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Effect of exposure to ambient air volatile organic compounds on the severity of atopic dermatitis and lag-day effect

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Abstract

Background: Previous studies reported positive associations between exposure to air volatile organic compounds (VOCs) and daily visits for atopic dermatitis (AD).

Objective: This population-based study investigated associations between air VOCs exposure and daily hospitals visits for AD, severity subgroup (mild and severe), and lag-day effect in central-southern Taiwan.

Methods: The dependent variable was AD with diagnostic codes (ICD-9-CM 691.8 and ICD-10-CM L20) retrieved from the Taiwan National Health Insurance Research Database from 2008/01/01 to 2018/12/31. Independent variables included one-day 75th-percentile value of each VOC (benzene, ethylbenzene, toluene, m-/p-xylene, o-xylene, 1,3,5-trimethylbenzene, 1,2,4-trimethylbenzene, isopentane, n-pentane, n-hexane, methylcyclohexane, and cyclohexane) and four meteorological conditions from the Taiwan Air Quality Monitoring Network Database. This was a case-crossover design with multivariable conditional logistic regression, and the adjusted odds ratios (AORs) were reported.

Results: Concentrations of the 12 air VOCs significantly positively affected the total number of daily visits for AD (AOR = 1.02~1.69, $P < 0.001$) and subgroups of mild (AOR = 1.001~1.049, $P < 0.001$) and severe (AOR = 1.002~1.077, $P < 0.001$). The effect of air VOCs on the severe AD group was higher than that on the mild group. Values of the six VOCs on the 1st lag day (benzene: AOR = 1.16, 1,3,5-trimethylbenzene: AOR = 1.5, 1,2,4-trimethylbenzene: AOR = 1.13, isopentane: AOR = 1.07, n-pentane: AOR = 1.08, methylcyclohexane: AOR = 1.5, all $P < 0.05$) were significantly positively associated with the number of daily visits for AD.

Conclusions: Exposure to the 12 air VOCs on the visit days increased the risks of daily visits for AD in total and severity subgroup. The effects of six certain VOCs on the 1st lag day were significant positive.

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

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Introduction

Air pollutions, including air volatile organic compounds (VOCs), can be regarded as significant exacerbating factors for the symptoms of atopic dermatitis (AD) and urticaria in previous studies.[1-5] AD is a common chronic recurrent cutaneous inflammatory disease. Patients with AD usually suffer from recurrent severe pruritic localized and/or generalized eczema, which can last from six months to years.[6] Although AD is a multifactorial disease, environmental factors such as allergens, meteorologic factors, and air pollutants are crucial to exacerbate symptoms of AD.[6]

The moderate-to-severe AD patients who have severe epidermal barrier impairment usually have genetic predisposition demonstrated by genetic studies, including loss-of-function variants in the *FLG* gene.[7] The *FLG* is the gene for the production of filaggrin protein which is present in keratohyalin granules in the spinous and granular layers of the upper epidermis. Loss-of-function variants in *FLG* is responsible to epidermal barrier impairment.[7] Moreover, loss-of-function variants in *FLG* have also been shown to be the strongest genetic risk factors for moderate-to-severe AD,[8] associated with a three- to four-fold increased risk of AD in one meta-analysis study.[9] In addition, a double-blind crossover study reported that exposure to air VOCs at common indoor concentrations could damage the epidermal barrier in sensitized patients with AD and enhance cutaneous reactions to patch tests for house dust and mite allergens.[10] One study demonstrated that both air pollution and genetic factors independently increased the risk of incident newly developed elderly-onset AD, and the effect of air pollutants was stronger than that of the explored genes.[11]

Toxicokinetic studies on the United States Environmental Protection Agency (USEPA) Integrated Risk Information System websites have demonstrated that the lipophilic characteristics of VOCs is capable to enter bodies of animals and humans and cause long-lasting effects.[12-14] They can penetrate through the epidermal barrier and mucosa of the nose and respiratory tract, dissolve in the blood stream, and then stimulate inflammatory reaction and affect cell function.

