio and adjusted relative risk between daily clinic visits for atopic dermatitis and daily 75th-percentile value of each VOC on the visit days in the total population and gender subgroup.

Air VOCs	Conditional logistic regression			Poisson Regression		
	AOR	95%CI	*P* value	ARR	95%CI	*P* value
Total						
benzene	1.281	1.262, 1.3	< 0.001	1.045	1.041, 1.048	< 0.001
toluene	1.049	1.047, 1.05	< 0.001	1.027	1.0268, 1.028	< 0.001
ethylbenzene	1.842	1.801, 1.883	< 0.001	1.412	1.4, 1.423	< 0.001
m-/p-xylene	1.082	1.076, 1.088	< 0.001	1.107	1.104, 1.109	< 0.001
o-xylene	1.618	1.589, 1.649	< 0.001	1.356	1.348, 1.364	< 0.001
1,3,5-trimethylbenzene	3.575	3.347, 3.818	< 0.001	3.740	3.646, 3.838	< 0.001
1,2,4-trimethylbenzene	1.261	1.24, 1.283	< 0.001	1.428	1.417, 1.438	< 0.001
isopentane	1.086	1.081, 1.092	< 0.001	1.073	1.071, 1.075	< 0.001
n-pentane	1.137	1.126, 1.148	< 0.001	1.110	1.106, 1.114	< 0.001
n-hexane	1.429	1.411, 1.448	< 0.001	1.297	1.291, 1.303	< 0.001
methylcyclohexane	3.547	3.37, 3.732	< 0.001	2.126	2.093, 2.159	< 0.001
cyclohexane	1.198	1.168, 1.228	< 0.001	1.179	1.166, 1.193	< 0.001
Woman subgroup						
benzene	1.341	1.313, 1.369	< 0.001	1.042	1.037, 1.048	< 0.001
toluene	1.052	1.049, 1.054	< 0.001	1.027	1.026, 1.028	< 0.001
ethylbenzene	1.871	1.814, 1.93	< 0.001	1.413	1.397, 1.429	< 0.001
m-/p-xylene	1.088	1.08, 1.097	< 0.001	1.107	1.104, 1.111	< 0.001
o-xylene	1.614	1.573, 1.657	< 0.001	1.357	1.345, 1.369	< 0.001
1,3,5-trimethylbenzene	3.881	3.538, 4.256	< 0.001	3.810	3.675, 3.951	< 0.001
1,2,4-trimethylbenzene	1.295	1.265, 1.326	< 0.001	1.441	1.425, 1.456	< 0.001
isopentane	1.08	1.072, 1.088	< 0.001	1.075	1.072, 1.078	< 0.001
n-pentane	1.118	1.104, 1.133	< 0.001	1.113	1.108, 1.119	< 0.001
n-hexane	1.442	1.417, 1.468	< 0.001	1.293	1.284, 1.302	< 0.001
methylcyclohexane	3.428	3.192, 3.683	< 0.001	2.092	2.047, 2.139	< 0.001
cyclohexane	1.306	1.261, 1.353	< 0.001	1.221	1.202, 1.241	< 0.001
Men subgroup						
benzene	1.222	1.196, 1.248	< 0.001	1.047	1.042, 1.053	< 0.001
toluene	1.046	1.043, 1.048	< 0.001	1.027	1.0267, 1.028	< 0.001
ethylbenzene	1.813	1.756, 1.871	< 0.001	1.411	1.395, 1.427	< 0.001
m-/p-xylene	1.076	1.068, 1.085	< 0.001	1.106	1.103, 1.11	< 0.001
o-xylene	1.623	1.581, 1.667	< 0.001	1.355	1.344, 1.367	< 0.001
1,3,5-trimethylbenzene	3.287	2.992, 3.611	< 0.001	3.670	3.539, 3.807	< 0.001
1,2,4-trimethylbenzene	1.227	1.198, 1.257	< 0.001	1.415	1.4, 1.43	< 0.001
isopentane	1.094	1.085, 1.102	< 0.001	1.070	1.067, 1.073	< 0.001
n-pentane	1.158	1.142, 1.174	< 0.001	1.107	1.101, 1.112	< 0.001
n-hexane	1.416	1.39, 1.442	< 0.001	1.301	1.292, 1.31	< 0.001
methylcyclohexane	3.67	3.413, 3.946	< 0.001	2.160	2.113, 2.208	< 0.001
cyclohexane	1.091	1.052, 1.131	< 0.001	1.137	1.118, 1.156	< 0.001