Indoor and outdoor air VOCs may cause allergic and inflammatory reactions of the skin and mucous membrane.[15, 16] They have been associated with provoking symptoms and increasing the number of daily visit for AD and urticaria.[1-3] In addition, several Korean studies demonstrated that the symptoms of AD patients were positively influenced by higher values of outdoor and indoor air pollution, including VOCs.[1,17-19]

Our previous study showed the positive effects of the 12 ambient VOCs on the number of daily visits of AD in central-southern Taiwan, and in subgroup analyses of age, gender and five highly polluted areas.[2] However, it would also be interesting to investigate the influence of exposure to air VOCs regarding the severity of AD patients and lag-day effects.

Therefore, the aim of this study was to investigate the effects of short-term changes in 12 ambient air VOC concentrations on daily clinic visits in AD patients, including subgroup analysis of mild and severe AD, and lag-day effects in central-southern Taiwan, using data from the Taiwan National Health Insurance Research Database (NHIRD) and Taiwan Air Quality Monitoring Network Database (TAQMND). This population-based study was a case-crossover study design with conditional logistic regression analysis.

Methods

Data source of daily outpatient clinic visits for AD

Information on daily clinic visits of patients with AD were gathered retrospectively from the Taiwan NHIRD from January 1, 2008 to December 31, 2018. The NHIRD contain the health data of nearly the entire population of Taiwan. This study included patients with AD of all ages who visited at local hospitals, regional hospitals, and medical centers. The patients' identification numbers are anonymized to protect their privacy in the NHIRD, and the Institutional Review Board exempted the patients' informed consent. The definition of an AD case required a diagnostic code with International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification code for AD (ICD-9-CM code 691.8 and ICD-10-CM code L20) three or more times on the dates of outpatient clinic visits within one year by dermatologists, rheumatologists, or pediatrists. These diagnostic codes and definitions have been utilized in previous studies.[2,20] The visit date with a diagnosis of AD was defined as the event date for the patients with AD.

Data sources of ambient air VOCs and meteorological conditions

Ambient air pollutants data were retrieved from the TAQMND[21,22] which provides hourly monitoring data for air VOCs (concentrations: parts-per-billion as carbon (ppbC); ppbC = ppb * (number of carbon atoms)) and meteorological data from air quality monitoring stations. The one-day 75th-percentile value of each VOC (benzene, ethylbenzene, toluene, m-/p-xylene, o-xylene, 1,3,5-trimethylbenzene, 1,2,4-trimethylbenzene, isopentane, n-pentane, n-hexane, methylcyclohexane, and cyclohexane) and meteorological data was calculated from the 24-hourly data of each date.[21,22]

Study areas

The study areas included Taichung City, Changhua County, Yunlin County, Tainan City, and Kaohsiung City in central and southern Taiwan that have had high air pollution levels for years.[22,23] This study included patients whose registered addresses were listed in these five areas in the NHIRD. This study used data from the fixed monitoring stations for photochemicals located in Taichung City (n = 1), Yunlin County (n = 1), Tainan City (n = 1), and Kaohsiung City (n = 2), and a mobile monitoring truck in Changhua County (n = 1).

Study design and statistical methods

This study was a case-crossover design with conditional logistic regression analysis. The multivariable model included one kind of VOC and four kinds of meteorological data (weather temperature (°C), wind speed (m/sec), humidity (%), and rainfall (mm/hour)) as confounding factors for adjustment. The associations between daily clinic visits for AD and one-day 75th-percentile concentration value of each VOC and meteorological factors were presented as adjusted odds ratios (AORs) with 95% confidence interval (CI) and *P*-value. A two-tailed *P*-value of < 0.05 was defined as statistical significance. Data management and the statistical analyses were using SAS, version 9.4 (SAS Institute, Cary, NC). The study design was similar to our previous study[2] except that the patients' allergic diseases were not included as confounding factors due to comparison between severity subgroup.

Subgroups analysis was also performed for the severity of AD (mild and severe).[20] Severe AD patients were those who received systemic therapy (any of the following: systemic corticosteroids, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, and/or ultraviolet ray phototherapy) that was prescribed by dermatologists or rheumatologists after diagnosis of AD; otherwise, they were categorized as having mild AD. The lag-day effect of air VOCs was examined for 1st-6th lag days.[4]

The case-crossover design used the patients' exposure periods before and after the event dates as controls. The case event day was defined as the date of clinic visit for AD, and the air VOCs exposure on that day was considered to affect the patients' health. The control days were defined as being the same weekday in other weeks in the same month and year. Using this strategy, eight control days for each case day were selected, with four (the 1st, 2nd, 3rd, and 4th same weekday) before and four after the case day, respectively.[24-26]

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

Data on a total of 6,801,958 visits were retrieved from the NHIRD from January 1, 2008 to December 31, 2018, of which 6,054,423 (89.01%) were for patients with mild AD and 747,535 (10.99%) were for patients with severe AD. The ratio of mild to severe AD was 8:1. Of the total visits, 3,465,600 (51%) were made by children and adolescents (< 20 years), and 3,336,358 (49%) were made by adults (≥ 20 years). In addition, 3,322,321 (48.8%) were by male patients, and 3,479,637 (51.2%) by female patients.

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

The total number of daily visits was significantly positively associated with higher values of the 12 VOCs on the visit days (**Table 1**) (benzene: AOR = 1.08; toluene: AOR = 1.02; ethylbenzene: AOR = 1.24; m-/p-xylene: AOR = 1.07; o-xylene: AOR = 1.19; 1,3,5-trimethylbenzene: AOR = 1.69; 1,2,4-trimethylbenzene: AOR = 1.19; isopentane: AOR = 1.08; n-pentane: AOR = 1.10; n-hexane: AOR = 1.13; methylcyclohexane: AOR = 1.58; cyclohexane: AOR = 1.13; all *P* < 0.001), and the effect was especially strong for 1,3,5-trimethylbenzene and methylcyclohexane.

Table 1. The adjusted odds ratios between the total number of daily visits for atopic dermatitis and the daily 75th-percentile values of each VOC on the visit days and 1st-6th lag days.

Variables	Lag Day	AOR	(95%CI)	*p*-value	AOR	(95%CI)	*p*-value	AOR	(95%CI)	*p*-value
VOCs		benzene			o-xylene			n-pentene		
	0 day	**1.08**	**(1.07, 1.09)**	**< 0.001**	**1.19**	**(1.18, 1.21)**	**< 0.001**	**1.10**	**(1.09, 1.11)**	**< 0.001**
	1 day before	**1.16**	**(1.03, 1.31)**	**0.016**	1.05	(0.95, 1.17)	**0.334**	**1.08**	**(1.02, 1.14)**	**0.013**
	2 days before	0.87	(0.74, 1.04)	0.122	0.99	(0.85, 1.16)	0.908	0.97	(0.87, 1.08)	0.577
	3 days before	0.97	(0.82, 1.16)	0.747	1.01	(0.86, 1.19)	0.868	1.04	(0.92, 1.18)	0.520
	4 days before	0.98	(0.82, 1.16)	0.799	0.97	(0.83, 1.13)	0.657	0.95	(0.86, 1.06)	0.360
	5 days before	1.01	(0.86, 1.19)	0.909	0.98	(0.85, 1.13)	0.781	1.00	(0.92, 1.10)	0.924
	6 days before	1.01	(0.86, 1.18)	0.925	0.99	(0.86, 1.14)	0.906	0.98	(0.87, 1.09)	0.671

Table 1. (Continued)