The concentration of air volatile organic compounds (VOCs): parts per billion (ppb)
AOR: adjusted odds ratio, ARR: adjusted relative risk, CI: confidence interval,
AOR and ARR: the multivariable model included one kind of VOC, 4 kinds of meteorologic data, and allergic diseases. Statistical significance: a two-tailed *P*-value of < 0.05.

Subgroup analysis of gender on the visit days

Regarding gender subgroup analysis, both women and men groups consistently showed significantly positive associations between the daily visits for AD and higher levels of the 12 VOCs in both statistical methods (**Table 2**). In the women, 1,3,5-trimethylbenzene (AOR = 3.88, ARR = 3.81, $P < 0.001$) and methylcyclohexane (AOR = 3.43, ARR = 2.09, $P < 0.001$) were especially highest, and the other 10 VOCs showed similar high effects on the visit days (benzene, ethylbenzene, toluene, m-/p-xylene, o-xylene, 1,2,4-trimethylbenzene, isopentane, n-pentane, n-hexane, and cyclohexane: AOR: 1.05-1.87, ARR: 1.03-1.44, $P < 0.001$). In the men, methylcyclohexane (AOR = 3.67, ARR = 2.16, $P < 0.001$) and 1,3,5-trimethylbenzene (AOR = 3.29, ARR = 3.67, $P < 0.001$) were especially high, and the other 10 VOCs showed similar high effects on the visit days (AOR: 1.05-1.8, ARR: 1.03-1.4; $P < 0.001$)

Subgroup analysis of age on the visit days

In subgroup analysis of age using two statistical methods (**Table 3**), children were the most vulnerable group to methylcyclohexane (AOR = 6.18, ARR = 2.35, $P < 0.001$), followed by the older adults (AOR = 4.12, ARR = 2.27, $P < 0.001$), adolescents (AOR = 2.83, ARR = 1.69, $P < 0.001$), and younger adults (AOR = 1.70, ARR = 1.79, $P < 0.001$). Regarding exposure to 1,3,5-trimethylbenzene, children were also the most vulnerable (AOR = 6.08, ARR = 4.62, $P < 0.001$), the results were also significantly positive association for adolescents (AOR = 5.92, ARR = 3.09, $P < 0.001$), older adults (AOR = 3.21, ARR = 3.67, $P < 0.001$), and younger adults (AOR = 1.86, ARR = 2.78, $P < 0.001$). Adolescents (AOR = 2.35, ARR = 1.34, $P < 0.001$) and children (AOR = 2.09, ARR = 1.47, $P < 0.001$) were more vulnerable to ethylbenzene exposure. The mostly AORs values of these VOCs were higher than ARR values in above subgroups. The other VOCs showed similar high effects (AOR: 1.03-1.99, ARR: 1.02-1.49, $P < 0.001$).

Table 3. The adjusted odds ratio and adjusted relative risk in age subgroups between daily clinic visits for atopic dermatitis and daily 75th-percentile value of each VOC on the visit days.