Variables	Lag Day	AOR	(95%CI)	*p*-value	AOR	(95%CI)	*p*-value	AOR	(95%CI)	*p*-value
VOCs		**toluene**			**1,3,5-trimethylbenzene**			**n-hexane**		
	0 day	**1.02**	**(1.013, 1.022)**	**< 0.001**	**1.69**	**(1.64, 1.74)**	**< 0.001**	**1.13**	**(1.12, 1.14)**	**< 0.001**
	1 day before	1.01	(1.00, 1.02)	0.215	**1.50**	**(1.10, 2.04)**	**0.011**	1.07	(0.97, 1.17)	0.169
	2 days before	1.00	(0.99, 1.02)	0.777	0.61	(0.38, 0.99)	0.044	0.92	(0.81, 1.05)	0.213
	3 days before	1.00	(0.98, 1.01)	0.563	1.11	(0.67, 1.86)	0.683	0.98	(0.86, 1.11)	0.745
	4 days before	1.00	(0.99, 1.01)	0.985	0.94	(0.59, 1.52)	0.808	1.04	(0.92, 1.17)	0.524
	5 days before	1.00	(0.99, 1.01)	0.963	0.83	(0.53, 1.30)	0.413	1.00	(0.89, 1.12)	0.968
	6 days before	1.00	(0.99, 1.01)	0.899	1.12	(0.72, 1.74)	0.607	1.03	(0.92, 1.16)	0.621
VOCs		**ethylbenzene**			**1,2,4-trimethylbenzene**			**methylcyclohexane**		
	0 days	**1.24**	**(1.22, 1.25)**	**< 0.001**	**1.19**	**(1.18, 1.20)**	**< 0.001**	**1.58**	**(1.53, 1.64)**	**< 0.001**
	1 days before	1.04	(0.94, 1.16)	0.402	**1.13**	**(1.04, 1.22)**	**0.004**	**1.50**	**(1.12, 2.03)**	**0.007**
	2 days before	1.04	(0.87, 1.24)	0.664	0.89	(0.77, 1.02)	0.098	0.70	(0.46, 1.06)	0.096
	3 days before	0.98	(0.80, 1.20)	0.853	1.04	(0.88, 1.22)	0.665	0.98	(0.64, 1.51)	0.933
	4 days before	0.96	(0.79, 1.16)	0.687	0.97	(0.84, 1.13)	0.691	0.93	(0.61, 1.43)	0.755
	5 days before	0.99	(0.83, 1.17)	0.889	0.97	(0.85, 1.11)	0.673	1.04	(0.70, 1.54)	0.859
	6 days before	0.96	(0.81, 1.13)	0.600	1.02	(0.89, 1.17)	0.784	1.01	(0.68, 1.49)	0.978
VOCs		**m-/p-xylene**			**isopentene**			**cyclohexane**		
	0 day	**1.07**	**(1.068, 1.082)**	**< 0.001**	**1.08**	**(1.067, 1.083)**	**< 0.001**	**1.13**	**(1.11, 1.15)**	**< 0.001**
	1 day before	1.02	(0.98, 1.06)	0.275	**1.07**	**(1.03, 1.11)**	**< 0.001**	1.03	(0.92, 1.15)	0.578
	2 days before	1.00	(0.94, 1.05)	0.881	0.96	(0.91, 1.02)	0.154	1.03	(0.87, 1.20)	0.755
	3 days before	1.00	(0.95, 1.07)	0.903	1.01	(0.95, 1.08)	0.760	1.03	(0.88, 1.21)	0.717
	4 days before	0.99	(0.93, 1.05)	0.654	0.98	(0.92, 1.04)	0.551	0.99	(0.84, 1.18)	0.934
	5 days before	0.99	(0.94, 1.04)	0.614	0.98	(0.93, 1.04)	0.577	0.99	(0.83, 1.18)	0.934
	6 days before	1.00	(0.95, 1.05)	0.942	0.99	(0.94, 1.05)	0.756	0.97	(0.82, 1.16)	0.774

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

Lag-day effect analysis.

In analysis of the lag-day effect (**Table 1**), higher levels of six ambient air VOCs showed significant positive associations with the number of daily visits for AD on the 1st lag-day (benzene: AOR = 1.16, P = 0.016; 1,3,5-trimethylbenzene: AOR = 1.50, P = 0.011; 1,2,4-trimethylbenzene: AOR = 1.13, P = 0.004; isopentane: AOR = 1.07, P < 0.001; n-pentane: AOR = 1.08, P = 0.013; methylcyclohexane: AOR = 1.50, P = 0.007), and the effect was especially strong for 1,3,5-trimethylbenzene and methylcyclohexane.

The 1st lag-day values of toluene, ethylbenzene, m-/p-xylene, o-xylene, n-hexane, and cyclohexane were not significantly associated with the number of daily visits for AD. The values of other lag days (2nd-6th) of the 12 VOCs were not significantly associated with the number of daily visits for AD.

Subgroup analysis of mild and severe AD

Regarding the effect of VOC exposure on mild AD, the total number of daily visits was significantly positively associated with higher values of all 12 air VOCs on the visit days (**Table 2**) (benzene: AOR = 1.013, toluene: AOR = 1.001, ethylbenzene: AOR = 1.019, m-/p-xylene: AOR = 1.006, o-xylene: AOR = 1.016, 1,3,5-trimethylbenzene: AOR = 1.046, 1,2,4-trimethylbenzene: AOR = 1.012, isopentane: AOR = 1.003, n-pentane: AOR = 1.004, n-hexane: AOR = 1.013, methylcyclohexane: AOR = 1.049, cyclohexane: AOR = 1.012, all P < 0.001)

Table 2. The adjusted odds ratio between the number of daily visits for atopic dermatitis and daily 75th-percentile value of each VOC on the visit days in subgroup of severity.

Severity subgroup	Mild			Severe		
Volatile organic compounds	AOR	95%CI	*p*-value	AOR	95%CI	*p*-value
benzene (ppb)	1.013	1.012, 1.014	< 0.001	1.017	1.013, 1.02	< 0.001
toluene (ppb)	1.001	1.0008, 1.0012	< 0.001	1.002	1.0016, 1.0023	< 0.001
ethylbenzene (ppb)	1.019	1.018, 1.02	< 0.001	1.021	1.018, 1.024	< 0.001
m-/p-xylene (ppb)	1.006	1.0054, 1.0063	< 0.001	1.006	1.005, 1.007	< 0.001
o-xylene (ppb)	1.016	1.015, 1.017	< 0.001	1.018	1.016, 1.021	< 0.001
1,3,5-trimethylbenzene (ppb)	1.046	1.043, 1.049	< 0.001	1.077	1.068, 1.085	< 0.001
1,2,4-trimethylbenzene (ppb)	1.012	1.011, 1.013	< 0.001	1.020	1.017, 1.022	< 0.001
isopentane (ppb)	1.003	1.0024, 1.0034	< 0.001	1.004	1.003, 1.005	< 0.001
n-pentane (ppb)	1.004	1.003, 1.005	< 0.001	1.008	1.006, 1.010	< 0.001
n-hexane (ppb)	1.013	1.013, 1.014	< 0.001	1.017	1.014, 1.019	< 0.001
methylcyclohexane (ppb)	1.049	1.046, 1.052	< 0.001	1.055	1.047, 1.063	< 0.001
cyclohexane (ppb)	1.012	1.011, 1.014	< 0.001	1.018	1.014, 1.022	< 0.001

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

Regarding the effect on severe AD, the total number of daily visits was significantly positively associated with higher values of all 12 VOCs on the visit days (benzene: AOR = 1.017, toluene: AOR = 1.002, ethylbenzene: AOR = 1.021, m-/p-xylene: AOR = 1.006, o-xylene: AOR = 1.018, 1,3,5-trimethylbenzene: AOR = 1.077, 1,2,4-trimethylbenzene: AOR = 1.02, isopentane: AOR = 1.004, n-pentane: AOR = 1.008, n-hexane: AOR = 1.017, methylcyclohexane: AOR = 1.055, cyclohexane: AOR = 1.018, all $P < 0.001$). The AORs of 1,3,5-trimethylbenzene and methylcyclohexane were the highest among all VOCs.

The AORs of the 12 air VOCs for the number of daily visits for severe AD were slightly higher than those for mild AD. This implied that the number of severe AD patients who sought treatment when exposed to high values of air VOCs was higher than the number of mild AD patients.

Discussion

Previous epidemiological studies, animal models, and in vitro experiments have demonstrated associations between exposure to air VOCs indoors and outdoors with cutaneous allergic inflammation and the symptoms exacerbation of AD.[27,28] However, few studies have focused on the effect of air VOCs on the severity of AD and lag-day effect.

Regarding indoor and outdoor exposure to air VOCs on the skin, building-related symptoms have been proposed to reflect the effect of indoor air quality on human health, including AD, irritation of mucosal membranes, headaches, and asthma. Suzuki et al. reported the results of the study "Chemiless Town Project Phase 3" at Chiba University in 2017, which compared 141 participants in two similar laboratories with different levels of indoor air total VOCs, and showed a significant positive association between higher VOC levels and the occurrence of building-related symptoms, especially in people with allergic history and those with higher sensitivity to chemicals.[29] Lim et al. reported that the results of comparison between conventional buildings and energy-efficient houses and showed that indoor concentrations of air VOCs, particulate matter (PM), and carbon dioxide, were closely related to the indoor ventilation rate, and that they were lower in the energy-efficient houses after controlling for seasonality. In addition, increased levels of indoor air quality parameters were positively associated with the daily symptoms of AD and allergic rhinitis.[30]