Air VOCs	Conditional logistic regression			Poisson Regression		
	AOR	95%CI	*P* value	ARR	95%CI	*P* value
	Children	< 12 years				
benzene	1.47	1.439, 1.502	< 0.001	1.070	1.064, 1.075	< 0.001
toluene	1.061	1.058, 1.063	< 0.001	1.030	1.029, 1.031	< 0.001
ethylbenzene	2.09	2.024, 2.159	< 0.001	1.470	1.454, 1.487	< 0.001
m-/p-xylene	1.112	1.103, 1.121	< 0.001	1.123	1.12, 1.127	< 0.001
o-xylene	1.799	1.752, 1.848	< 0.001	1.408	1.396, 1.42	< 0.001
1,3,5-trimethylbenzene	6.08	5.518, 6.699	< 0.001	4.619	4.453, 4.792	< 0.001
1,2,4-trimethylbenzene	1.399	1.364, 1.434	< 0.001	1.493	1.477, 1.509	< 0.001
isopentane	1.139	1.131, 1.148	< 0.001	1.080	1.077, 1.083	< 0.001
n-pentane	1.212	1.196, 1.229	< 0.001	1.118	1.112, 1.123	< 0.001
n-hexane	1.674	1.643, 1.705	< 0.001	1.350	1.341, 1.36	< 0.001
methylcyclohexane	6.179	5.74, 6.652	< 0.001	2.353	2.304, 2.403	< 0.001
cyclohexane	1.268	1.22, 1.319	< 0.001	1.242	1.222, 1.264	< 0.001
	Adolescents	12-19 years				
benzene	1.246	1.156, 1.343	< 0.001	1.030	1.012, 1.049	< 0.001
toluene	1.057	1.049, 1.065	< 0.001	1.024	1.021, 1.027	< 0.001
ethylbenzene	2.35	2.104, 2.625	< 0.001	1.343	1.29, 1.398	< 0.001
m-/p-xylene	1.117	1.088, 1.147	< 0.001	1.084	1.072, 1.096	< 0.001
o-xylene	1.98	1.805, 2.173	< 0.001	1.282	1.243, 1.321	< 0.001
1,3,5-trimethylbenzene	5.918	4.296, 8.15	< 0.001	3.086	2.72, 3.501	< 0.001
1,2,4-trimethylbenzene	1.481	1.368, 1.604	< 0.001	1.399	1.349, 1.452	< 0.001
isopentane	1.112	1.083, 1.141	< 0.001	1.059	1.049, 1.069	< 0.001
n-pentane	1.097	1.047, 1.148	< 0.001	1.078	1.06, 1.096	< 0.001
n-hexane	1.451	1.361, 1.546	< 0.001	1.226	1.197, 1.256	< 0.001
methylcyclohexane	2.83	2.191, 3.655	< 0.001	1.692	1.561, 1.833	< 0.001
cyclohexane	1.198	1.06, 1.354	< 0.01	1.052	0.994, 1.113	0.08

Table 3. (Continued)

Air VOCs	Conditional logistic regression			Poisson Regression		
	AOR	95%CI	*P* value	ARR	95%CI	*P* value
	Young adults	**20-64 years**				
benzene	1.071	1.045, 1.097	< 0.001	1.006	0.999, 1.012	0.08
toluene	1.03	1.028, 1.033	< 0.001	1.023	1.022, 1.023	< 0.001
ethylbenzene	1.503	1.45, 1.558	< 0.001	1.308	1.29, 1.325	< 0.001
m-/p-xylene	1.045	1.035, 1.054	< 0.001	1.082	1.078, 1.086	< 0.001
o-xylene	1.362	1.322, 1.404	< 0.001	1.274	1.261, 1.287	< 0.001
1,3,5-trimethylbenzene	1.859	1.672, 2.068	< 0.001	2.780	2.665, 2.9	< 0.001
1,2,4-trimethylbenzene	1.108	1.078, 1.138	< 0.001	1.333	1.316, 1.349	< 0.001
isopentane	1.031	1.022, 1.04	< 0.001	1.061	1.057, 1.064	< 0.001
n-pentane	1.054	1.038, 1.07	< 0.001	1.095	1.088, 1.101	< 0.001
n-hexane	1.199	1.175, 1.224	< 0.001	1.224	1.214, 1.234	< 0.001
methylcyclohexane	1.704	1.568, 1.852	< 0.001	1.794	1.746, 1.843	< 0.001
cyclohexane	1.178	1.133, 1.225	< 0.001	1.115	1.095, 1.136	< 0.001
	Older adults	**≥ 65 years**				
benzene	1.308	1.249, 1.369	< 0.001	1.059	1.047, 1.072	< 0.001
toluene	1.057	1.052, 1.062	< 0.001	1.029	1.027, 1.031	< 0.001
ethylbenzene	1.987	1.857, 2.125	< 0.001	1.492	1.455, 1.529	< 0.001
m-/p-xylene	1.081	1.064, 1.099	< 0.001	1.113	1.105, 1.121	< 0.001
o-xylene	1.692	1.598, 1.792	< 0.001	1.379	1.353, 1.406	< 0.001
1,3,5-trimethylbenzene	3.211	2.632, 3.918	< 0.001	3.668	3.392, 3.967	< 0.001
1,2,4-trimethylbenzene	1.219	1.158, 1.283	< 0.001	1.445	1.412, 1.479	< 0.001
isopentane	1.05	1.033, 1.068	< 0.001	1.079	1.072, 1.085	< 0.001
n-pentane	1.138	1.105, 1.172	< 0.001	1.130	1.118, 1.142	< 0.001
n-hexane	1.355	1.304, 1.408	< 0.001	1.294	1.275, 1.314	< 0.001
methylcyclohexane	4.118	3.526, 4.811	< 0.001	2.266	2.156, 2.382	< 0.001
cyclohexane	1.021	0.949, 1.098	0.58	1.182	1.141, 1.224	< 0.001