In addition to evaluating levels of air VOCs, urinary concentrations of VOC metabolites, including those of benzene, toluene, xylene, styrene, and formaldehyde, are practical methods for quantifying VOCs exposure via different routes of personal exposure. Ha et al. investigated the associations between AD and urinary concentrations of nine representative metabolites of VOCs in 149 seven-year-old school children. Children with AD who had toluene metabolite and the highest quartile concentration of benzene metabolite detected in urine were positively associated with the presence of AD and positive SCORing Atopic Dermatitis (SCORAD) index values, respectively.[31] Tang et al. demonstrated that creatinine-corrected urine metabolite levels of toluene and 1,3-butadiene were all elevated in the patients with AD compared with the controls, although without statistical significance after correction in a multivariate linear regression model adjusted for age and sex.[32]

Two other studies have demonstrated that air pollutants were important risk factors for the exacerbation of AD symptoms among severe AD patients, and that most of these patients had genetic predispositions.[11,33] Gu et al. investigated whether air pollutant mixture was associated with incident elderly-onset AD within genetic risk groups. The results showed that among the 2,545 incident cases of AD identified among the 337,910 recruited participants from the UK Biobank, both air pollution and genetic factors independently increased the risk of newly developed elderly-onset AD, and that the effect of air pollutants on elderly-onset AD was stronger than the investigated genes.[11] Bellinato et al. reported that in a total 169 moderate-to-severe AD patients treated with dupilumab at the University Hospital of Verona in Italy between December 2018 and December 2021, acute air pollution exposure (PM10, PM2.5, nitrogen oxides, and nitrogen dioxide) was associated with an increased risk of AD flare with a dose-response relationship.[33]

In this study, daily visits of both mild and severe AD patients were highly affected by air VOCs, and severe AD patients were more easily affected than mild AD patients. The results indicated that exposure to higher values of air VOCs positively influenced the treatment-seeking behavior of severe AD patients, even though they were already receiving systemic corticosteroid, immunosuppressive, immune-modulater, or biologics medication. It is possible that the air pollutants can be more irritating and more easily penetrate into the severely impaired epidermal barrier of patients with moderate-to-severe AD and consequently induce higher inflammatory symptoms. This effect cannot be totally controlled by systemic medication. Therefore, the higher number of daily visits can reflect the number of patients who sought treatment according to their subjective symptoms was higher when exposed to higher concentrations of air VOCs.

The lag-day effect in this study showed that the values of six VOCs on the 1st lag day were significantly positively associated with daily visits for AD. A few studies have investigated lag-day effects,[13-15] and reported that exacerbation of AD symptoms was particularly positively associated with the levels of air VOCs on the 1st and 2nd lag days. A prospective study reported that among 22 children with AD (17 boys and 5 girls, age 16-85 months), the concentrations of outdoor benzene, toluene, and total VOCs were higher on the days when they had symptoms of AD than on the days when they reported no symptoms with AD. An increased concentration of total VOCs and benzene were positively associated with an increase in AD symptoms on the 1st lag day respectively. However, the statistical significance disappeared 2 days after exposure.[17] The other study reported that AD symptoms among 30 children with AD in a day-care center became worse after they moved into a new building, and that the symptoms lessened after a ventilation system eliminated indoor air pollutants. Higher indoor air toluene levels on the 2nd lag day were significantly positively associated with the symptoms of AD.[18] The daily visit counts of urticaria were also affected by higher daily levels of air VOCs. Our previous study showed that significant positive associations were reported between the total daily visits of urticaria and higher levels of four kinds of VOCs on the visit days, including ethylbenzene, toluene, m-/p-xylene, and o-xylene; and ten kinds of VOCs (benzene, ethylbenzene, toluene, m-/p-xylene, o-xylene, 1,3,5-trimethylbenzene, n-hexane, methylcyclohexane, cyclohexane, and ethylene) on the 4th lag days.[3]

This study has strengths and limitations. The strengths are the case-crossover study design, severity subgroup, lag-day effect, and big data analyses. The advantage of the case-crossover study is that it minimize bias and autocorrelation in the participants' exposure among the case and control days because the method of selecting the control used an ambi-directional sampling before and after the case event day with a 7-day interval to match the day of the week.[25] In addition, the effect of air VOCs on mild and severe AD and the 1st lag-day effect provided important information in clinical practice. In the Taiwan National Health Insurance System, patients with AD can make ether scheduled or non-scheduled appointments. In other words, they can make appointment by themselves, and then visit to any hospital, including medical center, on any weekdays if they need to receive treatment at that time. Therefore, the other strength is the analysis of a large-scale population in highly polluted areas using real data from the NHIRD and TAQMND, which can provide reliable evidence for positive associations.