The concentration of air volatile organic compounds (VOCs): parts per billion (ppb),
AOR: adjusted odds ratio, ARR: adjusted relative risk, CI: confidence interval,
AOR and ARR: the multivariable model included one kind of VOC, meteorologic data, and allergic diseases. Statistical significance: a two-tailed *P*-value of < 0.05.

Subgroups analysis of the five areas

In subgroup analysis of areas (**Table 4**), methylcyclohexane had the significantly highest association using conditional logistic regression analysis in Changhua County (AOR = 9.54, ARR = 1.81, *P* < 0.001), followed by Kaohsiung City (AOR = 5.29, ARR = 1.67, *P* < 0.001), Tainan City (AOR = 5.18, ARR = 2.22, *P* < 0.001), Yunlin County (AOR = 2.83, ARR = 2.00, *P* < 0.001), and Taichung City (AOR = 1.54, ARR = 1.66, *P* < 0.001). In addition, 1,3,5-trimethylbenzene showed the significantly highest association in Yunlin County (AOR = 6.72, ARR = 3.14, *P* < 0.001), followed by Changhua County (AOR = 6.6, ARR = 2.93, *P* < 0.001), Kaohsiung City (AOR = 3.52, ARR = 2.56, *P* < 0.001), Tainan City (AOR = 3.16, ARR = 2.72, *P* < 0.001), and Taichung (AOR = 1.44, ARR = 2.69, *P* < 0.001). Ethylbenzene showed higher effects in Kaohsiung City (AOR = 2.58, ARR = 1.25, *P* < 0.001) and Changhua County (AOR = 2.64, ARR = 1.33, *P* < 0.001). The other VOCs showed similar significantly high effects (AOR = 1.02-1.96, ARR = 1.02-1.67, *P* < 0.05). The significantly positive results using Poisson regression for each VOC were similar in 5 areas.

Table 4. The adjusted odds ratio and adjusted relative risk in five areas between daily clinic visits for atopic dermatitis and daily 75th-percentile value of each VOC on the visit days.

Air VOCs	Conditional logistic regression			Poisson Regression		
	AOR	95%CI	*P* value	ARR	95%CI	*P* value
Kaohsiung City						
benzene	1.239	1.18, 1.301	< 0.001	1.028	1.019, 1.037	< 0.001
toluene	1.056	1.052, 1.061	< 0.001	1.020	1.019, 1.022	< 0.001
ethylbenzene	2.58	2.401, 2.772	< 0.001	1.253	1.228, 1.278	< 0.001
m-/p-xylene	1.07	1.052, 1.087	< 0.001	1.070	1.064, 1.076	< 0.001
o-xylene	1.937	1.825, 2.057	< 0.001	1.222	1.204, 1.24	< 0.001
1,3,5-trimethylbenzene	3.517	2.887, 4.284	< 0.001	2.559	2.401, 2.728	< 0.001
1,2,4-trimethylbenzene	1.17	1.113, 1.229	< 0.001	1.305	1.281, 1.331	< 0.001
isopentane	1.072	1.056, 1.089	< 0.001	1.043	1.038, 1.048	< 0.001
n-pentane	1.117	1.088, 1.147	< 0.001	1.062	1.053, 1.07	< 0.001
n-hexane	1.612	1.555, 1.672	< 0.001	1.196	1.182, 1.211	< 0.001
methylcyclohexane	5.292	4.545, 6.161	< 0.001	1.671	1.609, 1.736	< 0.001
cyclohexane	1.26	1.175, 1.351	< 0.001	1.061	1.03, 1.092	< 0.001
Tainan City						
benzene	1.205	1.115, 1.302	< 0.001	1.039	1.024, 1.054	< 0.001
toluene	1.032	1.025, 1.04	< 0.001	1.020	1.018, 1.022	< 0.001
ethylbenzene	1.669	1.488, 1.872	< 0.001	1.377	1.333, 1.423	< 0.001
m-/p-xylene	1.086	1.059, 1.115	< 0.001	1.093	1.083, 1.103	< 0.001
o-xylene	1.862	1.686, 2.056	< 0.001	1.295	1.263, 1.327	< 0.001
1,3,5-trimethylbenzene	3.163	2.309, 4.333	< 0.001	2.715	2.45, 3.009	< 0.001
1,2,4-trimethylbenzene	1.083	1.001, 1.172	0.049	1.315	1.276, 1.356	< 0.001
isopentane	1.064	1.035, 1.094	< 0.001	1.082	1.073, 1.091	< 0.001
n-pentane	1.159	1.102, 1.218	< 0.001	1.139	1.123, 1.154	< 0.001
n-hexane	1.439	1.356, 1.527	< 0.001	1.254	1.229, 1.279	< 0.001
methylcyclohexane	5.183	4.053, 6.629	< 0.001	2.215	2.071, 2.369	< 0.001
cyclohexane	1.866	1.673, 2.082	< 0.001	1.277	1.218, 1.339	< 0.001
Yunlin County						
benzene	1.395	1.262, 1.542	< 0.001	1.050	1.03, 1.07	< 0.001
toluene	1.063	1.052, 1.073	< 0.001	1.022	1.019, 1.025	< 0.001
ethylbenzene	1.956	1.694, 2.258	< 0.001	1.402	1.342, 1.464	< 0.001
m-/p-xylene	1.106	1.069, 1.144	< 0.001	1.095	1.081, 1.108	< 0.001
o-xylene	1.714	1.515, 1.94	< 0.001	1.294	1.252, 1.337	< 0.001
1,3,5-trimethylbenzene	6.723	4.415, 10.237	< 0.001	3.137	2.728, 3.606	< 0.001
1,2,4-trimethylbenzene	1.518	1.369, 1.684	< 0.001	1.405	1.348, 1.464	< 0.001
isopentane	1.06	1.024, 1.098	0.001	1.066	1.054, 1.078	< 0.001
n-pentane	1.279	1.205, 1.357	< 0.001	1.135	1.114, 1.156	< 0.001
n-hexane	1.633	1.513, 1.763	< 0.001	1.305	1.271, 1.34	< 0.001
methylcyclohexane	2.825	2.046, 3.903	< 0.001	1.997	1.827, 2.182	< 0.001
cyclohexane	0.749	0.645, 0.87	< 0.001	1.067	1.0, 1.138	0.049

Table 4. (Continued)