However, there were also several limitations. The information of the clinical AD severity scores was not provided in the NHIRD, including the "Eczema Area and Severity Index (EASI) score", "Investigator's Global Assessment score", "Dermatology Life Quality Index", "SCORAD", and "Pruritus Numerical Rating score". Therefore, the effect of the air VOCs on the clinical AD severity scores could not be analyzed in this study. In addition, the TAQMND contains data from fixed monitoring stations. Direct data of personal exposure to air pollutants were lacked. The misclassification of diagnostic codes in NHIRD could have led to information bias, although the use of these codes has been validated.

Conclusion

In this study, the case-crossover study design demonstrated short-term changes in the concentrations of the 12 studied ambient air VOCs were significantly positively associated with the number of daily visits for AD among the total population and subgroups with mild and severe AD. The effect of air VOCs on the number of daily visits was higher in the patients with severe AD than in those with mild AD, even though severe AD patients were already receiving systemic treatments and phototherapy. Concentrations of six VOCs on the 1st lag day showed significant positive association with the number of daily visits for AD.

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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))

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References

1. Kwon JH, Kim E, Chang MH, Park EA, Hong YC, Ha M, et al. Indoor total volatile organic compounds exposure at 6 months followed by atopic dermatitis at 3 years in children. Pediatr Allergy Immunol. 2015;26: 352-8.
2. Tseng HW. Positive effect of exposure to ambient air volatile organic compounds on clinic visits for atopic dermatitis. Asian Pac J Allergy Immunol. 2024; doi: 10.12932/ap-250224-1796 [Epub ahead of print]
3. Tseng HW, Lu LY. Short-term impact of exposure to ambient air volatile organic compounds on daily clinic visits for urticaria in Kaohsiung, Taiwan. Asian Pac J Allergy Immunol. 2024; doi: 10.12932/ap-290823-1677 [Epub ahead of print]
4. Tseng HW, Lu LY, Shiue YL. Short-term impact of ambient air pollution exposure on daily clinic visits for patients with urticaria in Kaohsiung, Taiwan. Air Qual. Atmos. Health 2021;14:1063–70.
5. Tseng H-W. Effect of Ambient Air Pollutants Exposure on Clinic Visits for Atopic Dermatitis, a Nationwide Study in Central-Southern Taiwan. Aerosol and Air Quality Research. 2024;24:240130. doi: 10.4209/aaqr.240130 [Epub ahead of print]
6. Katoh N, Ohya Y, Ikeda M, Ebihara T, Katayama I, Saeki H, et al. Japanese guidelines for atopic dermatitis 2020. Allergol Int. 2020;69: 356-69.
7. McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. J Allergy Clin Immunol. 2013;131:280-91.
8. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006;38:441-6.
9. van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. BMJ. 2009;339:b2433.
10. Huss-Marp J, Eberlein-Konig B, Breuer K, Mair S, Ansel A, Darsow U, et al. Influence of short-term exposure to airborne Der p 1 and volatile organic compounds on skin barrier function and dermal blood flow in patients with atopic eczema and healthy individuals. Clin Exp Allergy. 2006;36:338-45.
11. Gu X, Jing D, Xiao Y, Zhou G, Yang S, Liu H, et al. Association of air pollution and genetic risks with incidence of elderly-onset atopic dermatitis: A prospective cohort study. Ecotoxicol Environ Saf. 2023; 253:114683.
12. Montero-Montoya R, Lopez-Vargas R, Arellano-Aguilar O. Volatile Organic Compounds in Air: Sources, Distribution, Exposure and Associated Illnesses in Children. Ann Glob Health. 2018;84:225-38.
13. Riechelmann H. Cellular and molecular mechanisms in environmental and occupational inhalation toxicology. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2004;3:Doc02.