Air VOCs	Conditional logistic regression			Poisson Regression		
	AOR	95%CI	*P* value	ARR	95%CI	*P* value
Changhua County						
benzene	1.018	0.936, 1.108	0.67	1.016	1.001, 1.032	0.04
toluene	1.064	1.056, 1.073	< 0.001	1.023	1.021, 1.026	< 0.001
ethylbenzene	2.64	2.338, 2.98	< 0.001	1.325	1.278, 1.374	< 0.001
m-/p-xylene	1.131	1.101, 1.161	< 0.001	1.082	1.071, 1.093	< 0.001
o-xylene	2.274	2.053, 2.518	< 0.001	1.262	1.229, 1.296	< 0.001
1,3,5-trimethylbenzene	6.595	4.715, 9.224	< 0.001	2.829	2.522, 3.174	< 0.001
1,2,4-trimethylbenzene	1.495	1.379, 1.621	< 0.001	1.347	1.302, 1.393	< 0.001
isopentane	1.146	1.114, 1.178	< 0.001	1.046	1.037, 1.055	< 0.001
n-pentane	1.164	1.111, 1.22	< 0.001	1.067	1.051, 1.083	< 0.001
n-hexane	1.637	1.535, 1.746	< 0.001	1.298	1.27, 1.327	< 0.001
methylcyclohexane	9.545	7.274, 12.524	< 0.001	1.814	1.693, 1.944	< 0.001
cyclohexane	1.526	1.345, 1.731	< 0.001	1.207	1.144, 1.273	< 0.001
Taichung City						
benzene	0.925	0.886, 0.966	< 0.001	1.015	1.006, 1.025	0.002
toluene	1.024	1.02, 1.028	< 0.001	1.018	1.017, 1.02	< 0.001
ethylbenzene	1.199	1.128, 1.275	< 0.001	1.237	1.212, 1.262	< 0.001
m-/p-xylene	0.987	0.973, 1.002	0.09	1.070	1.064, 1.077	< 0.001
o-xylene	1.072	1.018, 1.129	0.009	1.226	1.207, 1.245	< 0.001
1,3,5-trimethylbenzene	1.435	1.203, 1.711	< 0.001	2.692	2.523, 2.872	< 0.001
1,2,4-trimethylbenzene	1.016	0.972, 1.063	0.47	1.299	1.274, 1.324	< 0.001
isopentane	0.992	0.978, 1.006	0.26	1.052	1.046, 1.057	< 0.001
n-pentane	0.969	0.945, 0.993	0.01	1.073	1.064, 1.082	< 0.001
n-hexane	1.136	1.099, 1.175	< 0.001	1.205	1.19, 1.22	< 0.001
methylcyclohexane	1.54	1.333, 1.779	< 0.001	1.664	1.597, 1.733	< 0.001
cyclohexane	0.945	0.886, 1.008	0.088	1.177	1.144, 1.211	< 0.001

The concentration of air volatile organic compounds (VOCs): parts per billion (ppb),
AOR: adjusted odds ratio, ARR: adjusted relative risk, CI: confidence interval,
AOR and ARR: the multivariable model included one kind of VOC, meteorologic data, and allergic diseases. Statistical significance: a two-tailed *P*-value of < 0.05.

Discussion

The major anthropogenic contributors to air VOCs in the five cities and counties included the burning of fossil fuels in heavy industrial areas, pollutants leakage during industrial production processes, emissions from transportation and construction, and the use of pesticides in agriculture. In addition, in Kaohsiung City, the main contributing factors included the emission from petrochemical activities at petroleum oil refineries, petroleum and natural gas extraction, coal-fired thermal power generation plants, steel production, and ships and airplanes at the international harbor and airport.[18,26] In Yunlin County, there are petrochemical plants involved in oil refinery and naphtha cracking for PVC resin and plastic production at Mailiao. In Changhua County, there are factories involved in paper, chemicals, and fibers production. In Taichung, there are coal-fired thermal power generation plants, petroleum oil refineries, and international harbor and airport.

Several *in vitro*, *in vivo*, and epidemiology studies have reported that an association between higher VOCs concentrations and AD. In a mice model, among the aromatic compounds applied on the earlobes of BALB/c mice, xylene, especially m-xylene, and trimethylbenzene caused apparent thymic stromal lymphopoietin (TSLP) production in the ears and resulted exacerbation of allergic inflammation.[27] TSLP has been demonstrated to be critical in regulating inflammatory responses among various allergic disorders, including AD and asthma.[28] A systemic review showed that short-term and long-term exposure of outdoor air pollutants, including $PM_{2.5}$, PM_{10}, NO_2, and SO_2, caused adverse effects on adult AD, and contributed to the development and exacerbation of AD symptoms.[29]

Regarding indoor exposure to air pollutants, Huss-Marp et al. investigated the effect of airborne VOCs on the skin of patients with AD and controls in the presence or absence of house dust mite allergen in a double-blind crossover study. They found that skin exposure to VOC at concentrations common in an indoor environment could damage the epidermal barrier and enhance atopy patch test reactions to house dust and mite allergen in sensitized subjects with AD.[30]

Kwon et al. studied that a birth cohort of 257 infants enrolled in the MOthers and Children's Environmental Health (MOCEH) study, whose parents agreed with the environmental measurement. Total VOCs were measured in the infants' bedrooms at the age of 6 months. A total of 105 parents answered a questionnaire after 36 months. An increased risk of AD was observed in the high total VOCs exposure group (75^{th} percentile of the distribution 242.1 μg/m^3) followed at 3 years, after adjusting for a parental history of allergy, household income, and breast-feeding (OR = 3.116, 95%Cl: 1.041-9.323). In addition, the risk of AD was increased within 1 year when the family bought new furniture.[12]

A prospective study evaluated the effect of indoor air pollution on children's AD symptoms in a day-care center, and found that the rate of positive AD symptoms increased after the children moved into a new building and decreased after the indoor air pollutants had been eliminated through ventilation and bake-out by heating ($P < 0.0001$). Analysis of the two-day delayed effects of toluene on AD symptoms showed that AD symptoms increased by 12.7% for each by 1 ppb increase in toluene levels ($P = 0.05$).[15]

Regarding outdoor exposure to air pollutants, Kim et al. investigated that the effects of outdoor air pollutants concentrations on AD patients. Throughout the study period, concentrations of outdoor benzene, toluene, and total VOCs were higher on the days when the patients had symptoms of AD than on the days when they reported no AD symptoms. Increased concentrations of total VOCs and benzene were associated with increase in AD symptoms on the following day.[14]

Aromatic VOCs (benzene, toluene, ethylbenzene, xylenes isomers, and trimethylbenzene) are the most studied VOCs regarding exposure and their association with the development and exacerbations of asthma and allergy in urban and suburban areas.[5,31] Other VOCs were rarely investigated. In addition,1,3,5-trimethylbenzene is widely used in machine wash liquids/detergents, automotive care products, painting, coating, adhesives, fragrances, air fresheners, fuels, in the products of pH regulators and water treatment, laboratory chemicals, health services, scientific research and development. The long-term occupational exposure limit is 20 ppm (100 mg/m^3).[32,33] Methylcyclohexane is widely used in many products including coating, anti-freeze, washing and cleaning, welding and soldering, biocides, lubricants and grease.[34] The health data of methylcyclohexane have not been reported in USEPA IRIS. Tseng et al. reported that the 11 VOCs, particularly 1,3,5-trimethylbenzene and methylcyclohexane, were highly affected the daily visits of urticaria in Kaohsiung, Taiwan.[13] Despite their widespread use, the human health effects of these two kinds of VOCs have rarely been discussed in the literature.