14. United States Environmental Protection Agency [Internet]. Integrated Risk Information System, IRIS Assessments. 2021 [cited 2021 Aug 22]; Available from: https://www.epa.gov/iris.
15. World Health Organization. Assessment of exposure to indoor air pollutants. In: Jantunen M, Jaakkola JJK, Krzyzanowsk M, editors. Copenhagen: WHO Regional Office for Europe.; 1997. p. 54-65.
16. United States Environmental Protection Agency [Internet]. Volatile Organic Compounds' Impact on Indoor Air Quality. United States Environmental Protection Agency; 2021 [cited 2021 May 22]; Available from: https://www.epa.gov/indoor-air-quality-iaq/volatile-organic-compounds-impact-indoor-air-quality.
17. Kim J, Kim EH, Oh I, Jung K, Han Y, Cheong HK, et al. Symptoms of atopic dermatitis are influenced by outdoor air pollution. The Journal of allergy and clinical immunology. 2013;132:495-8 e1.
18. Kim EH, Kim S, Lee JH, Kim J, Han Y, Kim YM, et al. Indoor air pollution aggravates symptoms of atopic dermatitis in children. PloS one. 2015;10:e0119501.
19. Kim JK, Kim HJ, Lim DH, Lee YK, Kim JH. Effects of Indoor Air Pollutants on Atopic Dermatitis. Int J Environ Res Public Health. 2016;13:1220-.
20. Chen TL, Huang WT, Loh CH, Huang HK, Chi CC. Risk of Venous Thromboembolism Among Adults With Atopic Dermatitis. JAMA dematol. 2023;159:720-7.
21. Taiwan Air Quality Monitoring Network databases [Internet]. Environmental Protection Administration Executive Yuan, R.O.C, Taiwan 2018. [cited 2020 May 26] Available from: https://airtw.moenv.gov.tw/CHT/EnvMonitoring/Central/CentralMonitoring.aspx.
22. Data from Photochemical Assessment Monitoring Stations [Internet]. Environmental Protection Administration Executive Yuan, R.O.C, Taiwan. 2020 [cited 2020 May 26]. Available from: https://airtw.moenv.gov.tw/CHT/TaskMonitoring/Photochemical/PhotochemicalMonitoring.aspx.
23. Taiwan News [Internet]. Kaohsiung ranks as having worst PM2.5 levels in Taiwan in 2018. 2019 [cited 2020 Oct 25]; Available from: https://www.taiwannews.com.tw/en/news/3608557.
24. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. Epidemiology. 2005;16:717-26.
25. Levy D, Lumley T, Sheppard L, Kaufman J, Checkoway H. Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiology. 2001;12:186-92.
26. Lu Y, Zeger SL. On the equivalence of case-crossover and time series methods in environmental epidemiology. Biostatistics. 2007;8:337-44.
27. Dijkhoff IM, Drasler B, Karakocak BB, Petri-Fink A, Valacchi G, Eeman M, et al. Impact of airborne particulate matter on skin: a systematic review from epidemiology to in vitro studies. Part Fibre Toxicol. 2020;17:35.
28. Magnani ND, Muresan XM, Belmonte G, Cervellati F, Sticozzi C, Pecorelli A, et al. Skin Damage Mechanisms Related to Airborne Particulate Matter Exposure. Toxicol Sci. 2016;149:227-36.

29. Suzuki N, Nakaoka H, Nakayama Y, Tsumura K, Takaguchi K, Takaya K, et al. Association between sum of volatile organic compounds and occurrence of building-related symptoms in humans: A study in real full-scale laboratory houses. Sci Total Environ. 2021;750:141635.
30. Lim AY, Yoon M, Kim EH, Kim HA, Lee MJ, Cheong HK. Effects of mechanical ventilation on indoor air quality and occupant health status in energy-efficient homes: A longitudinal field study. Sci Total Environ. 2021;785:147324.
31. Ha EK, Kim JH, Park D, Lee E, Lee SW, Jee HM, et al. Personal Exposure to Total VOC Is Associated With Symptoms of Atopic Dermatitis in Schoolchildren. J Korean Med Sci. 2022;37:e63.
32. Tang KT, Chen YS, Lee MF, Chen TT, Lai CC, Lin CC, et al. Exposure to Volatile Organic Compounds May Contribute to Atopic Dermatitis in Adults. Biomedicines. 2024;12:1419
33. Bellinato F, Adami G, Furci A, Cattani G, Schena D, Girolomoni G, et al. Association between short-term exposure to environmental air pollution and atopic dermatitis flare in patients treated with dupilumab. JAAD Int. 2023;11:72-7.