The strength of this study is using two study designs that demonstrated consistently positive findings on the association between air VOCs and daily visits of the patients with AD. The daily concentrations of air VOCs on the visit days influenced the number of visits in Poisson model, and the association was also confirmed by short-term changes in air VOCs using case-crossover study. The results (AORs) of the case-crossover study showed stronger effects of air VOCs on AD than the results (ARRs) of Poisson regression. Compatible significantly positive associations on both study designs strengthen this positive effect. The other strength is the large-scale nationwide analysis including five highly-polluted areas provided reliable evidence using real data from NHIRD and TAQMND. Higher daily visit counts can reflect the number of patients who needed to seek treatment according to their subjective symptoms due to higher concentration of air VOCs. The analysis using big data from NHIRD can demonstrate such trend. However, there are also several limitations. The NHIRD is a claims database that lacks direct data on personal air pollutants exposure, allergy laboratory tests, and disease severity. Although the diagnostic codes have been validated, misclassification cannot be completely ruled out.

The two study methods have their own advantage and limitations. The method of selecting the controls for exposure in case-crossover study is robust. It used an ambi-directional referent sampling window restricted to 30 days before and after the case event day and fixed-interval match for the day of the week. This is likely to result in small bias, and minimal autocorrelation in individuals' exposure among the case and referent days.[23] The negative effect by case-crossover study showed the possibility of lag-day effect of such VOC,[13] for example, benzene and n-pentane in Taichung City. Lag-day effects had been mentioned in several previous studies,[13-15] and the concentrations of air VOCs on the 1^{st} and 2^{nd} lag day particularly caused the exacerbation of AD symptoms. The analysis for lag-day effect was not performed in this study. Further investigation would be needed to clarify this effect.

The advantages of a Poisson model using Poisson distribution are as follows. Poisson distribution is basically a skewed model and the estimates are adapted to the actual data. It allows a minimum value of 0, and will not predict negative values. In addition, the Poisson model usually lessens the problem of over- or under-estimating the number of incidents for most records and gives a better estimate of the counts for each record compared to the normal distribution model. The limitation of a Poisson model is that the real-world distributions mostly are high-degree skewed and over-dispersion, much more than that are expected by Poisson distribution.[35]

Conclusion

The 12 studied ambient air VOCs concentrations significantly positively affected total number of daily visits for the patients with AD and each subgroup in both study designs, especially highest for 1,3,5-trimethylbenzene and methylcyclohexane. Men and women group showed similar significantly positive association. Children was the highest vulnerable subgroup regarding exposure to 1,3,5-trimethylbenzene and methylcyclohexane. The results for older adults, adolescents, and younger adults are also significantly higher. The other VOCs showed similar high effects in each subgroup. In the analysis of five cities, mostly VOCs showed significantly higher effects using two methods. Using conditional logistic regression analysis, methylcyclohexane and 1,3,5-trimethylbenzene had particularly higher association with the daily visits on five areas. Ethylbenzene showed significantly higher effects in Kaohsiung City and Changhua County. The positive associations of each VOC in five areas were similar using Poisson regression. Even though the air concentrations of methylcyclohexane and 1,3,5 trimethylbenzene were lowest, they had the highest effect on AD. Air VOCs concentrations can be considered as risk factors of visits for patients with AD.

Acknowledgement

The author expressed appreciation to Health Data Science Center, China Medical University Hospital for funding support, providing administrative and technical assistance in data processing and analysis for National Health Insurance Research Database and Taiwan Air Quality Monitoring Network Database.

Disclosure statement

No potential conflict of interest was reported by the author.

Data availability

The datasets from Taiwan Air Quality Monitoring Network Database are open database. The dataset from NHIRD used in this study is held by the Taiwan Ministry of Health and Welfare. The Taiwan Ministry of Health and Welfare must approve the application to access this data. Researchers interested in accessing this dataset can submit an application form to the Taiwan Ministry of Health and Welfare requesting access (Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan R.O.C. Phone: +886-2-8590-6848).

Ethical approval

Institutional Review Board of China Medical University Hospital (approval no. CMUH109-REC2-031(CR3))

Funding

This fundings of study were supported in part by China Medical University Hospital (DMR-111-105; DMR-112-087) and National Science and Technology Council (MOST 110-2314-B-075B-010). The funders had no role in the study design, data collection and analysis, the decision to publish, or preparation of the manuscript.

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